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Effects of Erythropoietin on Lung Injury Induced by Cardiopulmonary Bypass After Cardiac Surgery

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Background: Lung injury after cardiopulmonary bypass (CPB) is a serious postoperative complication and can affect the postoperative recovery. The purpose of this study was to explore whether erythropoietin (EPO) has an effect on lung injury caused by CPB.

Material/Methods: Sixty patients who received the CPB were randomly divided into a saline group and the EPO group. All the patients received saline or EPO preoperatively, respectively. The ventilation function, including dynamic compliance, peak airway pressure, and plateau pressure, were recorded. The level of tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-10 in serum and arterial blood gas were analyzed. The mechanical ventilation time in the intensive care unit (ICU), the length of time spent in the ICU, the time from operation to discharge, and the total time of hospitalization were recorded. Adverse events in the ICU were monitored and recorded.

Results: EPO significantly decreased the level of TNF-α and IL-1β, but increased the level of IL-10 after CPB. EPO significantly improved pulmonary ventilated function and gas exchange function after CPB. EPO significantly shortened the mechanical ventilation time and stay in the ICU.

Conclusions: Preoperative EPO injection reduced lung injury and promoted lung function in patients who underwent CPB. The protection effect of EPO may be associated with inhibition of inflammatory response.

MeSH Keywords: Cardiopulmonary Bypass • Erythropoietin • Inflammation • Lung Injury

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Background

Cardiopulmonary bypass (CPB) is an important method used to maintain organ blood flow and oxygenation during cardiac surgery, but can induce a persistent severe inflammatory response [1]. The inflammation induced by a CPB inevitably causes lung tissue damage after CPB [2]. Although the mechanisms of CPB-induced lung injury are yet to be elucidated fully, the release of oxygen free radicals, protease enzymes, endothelial injury, and sequential and persistent inflammatory cascade contribute to post-pump lung injury [1,3,4]. It has been reported that the increase in inflammatory factors in lung tissue was 1.5 to 3 times compared to the level in plasma after CPB. Generally, severely impaired pulmonary function and pulmonary inflammation may lead to respiratory symptoms including hypoxemia, lung edema, and a decrease of lung compliance. In patients with pre-lung dysfunction, lung injury associated with CPB can even lead to acute respiratory distress syndrome (ARDS). Postoperative pulmonary dysfunction may lengthen the time of ventilation and hospitalization in the intensive care unit (ICU), and subsequently increase mortality [5]. Therefore, therapy for postoperative pulmonary dysfunction is a crucial consideration when planning CPB.

As a hypoxia-induced cytokine, erythropoietin (EPO) is a key regulator of erythropoiesis. In past decades, the anti-inflammation and organ protection effect of EPO has been elucidated [6,7]. EPO can attenuate ischemia/reperfusion injury (IRI) by nuclear translocation of AP-1, serum and glucocorticoid-regulated kinase-1 [8], heme oxygenase-1 [9], and metallothioneins. EPO also reduced multiple lung injuries including endotoxin, hyperoxia [10], and IRI [11]. However, there have been no studies that evaluated the effect of EPO on pulmonary dysfunction induced by CPB. Considering the possible mechanism of lung injury after CPB and the therapeutic mechanism of EPO on inflammation, we hypothesized that EPO could reduce lung injury and inflammation induced by CPB. In this study, we injected EPO preoperatively to estimate the effect of EPO on pulmonary dysfunction induced by CPB.

Material and Methods

This clinical trial (Chinese Clinical Trial Registration: ChiCTR-IPC-1800014722) was approved by the Ethics Committee of the Second Affiliated Hospital, Harbin Medical University. A total of 54 adult patients were randomly allocated to a saline or EPO group (30 patients each group). The patients in the saline group or EPO group received the intravenous injection of saline or EPO 100 IU/kg, diluted into 50 mL saline, which was continuously applied for 3 days.

The exclusion criteria were as follows: patients with body mass index over 35 kg/m^2, polycythemia, smoking cessation less than 2 weeks, severe lung dysfunction including forced vital capacity (FVC) and the forced expiratory volume in first second (FEV1) <50% of the predicted values). Patients with history of severe anemia, immune dysfunction, systemic infection, hypoproteinemia, serious lung infection, pleural effusion were also excluded from this study. In addition, those patients with hepatic, renal, or coagulation disorder, COPD, or asthma were also excluded, as were patients who received a second cardiac surgery. This study was a double-blinded clinical trial. Three anesthesiologists were recruited to perform the randomization, anesthesia, and observation. The first anesthesiologist randomized all the patients using the random number table generated by the computer and prepared the saline or EPO. The second anesthesiologist only performed the general anesthesia for all the patients. The last anesthesiologist only collected research sample and recorded the data.

All the preoperative cardiac treatments were continuous administrated until the morning of operation except angiotensin II antagonists and angiotensin-converting enzyme inhibitors. Then 0.5 mg/kg midazolam was intravenously injected to maintain sedation. Under local anesthesia with 1% lidocaine, the radial artery was cannulated to monitor the hemodynamic change and analyze the arterial blood gas (ABG). The anesthesia was induced with lidocaine 1 mg/kg, fentanyl 10 μg/kg, pipecuronium 0.1 mg/kg, and etomidate 0.2 mg/kg. After anesthesia was induction, all the patients received intratracheal intubation, and then the right internal carotid was cannulated. The mechanical ventilation parameters were tidal volume with 8 mL/kg, post-expiratory end pressure with 5 cmH_2O, and the fraction of inspired oxygen (FiO_2) 80±5%. The ratio of inspiratory/expiratory ratio was set 1: 2. The respiratory rate was adjusted to maintain SpO_2 >95%, and partial arterial carbon dioxide tension ($PaCO_2$) within 35 to 40 mmHg. The anesthesia of the non-CPB period was maintained with sevoflurane (1.5%) and fentanyl (10 μg/kg/hour), and changed to fentanyl and propofol during CPB.

All patients received the standardized CPB procedure. During CPB, the mean arterial blood pressure was kept within 40 to 60 mmHg. The value of ABG pH and $PaCO_2$ were maintained at within 7.35 to 7.45 and 35 to 40 mmHg, respectively. The arterial partial pressure of oxygen (PaO_2)/FiO_2 ratio was maintained >150 mmHg. The temperature was maintained within 30°C to 32°C. During CPB, all the patients received 5 cmH_2O CPAP for 2 lungs with 50% O_2 and 50% N_2. At the end of the CPB, all the patients received 2 minutes of manual ventilation and then the mechanical ventilation was restored to the previous respiratory parameters. After the operation, all patients were transferred to the cardiac ICU ward and received standardized treatment. In the ICU, all patients were weaned

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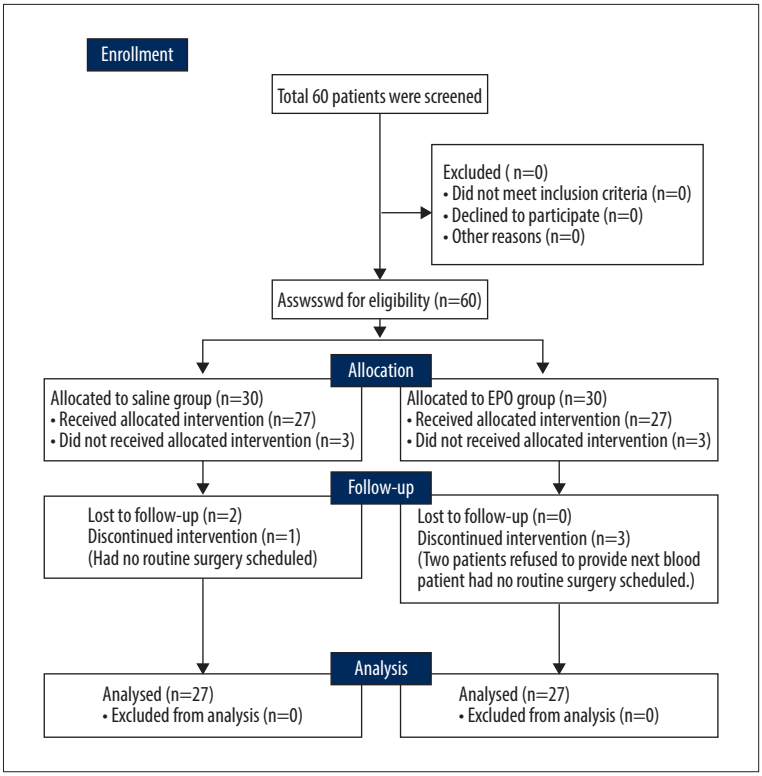

Figure 1. Flow diagram of enrolled patients.

from mechanical ventilation and extubated when they had a stable hemodynamic (by invasive measurements), no episode of uncontrolled arrhythmias, body temperature over 36.0°C, PaO_2/FiO_2 >300 mmHg, and pH greater than 7.3 [12]. After withdrawal of the mechanical ventilation and extubation, the patients were transferred to the cardiac ward. In the cardiac ward, additional oxygen or non-invasive ventilator was provided if the PaO_2/FiO_2 ratio of patients <150 mmHg,

To test the effect of EPO on pulmonary injury induced by CPB, the pulmonary dynamic compliance, and the peak and plateau pressure were monitored and recorded using S/5TM (Datex-Ohmeda Inc., Helsinki, Finland) before CPB, after sternum closure, and at 2 hour, 4 hours, and 6 hours in the ICU. Moreover, the PaO_2/FiO_2 ratios and blood samples were collected and measured before EPO, before incision, after sternum closure, and at postoperative 6 hours, 12 hours, 24 hours 48 hours, and 72 hours. The cytokines, such as the tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-10, in the serum samples were analyzed. The mechanical ventilation time in the ICU and the time of hospitalization of ICU were recorded. The length of hospital stay and time from the end of operation to discharge were also recorded. The postoperative complication including incidence of ARDS [13], lung edema, cerebrovascular accidents, new onset of atrial fibrillation, postoperative myocardial infarction (increase of CK-MB ≥25 ng/dL) and the new pathologic Q wave on ECG), acute postoperative kidney injury (upregulation of serum creatinine over 50% of baseline) were recorded. The patients needing noninvasive ventilation in the ward were recorded. After discharge from the hospital, the patients were continuous contacted to evaluate the respiratory complication including pneumonia, lung infection, and atelectasis, at 1 month, 2 months, and 6 months postoperatively.

Statistical analysis

The normally distributed data were presented with the mean±standard deviation (SD), and the skewed data were presented with medians (IQR). The primary endpoint was to compare postoperative lowest PaO_2/FiO_2 after CPB. The sample size of this study was based on a previous study and indicated that a sample size of 25 patients per group with a mean of 30 would reach approximately 80% power (α=0.05, 2-tail). We enrolled 27 patients per group to attain a statistically significant difference after the potential loss of disqualified participants.

The normally distributed data were analyzed using the 2-way repeated analysis and post-hoc Bonferroni correction. The repeated measurement data were analyzed with repeated measures data ANOVA. The skewed data were logarithmically transformed to achieve a normal distribution and analyzed with 2-tailed Student's *t*-tests. Nonparametric Friedman test was used to analyze the data of abnormal distribution. All data were analyzed by SPSS 11.5. There was significant difference between the 2-tails (P<0.05).

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Table 1. Demographic data and surgical characteristics.

	Saline group (n=27)	EPO group (n=27)
Age (years)	53.1±9.5	52.5±8.9
Gender (Male/Female)	10/17	12/15
Height (cm)	164.4±5.9	164.4±6.3
Weight (kg)	65.8±4.4	65.9±4.6
Smoking history (n)	9	8
Congestive heart failure (n)	3	4
Preoperative LVEF (%)	53.1±4.8	52.5±4.1
Surgical procedure (n)		
Aortic valve replacement	3	4
Mitral valve replacement	8	10
Left atrial myxoma resection	4	3
Closure of patent ductus arteriosus	2	1
Repair of endocardial cushion defect	2	2
Atrial septal defect	5	5
Ventricular septal defect	3	2

	Saline group (n=27)	EPO group (n=27)
Pulmonary function test		
FEV1; % predicted	79.6±5.1	80.5±4.6
FEV1/FVC (%)	86.7±5.6	87.2±4.9
Anesthesia time (min)	230.6±38.2	223.8±32.5
Operation time (min)	190.2±35.5	186.8±27.1
CPB time (min)	108.8±36.6	102.1±33.5
Blood lost volume (mL)	594±166	588±173
Urine volume (mL)	811±144	824±141
Red blood cell infusion (mL)	1265±355	1318±326
Plasma infusion (mL)	788±205	760±185
Platelets (U)	4	4
Preoperative length of hospital stay (days)	9.5±2.1	9.2±2.4
Postoperative complication		
Atrial fibrillation (n)	4	3
Hypoxemia (n)	5	6
Atelectasis (n)	3	2

The data are presented as mean±SD or and number. EPO – erythropoietin; LVEF – left ventricular ejection fraction; FEV1 – forced expiratory volume in one second; FVC – forced vital capacity; CPB – cardiopulmonary bypass; SD – standard deviation.

Results

A total of 54 patients were enrolled in this study (Figure 1). There was no statistical difference between the 2 groups in demographic data and postoperative complications ($P>0.05$) (Table 1). All the patients were weaned from CPB and mechanical ventilation in the ICU.

We monitored the peak pressure, plateau pressure, and dynamic compliance to test the effect of EPO on airway compliance. Compared with the saline group, the peak pressure and plateau pressure in the EPO group were significantly decreased, while the compliance significantly increased ($P<0.05$) (Table 2). Compared with the saline group, the EPO group had an increase in the postoperative PaO_2/FiO_2 ratio from postoperative 6th hour to 48th hour ($P<0.05$) (Table 3). Meanwhile, the hematocrit of the 2 groups was in the normal range at each time point. There was no risk of erythrocytosis caused by EPO application (Table 3).

We compared the mechanical ventilation time and time in the ICU to test the effect of EPO on the postoperative recovery of pulmonary function. The mechanical ventilation time and stay time in the ICU was shorter in the EPO group than the saline group ($P<0.05$) (Table 4). Although the time from surgery to discharge and the hospital stay time in the EPO group were shorter than those measures in the saline group, the difference was not statistically significant ($P>0.05$) (Table 4).

There were 15 patients in the saline group who needed additional oxygen over at least 24 hours to maintain optimal oxygenation. Compared with the saline group, significantly fewer patients needed additional oxygen ($P<0.05$) (Table 4). There were no patients who needed non-invasive ventilator assistance in the ward ($P>0.05$).

Compared to baseline, the concentration of TNF-α, IL-1β, and IL-10 were upregulated after sternum closure in the 2 groups ($P<0.05$) (Figure 2). Compared with the saline group, the TNF-α and IL-1β were significantly lower, but the IL-10 was significantly higher in the EPO group ($P<0.05$) (Figure 2).

None of the patients developed polycythemia before incision, after sternal closure, or at 6 hours, 12 hours, 24 hours, 48 hours, or 72 hours postoperatively. Furthermore, none of the patients developed the respiratory adverse complications

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Table 2. The ventilatory parameters in the 2 groups before CPB and after sternal closure.

	Saline group (n=27)	EPO group (n=27)	*P* value
Peak pressure (cmH_2O)			
Before CPB	14.87±1.66	14.30±3.27	0.327
After sternal closure	17.37±1.67	16.26±4.32	0.182
2 hours after operation	20.10±1.67	19.85±3.03	0.445
4 hours after operation	22.47±1.59	19.92±3.52	0.001
6 hours after operation	23.20±1.75	19.92±3.34	<0.0001
Plateau pressure (cmH_2O)			
Before CPB	12.90±1.52	12.37±3.10	0.372
After sternal closure	15.33±1.63	14.19±4.15	0.161
2 hours after operation	18.37±1.56	19.23±3.14	0.297
4 hours after operation	20.23±1.76	19.44±3.15	0.145
6 hours after operation	21.30±1.82	19.32±3.38	0.001
Dynamic compliance (mL/cmH_2O)			
Before CPB	41.10±5.33	44.85±5.21	0.152
After sternal closure	36.63±5.18	40.74±6.72	0.168
2 hours after operation	34.13±5.11	47.50±7.51	<0.0001
4 hours after operation	32.77±5.02	47.08±6.14	<0.0001
6 hours after operation	32.20±4.89	48.68±7.16	<0.0001

The data are presented as mean±SD. EPO – erythropoietin; CPB – cardiopulmonary bypass; SD – standard deviation.

Table 3. The PaO_2/FiO_2 ratio and hematocrit between the 2 groups.

		Before CPB	After sternal closure	Postoperative 6 hours	Postoperative 12 hours	Postoperative 24 hours	Postoperative 48 hours	Postoperative 72 hours
PaO_2/FiO_2 ratio	Saline group	398.8±12.6	361.9±16.4	306.7±12.9	313.8±9.1	258.9±9.9	341.4±26.3	388.6±14.2
	EPO group	408.9±13.3	381.5±14.9	322.1±14.7	353.2±11.3*	294.3±11.2*	430.9±23.9*	408.8±16.3
Hematocrit	Saline group	34.3±5.3	30.5±3.2	32.6±3.1	33.4±2.7	34.2±3.4	34.9±3.7	36.0±3.8
	EPO group	36.5±5.9	30.0±3.0	31.6±4.2	32.2±3.6	33.6±3.9	34.8±4.5	35.4±4.0

The data are presented as mean±SD. * $P<0.05$, compared with saline group. PaO_2 – arterial partial pressure of oxygen; FiO_2 – fraction of inspired oxygen; CPB – cardiopulmonary bypass; EPO – erythropoietin.

Table 4. Comparison of recovery times between 2 groups.

	Saline group (n=27)	EPO group (n=27)	*P* value
Time of ventilation in ICU (hours)	27.1±5.4	18.7±2.47	0.004
Time of stay in ICU (hours)	32.2±6.4	23.5±5.1	0.018
Time from end of surgery to discharge (days)	13.9±3.8	13.8±3.3	0.8
Length of hospital stay (days)	24.9±7.5	23.8±3.6	0.088
The number of patients who needed additional oxygen over at least 24 hours	15	0	<0.001

The data are presented as mean±SD. EPO – erythropoietin; ICU – Intensive Care Unit; SD – standard deviation.

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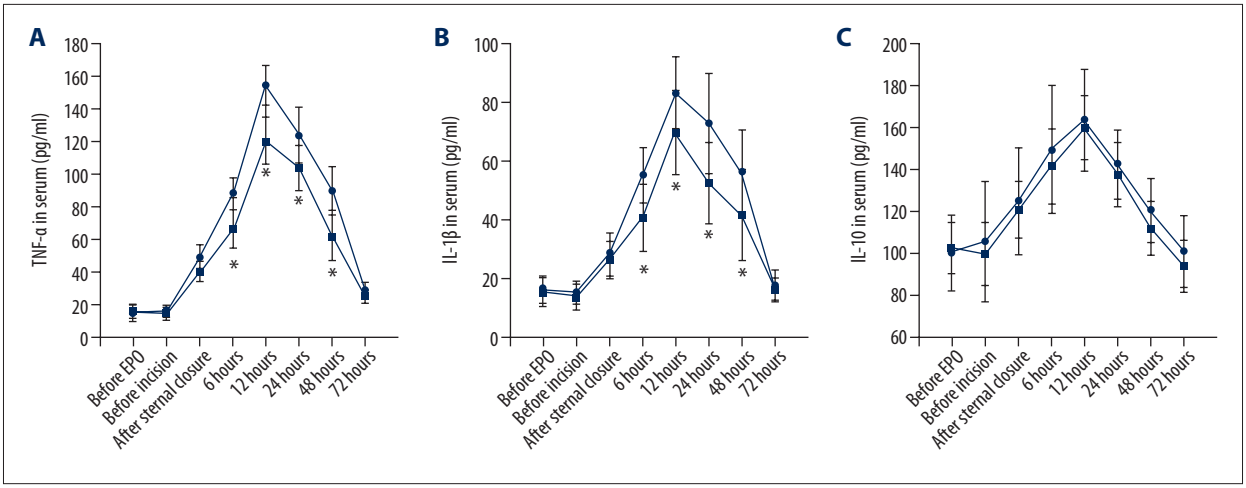

Figure 2. Cytokine concentrations in the serum in 2 groups. The levels of serum (**A**) TNF-α, (**B**) IL-1β, and (**C**) IL-10 in individual patients were determined. Data are expressed as the mean and SD of each group (n=27). ● and ■ represent the saline and EPO group, respectively. * *P*<0.05 compared with saline group. TNF – tumor necrosis factor; IL – interleukin; SD – standard deviations; EOP – erythropoietin.

including lung infection, atelectasis, or pneumonia as determined by telephone follow-up at 1 month, 2 months, and 6 months postoperatively.

Discussion

In this clinical trial, we found that the preoperative injection of EPO could significantly improve pulmonary function, reduced systemic inflammation, and shortened mechanical ventilation time and ICU stay.

Although material and surgical technology have improved, the postoperative pulmonary injury induced by CPB continues to be a severe complication and influences postoperative recovery. Postoperative lung injury is the main attributed to the serious inflammation induced by CPB, lung ischemia-reperfusion injury [2,14].

In this study, we found that EPO improved the respiratory mechanics after CPB. During CPB, contact of blood with the CPB circulation tube activates the inflammatory cell releasing lots of inflammatory factors [15]. These inflammatory factors can directly damage endothelial cells. The injured cells release chemoattractants and exacerbate inflammation. Moreover, during CPB the 2 lungs only receive less than a 5% supply of blood. The lung ischemia-reperfusion injury also contributes to lung inflammation [16]. The lung inflammation leads to an increase in pulmonary microvascular permeability and deteriorates lung compliance, increases airway resistance and then aggravates alveolar gas exchange [15,17]. Our study results suggested that prophylactic EPO improved lung compliance, increased gas exchange function, and reduced lung airway pressure. We speculated that the improvement effect of EPO on pulmonary function might also be attributed to anti-inflammation effect [18,19].

Contrary to the experimental expectation, there was a noted reduction in the PaO_2/FiO_2 ratio for the study patients in the EPO group between 48 hours and 72 hours (Table 3), although both the values were within the normal acceptable PaO_2/FiO_2 range. The reason for the fluctuation could be that 48 hours after the operation, the efficacy of prophylactic intravenous administration of 100 IU/kg of EPO in the EPO group gradually subsided, and its effect of inhibiting inflammatory lung injury gradually decreased, which led to the fluctuation of respiratory parameters, especially PaO_2/FiO_2 ratio. Of course, this is only a guess based on the experimental results, and further verification is needed in future larger sample size experiments.

There was no specific reason for the increase or decrease in the length of stay recorded for some patients in the saline group. The increase of length of stay in the saline group was probably because the former had more serious lung injury induced by CPB, which was reflected by the data such as more postoperative lung function indexes and more patients who need additional oxygen inhalation in this group. At the same time, in addition to lung injury induced by the CPB, cardiovascular dysfunction and renal function changes will occur one after another induced by the CPB [1,16]. The aforementioned organ dysfunction induced by the CPB will affect the prognosis of patients in varying degrees, including prolonging the length of stay. On the other hand, the hospitalization time of some patients in the saline group was relatively short, which may be attributed to the better preoperative basic state of these patients, the implementation of such operations as the repair

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of the interventricular septum and other operations requiring shorter CPB time, so the organ function damage induced by CPB was relatively light and thus the prognosis was better.

In this study, EPO significantly decreased the pro-inflammatory factors TNF-α and IL-1β after CPB. TNF-α and IL-1β are key pro-inflammatory factors and play a pivotal role during the pathogenesis of lung injury induced by CPB [20,21]. TNF-α and IL-1β not only directly injure the lung tissue after CPB but also contribute to aggravation of inflammation and induce endothelial cell apoptosis. In contrast to TNF-α and IL-1β, IL-10 can antagonize the pro-inflammatory effect of TNF-α and IL-1β, and inhibit inflammatory cell migration [22,23].

In the current study, we found that TNF-α and IL-1β were significantly increased in the peripheral blood after CPB. This result agreed with results of a previous study [24]. Compared with the saline group, the EPO group not only inhibited the release of pro-inflammatory cytokines but also promoted the release of anti-inflammatory factor IL-10. EPO can inhibit the activation of NF-κB in different injured models [18]. The inhibition of EPO on the phosphorylation of NF-κB may be one pathway of EPO effect on lung injury induced by CPB. Moreover, as a key regulator, COX-2 plays a key role in various pathological inflammations via the regulation of prostaglandin biosynthesis. It has been reported that EPO could reduce the COX-2 [25], and the inhibition of COX-2 may be another pathway of EPO effect on lung inflammation after CPB.

In general, due to the low affinity of EPO heteroreceptor, the dose of EPO for organ protection is much higher than that required for erythropoiesis [26,27]. The published reference shows that prophylactic intravenous administration of 300 IU/kg of EPO to patients undergoing coronary artery bypass grafting seems to reduce the incidence of acute kidney injury and improved postoperative renal function [28]. Contrary to the aforementioned study, another study found that single intravenous injection of 300 IU/kg EPO increased the risk of acute kidney injury in patients after complex valve heart surgery, and did not provide renal protection [29]. We comprehensively considered the advantages and disadvantages of the application dose and administration time schedule of the aforementioned literature, and cautiously selected the administration strategy of 100 IU/kg for 3 consecutive days – which did not exceed the upper limit of the drug safety dose in the drug specification, and avoided the disadvantages of single large dose administration that may lead to adverse complications.

Studies have shown that the preventive application of EPO for organ function protection is emerging as an important factor for efficacy. EPO may play a role in the prevention of cardiac surgery-associated acute kidney injury [30], which is also the main reason for the preoperative application of EPO. In addition, the authors were cautious about the cumulative effect of continuous and large doses of EPO. The reason why further analysis showed that EPO was not applied during the operation, is because EPO was not administered intravenously during CPB, as and it needed to be administered through the CPB pipeline. The priming solution of CPB would dilute EPO, so that the dose-response relationship of EPO would be affected, thus affecting the accuracy of the experimental data. At the same time, EPO was not applied postoperatively, because only the pulmonary function and inflammatory factors were observed during the operation and/or at 72 hours postoperatively rather than after 72 hours.

Limitation

Research shows that the CPB time has a bearing on the postoperative stay in the ICU, time of hospitalization stay and mortality, especially for patients with poor preoperative physical conditions [31,32]. In our study, EPO only curtail the time of mechanical ventilation and stay in the ICU. This result was mainly due to the preoperative condition of patients, and the shorter operation time of surgery. Considering the key role of inflammation in postoperative outcomes, EPO may be more valuable in those patients with poor preoperative conditions and patients who undergo complex cardiac surgery. This conclusion needs further clinical trials to validate.

Moreover, in the standard CPB, applying EPO to attenuate the inflammation after CPB may not be needed. The inflammation induced by CPB mainly influences the outcomes of those patients with poor preoperative conditions and patients who will undergo a complex operation. At present, the postoperative pulmonary dysfunction caused by CPB is still a problem that needs special attention in long-term CPB and deep hypothermia (such as aortic arch replacement). In these cases, EPO management and other strategies may be valuable. The conclusion of this study may provide a new and effective treatment for those patients with poor preoperative condition and complex cardiac surgery.

In addition, we did not perform bronchoalveolar lavage fluid (BALF) because the patients did not agree to have the procedure performed. Therefore, we cannot provide direct evidence of the therapeutic effect of EPO on local lung inflammation.

Conclusions

In conclusion, the results of this study indicated that EPO mitigated lung injury after CPB via the anti-inflammation pathway.

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