RESEARCH ARTICLE

Serum TNF- α levels in children with congenital heart disease undergoing cardiopulmonary bypass: A cohort study in China and a meta-analysis of the published literature

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Objective: To investigate the changes in tumor necrosis factor alpha (TNF- α) serum levels after cardiopulmonary bypass (CPB) in children with congenital heart disease (CHD), followed by a meta-analysis to analyze the clinical value of TNF- α in CPB.

Methods: Our cohort study enrolled 67 CHD children, assigned into off-pump group (n=32) and CPB group (n=35). The TNF- α serum levels in two groups were detected by ELISA before the operation (T1), at the end of the operation (0 hour, T2), and after 24 hours of the operation (T3). For meta-analysis, literature search was conducted to identify published case-control articles about the changes of TNF- α serum levels with CPB of CHD.

Results: The TNF- α levels in CPB group were lower than that in the off-pump group at T3 ($P=.006$). TNF- α level at T3 was significantly lower than that at T1 and T2 (all $P<.05$). Meta-analysis results further confirmed that the TNF- α levels of CHD children were dramatically decreased at T3 as compared to that at T1 and T2 (both $P<.001$).

Conclusion: The TNF- α serum levels showed a transient and dramatic decline after 24 hours of CPB, and it may act as an important biological indicator for monitoring the efficacy of CPB in CHD children.

KEYWORDS

cardiopulmonary bypass, children, congenital heart disease, meta-analysis, serum TNF- α level

1 | INTRODUCTION

Congenital heart disease (CHD) is a defect or malformation in one or more structures of the heart or blood vessels, which occurs in the early weeks of pregnancy during heart formation.¹ Children with CHD may suffer from cyanosis, poor feeding or growth, syncope, shortness of breath, heart murmur, dysplasia of limbs and muscles, as well as respiratory infections.² An analysis study based on the China Ministry of Health 2003-2010 annual reports demonstrated that the overall mortality rate of CHD increased from 141 per 10 000 000 person-years in 2003 to 229 per 10 000 000 person-years in 2010, a 62.4% relative increase.³ A wide range of environmental factors, including dietary, lifestyle, cocaine abuse, alcohol consumption, or taking certain medications during pregnancy are involved in the etiology of CHD in infants.^{4,5} The life expectancy of patients with CHD, however,

has significantly increased due to progress in cardiac surgery, pediatric and interventional cardiology, and intensive care medicine, such as off-pump fashion and the cardiopulmonary bypass (CPB) surgery.⁶ CPB is a technique in which two main units (pump and oxygenator) temporarily take over the function of the heart and lungs during surgery, maintaining blood circulation and adequate oxygen supply to the body.⁷ Recently, studies have showed that heart surgery may induce a systemic inflammatory response, and may result in the changes of various proinflammatory cytokine serum levels.^{8,9}

Tumor necrosis factor alpha (TNF- α) is an adipokine involved in systemic inflammation and is a member of cytokines that stimulate the acute phase reaction.¹⁰ As an inflammatory cytokine, TNF- α plays an important role in cell growth or death, tumor formation, stress response as well as immune response.^{11,12} TNF- α is chiefly produced by activated macrophages, although many other cell types

including neutrophils, eosinophils, mast cells, CD4⁺ lymphocytes, NK cells, and neurons, also produce TNF- α .¹³ TNF- α can upregulate the matrix metalloproteinase activity, increase the expression of its target genes, reduce the synthesis of collagen, and proteoglycans, stimulate inflammation response, and induce the production of cytokines, as well as involving in cell migration and increasing endothelial cell permeability.^{14,15} Dysregulation of TNF- α expression has been implicated in a variety of human diseases, such as cancer, clinical depression, CHD, Alzheimer's disease, and inflammatory bowel disease (IBD).^{16–19} Furthermore, as a proinflammatory cytokine, TNF- α may play a crucial role in inflammatory response secondary to surgical intervention, infection, or ischemia-reperfusion injury.²⁰ Previous reports have also showed that the TNF- α levels may be changed during cardiac surgery with CPB or off-pump fashion.^{21–24} However, defining a clear relationship between TNF- α serum levels and cardiac surgery with CPB or off-pump fashion has been elusive, and the precise role and pathogenic mechanisms of TNF- α serum levels in CPB is still unclear.

In the current study, serum levels of TNF- α in CHD patient were examined before and after cardiac surgery with CPB or off-pump fashion in a cohort study. Furthermore, a meta-analysis was performed to verify the results of our cohort study and further analyze the pooled data on TNF- α serum levels in CHD patients.

2 | MATERIALS AND METHODS

2.1 | Ethics statement

The protocol of this study was carried out with the approval of the Institutional Review Board of Cangzhou Central Hospital. Patients were enrolled in this study after obtaining informed written consent from their parents. All the study procedures were in line with the Declaration of Helsinki.²⁵

2.2 | Study participants

Between March 2012 and November 2014, a total of 67 patients (39 males and 28 females; mean age: 9.27 ± 3.26 years, range 3–18 years) previously diagnosed as CHD were recruited from Cangzhou Central Hospital and assigned into case group. Patients were excluded if they had the following diseases: congestive heart failure, coagulation disorders, renal failure (serum creatinine >2 mg/dL, oliguria or anuria, requiring dialysis),²⁶ hepatic insufficiency (aspartate aminotransferase >40 U/L and alanine aminotransferase >40 U/L),²⁷ dysfunction of the immune system or central nervous system, local or systemic infection and inflammation (*red, swell, hot, pain, fever, leukocytosis*). Of these 67 patients, 32 cases underwent extracardiac conduit Fontan procedure in an off-pump fashion and assigned as off-pump group. The off-pump maneuver was selected whenever feasible technically. Among the 32 patients in off-pump group, 18 patients were males and 14 patients were females, with an average age of 9.31 ± 3.02 years old and an average weight of 26.9 ± 6.8 kg. The remaining 35 cases (21 males and 14 females; average age: 9.18 ± 3.65 years; average weight: 27.8 ± 6.4 kg) received extracardiac

conduit Fontan procedure in CPB and were assigned as CPB group. The use of CPB was followed by the need of the intracardiac procedures, the extensive reconstruction of the pulmonary arteries, and the anatomical features causing technical difficulties during the anastomosis between an extracardiac conduit and the inferior caval vein.

2.3 | Surgical procedures

All patients received intravenous fentanyl in supine position. Patients in off-pump group received no perfusion pump or oxygenator. Venous cannula tubes (one or two) were used as a temporary bypass after the infusion with 0.2 mL/kg heparin. Venous cannula tube was initially placed between superior caval vein and atrial chamber for superior cavopulmonary anastomosis, and then placed between inferior caval vein and atrial chamber for the construction of extra-cardiac inferior venous channel. Pulmonary perfusion was maintained by a systemic-pulmonary shunt or pulmonary trunk from the ventricle in the process of superior cavopulmonary anastomosis. Subsequently, under the unilateral Glenn physiology, another anastomosis was conducted between the central part of pulmonary artery and a tube graft was used for extra-cardiac channel. Finally, the opposite end of the graft was anastomosed to the inferior caval vein under the bilateral Glenn physiology. Patients in CPB group received a hollow fiber oxygenator (Dideco, Mirandola, Italy). And the bypass circuit was not coated with heparin. For cardiopulmonary circuit, the priming solution consisted of 5% albumin and 30 mg/kg prednisolone. Heparinization (0.3 mL/kg) was performed before commencement of CPB, and 0.15 mL/kg of protamine was given about 10 minutes after coming off bypass. Cardiac arrest was induced using crystalloid cardioplegia under moderate hypothermia.

2.4 | Sample collection and ELISA

Blood samples were collected before operation (T1, 3 mL), at the end of the operation (0 hour, T2, 3 mL) and after 24 hours of the operation (T3, 3 mL) in vacutainer tubes. Ethylene diamine tetra acetic acid (EDTA) was added as an anticoagulant, and the samples were stored at -20°C for further usage. The serum concentration of TNF- α was detected by enzyme-linked immunosorbent assay (ELISA) using a commercially available ELISA kit (R&D Systems, Minneapolis, MN, USA) according to the instructions of the manufacturer.

2.5 | Statistical analysis

All data were analyzed by the Stata 12.0 software (Stata Corporation, College Station, TX, USA). Two authors (Chuan-Ming Bai and Ji-Wu Zhou) independently reviewed the main reports and supplementary materials, extracted the relevant information from the included trials with a predefined data extraction sheet. Categorical data are expressed as numbers or percentages, and are analyzed using χ^2 test. Continuous variables with normal distribution are expressed as mean $\pm$ standard deviation (SD). The *t* test was used to measure the differences between two groups of continuous variables. There is statistical significance if *P* value $< .05$.

TABLE 1 Baseline characteristics of patients with off-pump surgery (off-pump group) and cardiopulmonary bypass surgery (CPB group)

Preoperative variables	Off-pump group (n=32)	CPB group (n=35)	P value
Gender (M/F)	18/14	21/14	.756
Age (years)	9.31±3.02	9.18±3.65	.875
Weight (kg)	26.9±6.8	27.8±6.4	.579
Height (cm)	136.2±21.5	130.8±20.9	.301
BSA (m ²)	0.374±0.131	0.362±0.125	.703
PaO ₂ (mmHg)	50.6±7.1	51.2±7.9	.746
Hematocrit (%)	49.3±8.6	48.8±8.2	.808
pH	7.27±0.08	7.25±0.05	.220
Base deficit (mEq/L)	6.1±2.0	5.9±2.1	.692

CPB, cardiopulmonary bypass; M, male; F, Female; BSA, body surface area; PaO₂, partial pressure of oxygen in arterial blood.

A comprehensive search was conducted for relevant studies published on PubMed (1966-2014) and Chinese National Knowledge Infrastructure (1990-2014) database using the search strategy of medical subject headings (MESH) supplemented by the keywords with the following search terms: "tumor necrosis factor alpha" or "TNF- α ", "congenital heart disease", "congenital heart defects", "cardiopulmonary bypass", "extracorporeal circulation" and so on. The references of the eligible articles or textbooks were also reviewed to check through manual searches to find other potentially studies. Data from published studies were extracted independently by two authors to populate the necessary information. Any disagreement was resolved by discussion between the authors. A fixed or random effect model was used to measure the standardized mean difference (SMD) and its 95% confidence intervals (CIs) to evaluate the changes of TNF- α serum levels with CPB of CHD. The significance of the pooled estimate was made using the Z test.²⁸ Cochran's Q-statistic was applied to estimate the degree of heterogeneity among studies, and if $P < .05$, it is considered to be statistically significant.²⁹ The I^2 test was also used to quantify the heterogeneity (range from 0 to 100%).³⁰ The Cochran's Q and I^2 (range from 0% to 100%) statistics were carried out, if $P < .05$ or $I^2 > 50\%$, then the random effect model was adopted. Fixed-effects model (Mantel-Haenszel method) was adopted when there was no statistical heterogeneity.³¹

3 | RESULTS

3.1 | Baseline characteristics of study population

The baseline characteristics of subjects in both off-pump group and CPB group were shown in Table 1. No significant difference was observed in gender, age, height, weight, and body surface area (BSA) between patients in off-pump group and patients in CPB group (all $P > .05$). Furthermore, there were no significant differences observed between off-pump group and CPB group on the values of partial pressure of oxygen in arterial blood (PaO₂), hematocrit, pH, and base deficit (all $P > .05$).

TABLE 2 TNF- α serum levels in both patients with off-pump surgery (off-pump group) and cardiopulmonary bypass surgery (CPB group) before operation, at the end of operation and after 24 hours of the operation

Time	TNF- α (pg/mL)		P value
	Off-pump group (n=32)	CPB group (n=35)	
T1	7.69±2.15	7.52±2.41	.762
T2	8.34±1.96	8.17±2.03	.729
T3	6.53±1.45 ^{*,**}	5.67±1.01 ^{*,**}	.006

TNF- α , tumor necrosis factor- α ; CPB, cardiopulmonary bypass; T1, before operation; T2, at the end of surgery; T3, after 24 hours of the operation. Values expressed as mean±standard deviation. *Compared with the TNF- α serum levels at the time point of T1, $P < .05$; **Compared with the TNF- α serum levels at the time point of T2, $P < .05$.

3.2 | Changes in TNF- α serum levels

Table 2 showed the ELISA results of the serum levels of TNF- α at a different time point in off-pump group and CPB group. No significant difference was found in serum level of TNF- α between the time points T1 and T2 in the off-pump group ($t=1.26$, $P=.211$), but the serum level of TNF- α at the time point of T3 was significantly lower than that at the time points of T1 and T2, respectively (T3 vs T1: $t=2.53$, $P=.014$; T3 vs T2: $t=4.20$, $P<.001$). Furthermore, the TNF- α serum levels have no significant changes at the time points of T1 and T2 in the patients with CPB ($t=1.22$, $P=.227$), while the TNF- α serum levels at the time point of T3 were markedly lower than those at the time points T1 and T2, respectively (T3 vs T1: $t=4.19$, $P<.001$; T3 vs T2: $t=6.52$, $P<.001$). These results suggested that the serum levels of TNF- α in CHD patients may significantly decrease after receiving off-pump or CPB surgeries. As compared to the off-pump group, the serum levels of TNF- α in the CPB group had no significant differences at the time points of T1 and T2 (T1: $t=0.30$, $P=.762$; T2: $t=0.35$, $P=.729$), while the serum level of TNF- α in CPB group was markedly lower than that in the off-pump group at the time point of T3 ($t=2.84$, $P=.006$).

3.3 | Associations between the changes of TNF- α serum levels and the postoperative outcomes in children undergoing CPB surgery by meta-analysis

A total of 12 studies met our inclusion criteria for this meta-analysis.^{21,24,32-41} These 12 included studies were composed of 190 CHD patients treated with CPB surgery. The heterogeneity was significantly observed (T1 vs T2: $I^2=92.4\%$, $P_h<.001$; T2 vs T3: $I^2=93.7\%$, $P_h<.001$; T1 vs T3: $I^2=92.5\%$, $P_h<.001$); thereby the random effects model was carried out. Meta-analysis results showed that there was no significant difference in the TNF- α serum level at the time point of T1 and T2 (SMD=-0.70, 95%CI=-1.56-0.16, $P=.112$) (Figure 1). However, the serum level of TNF- α at the time point of T3 was apparently lower than that at the time point of T2 (SMD=2.00, 95%CI=0.99-3.02, $P<.001$) (Figure 2), and TNF- α serum level at the time point of T3 was also markedly decreased as compared to

T1 VS. T2

FIGURE 1 Forest plot of comparison of the differences on the serum levels of TNF- α in children with congenital heart disease at the time point of T1 and T2. Note: T1: before the operation; T2: at the end of the operation (0 hour).

T2 VS. T3

FIGURE 2 Forest plot of comparison of the differences on the serum levels of TNF- α in children with congenital heart disease at the time point of T2 and T3. Note: T2: at the end of the operation (0 hour); T3: after 24 hours of the operation.

that at the time point of T1 (SMD=1.70, 95%CI=0.81-2.60, $P<.001$) (Figure 3). The funnel plot was symmetrical and there was no obvious publication bias. Egger's linear regression test further confirmed the comparison of T2 and T3, and there was obvious publication bias of the comparison of T1 and T3 in the included literature (T1 vs T2: $P=.736$; T2 vs T3: $P=.005$; T1 vs T3: $P=.002$) (Figures 4-6).

4 | DISCUSSION

Cardiopulmonary bypass has been reported to result in systemic inflammatory response syndrome (SIRS) by inducing, among other major pathways, the production of inflammatory cytokines such as IL-6, IL-8, and TNF- α .^{42,43} Additionally, acting as a major proinflammatory cytokine, the expression of TNF- α may elevate in excessive

amounts after CPB surgery,^{44,45} but the underlying mechanism of the changes in TNF- α levels before and after cardiac surgeries is still incompletely understood. In this regard, we conducted a cohort study and a meta-analysis to explore the changes of serum TNF- α level in children with CHD treated with cardiac surgeries with CPB or off-pump fashion.

The present study has found that the TNF- α serum levels have no significant changes in the patients with CPB or off-pump surgeries before operation and at the end of the operation, while the TNF- α serum levels after 24 hours of CPB or off-pump surgeries were markedly lower than those before operation and at the end of the operation, respectively. These results suggested that the serum levels of TNF- α in CHD patients may be significantly decreased after receiving off-pump or CPB surgeries. As a proinflammatory cytokine, TNF- α can stimulate catabolism, and it has numerous immunologic and metabolic actions,

T1 VS. T3

FIGURE 3 Forest plot of comparison of the differences on the serum levels of TNF- α in children with congenital heart disease at the time point of T1 and T3
Note: T1: before the operation; T3: after 24 hours of the operation.

T1 VS. T2

FIGURE 4 Publication bias of comparison of the differences on the serum levels of TNF- α in children with congenital heart disease at the time point of T1 and T2
Note: T1: before the operation; T2: at the end of the operation (0 hour).

T2 VS. T3

FIGURE 5 Publication bias of comparison of the differences on the serum levels of TNF- α in children with congenital heart disease at the time point of T2 and T3
Note: T2: at the end of the operation (0 hour); T3: after 24 hours of the operation.

which can mediate the cachexia process.⁴⁶ It has been reported that TNF- α may play a major role in the pathophysiology of sepsis and may be implicated in the development of several complications after cardiac surgery, such as capillary leak syndrome and multisystem organ failure.⁴⁷ Meanwhile, circulating TNF- α can result in cardiac cachexia, which relates to weight loss, reduced muscle strength and function, and consequently compromised immune function.⁴⁸ TNF- α is a powerful inflammatory mediator released by activated leukocytes, including monocytes and lymphocytes, and is currently considered a factor responsible for fever and postoperative morbidity.^{49,50} It has been reported that the TNF- α may trigger the endothelium in the organs of the patients to produce and release adhesion molecules.⁵¹ Furthermore, TNF- α is an early response cytokines which is promptly

produced at the site of injury by resident macrophages.⁵² Although, it has been reported that CPB or off-pump surgeries may result in a systemic inflammatory response induced by the contact of circulating blood with the artificial surfaces of the extracorporeal circuit, which may lead to the development of SIRS and then result in postoperative organ dysfunction.⁵³ While, evidence also shown that the use of CPB results in reduced inflammatory cytokine responses, as determined by levels of TNF- α , IL-6, and IL-8.⁴⁴ Our meta-analysis results also confirmed that the serum level of TNF- α shows a marked decline after 24 hours of CPB when compared with the TNF- α level before operation and at the end of the operation, suggesting that TNF- α may act as an important biological indicator for monitoring the efficacy of CPB in children with CHD.

T1 VS. T3

FIGURE 6 Publication bias of comparison of the differences on the serum levels of TNF- α in children with congenital heart disease at the time point of T1 and T3

Note: T1: before the operation; T3: after 24 hours of the operation.

Meanwhile, other important findings in our study have revealed that the serum levels of TNF- α in CPB group had no significant differences before operation and at the end of the operation as compared to the off-pump group, while the serum level of TNF- α in CPB group was markedly lower than that in the off-pump group after 24 hours of CPB surgery, indicating that the inflammatory reactions were attenuated after CPB surgery rather than by the off-pump fashion. Previous studies have demonstrated that cardiac surgeries may induce or regulate the production of the proinflammatory cytokines including TNF- α , IL-8, and IL-6.⁵² Coronary artery bypass grafting (CABG) patients who received cardiac surgeries on beating heart without aortic clamping, which may contribute to the perioperative myocardial ischemia-reperfusion and may relate to relatively small in terms of inflammation.⁵⁴ A previous study revealed that there was a transient, but significant improvement in respiratory function after CPB, probably resulting from significantly lower serum levels of TNF- α .⁵⁵ Kawahira et al.³³ have found that patients underwent CPB were showed a decreased serum levels of TNF- α , suggesting that CPB may reduce the inflammatory reactions.

In conclusion, the current study suggests that CPB may attenuate the inflammatory reactions as compared with the off-pump surgery. Furthermore, TNF- α may act as an important biological indicator for monitoring the efficacy of CPB in children with CHD. When selecting literature, there were some studies missed in the process of manually retrieve, thus there existed limitations of the inclusion and exclusion criterion, which may affect the statistical power of this study, future larger scale prospective studies are needed to confirm the correlations and predict the value of TNF- α serum level with the efficacy of CPB in children with CHD.

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