

Alterations in Interleukin-6 and Other Parameters during Open-Heart Surgery

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Objectives: Cardiopulmonary bypass (CPB) using a heart-lung machine to perform open-heart surgery is known to be associated with numerous pathophysiologic changes in body systems. Soon after beginning extracorporeal circulation, an activation process of certain plasma protein systems occurs as blood contacts the foreign surfaces of the cardiopulmonary bypass circuit. During cardiac surgery with CPB, there is a systemic inflammatory reaction involving an enhanced release of inflammatory cytokines. In this study, we investigated the occurrence of systemic inflammatory response syndrome (SIRS) and the mechanisms that lead to the protraction of SIRS in patients who are operated under CPB. **Methods:** Blood samples from 27 patients (12 females and 15 males, aged 18-63 years) who underwent CPB were collected before and at several time points after surgery and analyzed for plasma levels of proinflammatory cytokines and white blood cells (WBC). **Results:** In patients with SIRS, the duration of CPB, interleukin-6 (IL-6) count, and WBC count after aortic declamping were significantly higher. The occurrence of SIRS was significantly correlated with the highest recorded level of IL-6 (OR 1.01, 95% CI 1.00-1.01, $p < 0.05$) and the duration of CPB ($r = 0.578$, $p < 0.001$). **Conclusion:** The study findings suggest that the duration of CPB and cytokinemia characterized by high IL-6 levels may play an important role in the development of the SIRS.

Keywords: Inflammatory Response, Cardiopulmonary Bypass, Cytokines, Interleukins

Introduction

Inflammation is the body's rapid, highly amplified, controlled humoral and cellular response to tissue injury [1]. To an organism triggered by extracorporeal circulation, one of the most important reactions is the systemic or generalized inflammatory response, formerly known as "post-perfusion syndrome",

"post-cardiotomy syndrome", "homologous blood syndrome", or "pump lung". The term "systemic inflammatory response syndrome" (SIRS) has been proposed to describe the entry point of a spectrum that overlaps with normal postoperative physiology, a subject that has been studied in depth by Kirklin and several other authors [2-5].

The Society of Thoracic Surgeons' database registers that

20% of preoperative “low-risk” patients develop postoperative complications, risk levels being determined according to Euroscore. A frequent complication of SIRS is the development of organ dysfunction, which includes acute lung injury, shock, renal failure, and multiple organ dysfunction syndromes. The incidence of multiple organ dysfunction syndrome following cardiopulmonary bypass is 11% with a mortality rate of 41% [6].

The activation of the acute phase reaction during cardiopulmonary bypass (CPB) is an extremely complex process. It occurs at different times and has various triggers: the surgical trauma itself, blood contact with nonphysiological surfaces of the extracorporeal circuit, endotoxemia, and ischemia. Several mediators which are involved in this complex mechanism exert synergistic effects, thereby amplifying this process [7]. Plasma interleukin (IL)-6 may play an important role in the development of SIRS [8]. Research has found that IL-6 level are significantly elevated one hour after initiation of CPB and peaks at six hours [9]. Surgical trauma, abnormal shear stress, ischemia, reperfusion, and hypothermia can activate the secretion of IL-6, which can remain elevated after surgery [10–16].

The inflammatory reaction during CPB seems to involve several innate immunity responses such as the cytokines (e.g. IL-6, 8) [17,18]. Notably, these responses have also been implicated in the development of postoperative morbidity after CPB, including infectious complications and organ dysfunction [19]. In this study, we investigated the occurrence of SIRS and the mechanisms that lead to the progression of SIRS, including the role of cytokines in patients who are operated on under CPB.

Materials and Methods

1. Patients and procedures

Twenty-seven patients, 15 males and 12 females, aged 18–63 years (mean age = 42.07 ± 11.66) undergoing open heart surgery with CPB at Shastin Central Hospital in Ulaanbaatar, Mongolia were analyzed for this study.

Eighteen patients underwent valves replacement, and 9 patients underwent atrial septal defect correction surgery. All the operations were elective, and all patients were in stable clinical condition. None of the patients used immunosuppressive drugs prior to operation or had any signs of clinical infection, chronic respiratory failure, renal or hepatic failure, or acute cardiogenic shock during the study period.

The patients were divided into two groups: a group with SIRS (group A, $n = 18$) and a group without SIRS (group B, $n = 9$). Perioperative parameters were compared between group A and group B, and those that significantly correlated with the SIRS—IL-6, white blood cells (WBC) and platelet counts—were investigated. The regional ethical committee approved the study, and signed informed consent was obtained from each patient.

2. Surgical technique

With all patients, the operative approach was a median sternotomy with CPB and systemic hypothermia. Blood cardioplegia and topical cooling with ice slush were used. CPB circuits included heparin coated tubes and oxygenator. In addition, an initial dosage of 4 mg/kg of heparin was given as an anticoagulant to achieve an activated clotting time (ACT) > 480s. After CPB was terminated, protamine sulfate was administered to re-establish preoperative ACT levels.

3. Anesthesia

Anesthesia was induced with propofol or thiopentone, fentanyl, and atracium, and continued with a mixture of sevoflurane and fentanyl. The patients were artificially ventilated with a mixture of air and oxygen and extubated in the intensive care unit. For postoperative pain relief, the patients were given morphine or paracetamol. The patients received antibiotic prophylactics with three doses of intravenous cefazolin per day until all drains or monitor lines were removed.

4. Blood sampling protocol

Venous blood was sampled before sternotomy, during CPB, and 1 hour, 24 hours, 48 hours, and 7 days after aortic declamping. No adjustments of the cytokine levels were made for hemodilution during the CPB. The blood samples were collected into sterile vacuum tubes containing EDTA and immediately centrifuged. The plasma was stored at -80°C until the cytokine assays were performed, a period of less than three months. Plasma IL-6 levels were measured by an enzyme-linked immune-sorbent assay using IL-6-Easia-CE (DRG Diagnostics, Germany), a commercially available kit. The WBC and platelet counts were not corrected for hemodilution.

Patients were cooled down to a rectal temperature of 32°C . SIRS is manifested by two or more of the following conditions: temperature $>38^{\circ}\text{C}$, heart rate >90 beats per minute, respiratory

rate >20 breaths per minute or PaCO₂ (carbon dioxide) <32 mmHg, WBC count >12,000/mm³ of the total number of neutrophils. In our study, respiratory rate and PaCO₂ during forced mechanical ventilation and postoperative pacing rate by the external pacemaker were excluded from the SIRS definition.

5. Statistical analysis

Study findings were analyzed with SPSS 17 statistical analysis software program. Key findings were expressed as mean values with standard deviation. Univariable and multivariable linear regression model was used to determine the association between study variables. Pearson's correlation coefficient was calculated to reveal the correlation between indicators, such as duration of SIRS and clinical data. Groups of patients were compared using t-test, and p-value of less than 0.05 was considered statistically significant.

Results

The patient's age, sex, body weight and height, operation procedure, CPB time, and aortic cross-clamp (ACC) time are shown in Table 1.

Compared to group B, group A had no statistically significant differences in age, operation time, and operative procedures but had a significantly longer duration of CPB and ACC. In addition, the plasma levels of IL-6, a proinflammatory cytokine, in group A was significantly elevated one hour after aortic declamping and significantly higher than in group B ($p = 0.0015$), as shown in Fig. 1. The WBC count rose in all the patients during CPB and remained elevated for 24 hours after the removal of the ACC in both groups, as shown Fig. 2. At 48 hours after aortic

declamping, the WBC count continued to drop in both groups. The perioperative parameter that is significantly correlated with SIRS is the highest recorded plasma IL-6 level (OR 1.01, 95% CI 1.00-1.01, $p < 0.05$), as shown Table 2. Furthermore, the highest recorded plasma IL-6 level is significantly correlated with the duration of CPB and ACC ($r = 0.578$, $p < 0.001$; $r = 0.608$, $p < 0.002$), as shown in Figure 3. Linear regression for IL-6, as presented in Table 3, shows that highest level of IL-6 is significantly correlated with the ACC time ($B = 4.37$, 95% CI 1.78-6.96, $p < 0.01$), ($r = 0.608$, $p < 0.01$).

Discussion

In this study, we demonstrated a complex set of changes in cytokines during and after CPB. A major finding of this study was that the early cytokine response during CPB was dominated by a marked increase in cytokines such as IL-6.

Twenty years ago, the concept of SIRS was officially proposed by the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM), as an extension of physiologic self-defense mechanisms [20]. However, the protraction of SIRS signifies organ failure and deterioration of the patient status [21]. Over the past decade, a number of studies have associated surgical stress with elevated plasma IL-6 levels following CPB [22]. Indeed, increased plasma IL-6 levels corresponds with both the duration of CPB and SIRS, indicating its key role in mediating the acute phase response for open-heart surgery patients under CPB [8]. SIRS may cause potential organ failure due to postoperative microcirculation damage.

Our study results showed that the highest circulating level of the inflammatory cytokines IL-6 occurs one hour after the

Table 1. Clinical characteristics of the 27 patients

Variable	Group A (n = 18)	Group B (n = 9)	p-value
Age	43.94±11.65	38.33±11.39	NS
Operation time (min)	383.05±10.07	341.67±9.94	$p < 0.01$
CPB time (min)	140.38±8.3	106.67±5.99	$p < 0.001$
ACC time (min)	98.16±6.4	81.55±4.67	$P < 0.01$
Operation procedure			
Valve replacement	12	6	
ASD	6	3	

Data is shown as mean value ± standard deviation of the mean.
ASD, atrial septal defect.

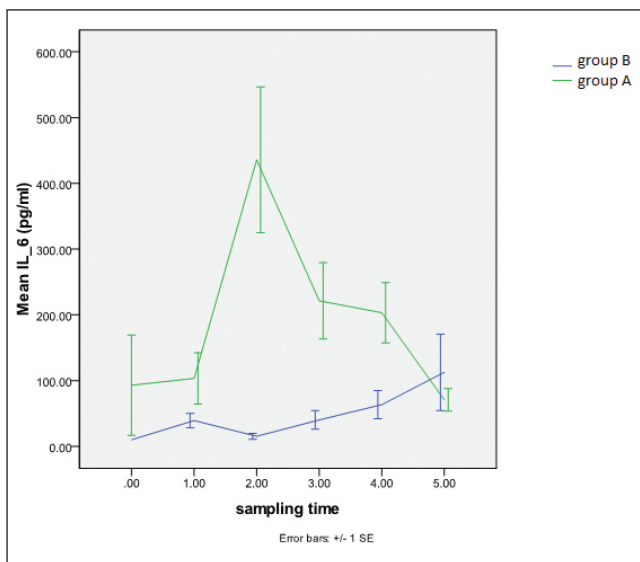


Figure 1. Plasma levels of IL-6 in groups A and B. Data shown as mean±SD of mean.

Sampling time: .00, before sternotomy; 1.00, during CPB; 2.00, 1 h after aortic declamping; 3.00, 24 h after aortic declamping; 4.00, 48 h after aortic declamping; 5.00, 7 days after aortic declamping;

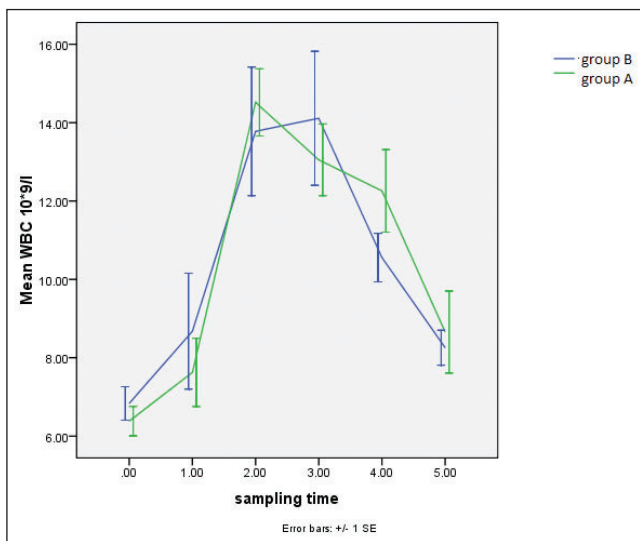


Figure 2. WBC count in group A and B. Data shown as mean±SD of mean.

Sampling time: .00, before sternotomy; 1.00, during CPB; 2.00, 1 h after aortic declamping; 3.00, 24 h after aortic declamping; 4.00, 48 h after aortic declamping; 5.00, 7 days after aortic declamping;

removal of the ACC, and the occurrence of SIRS is correlated with the duration of CPB and ACC.

Monocytes, lymphocytes, and endothelial cells produce IL-6.

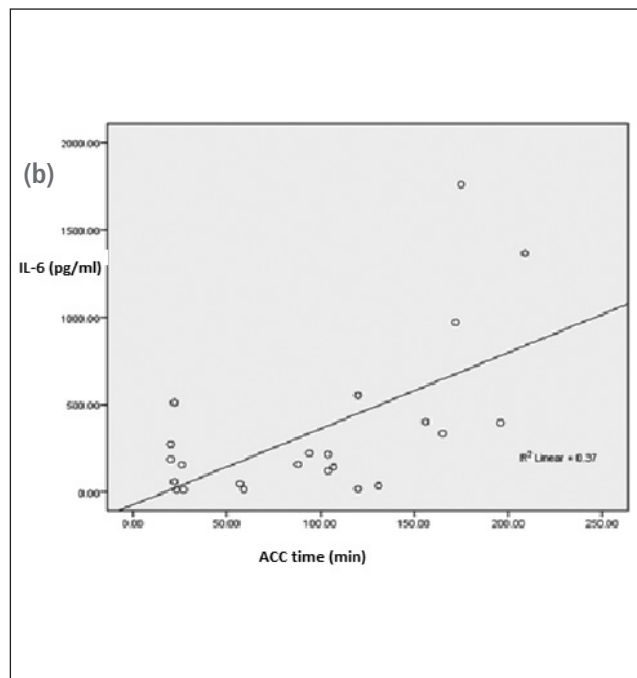
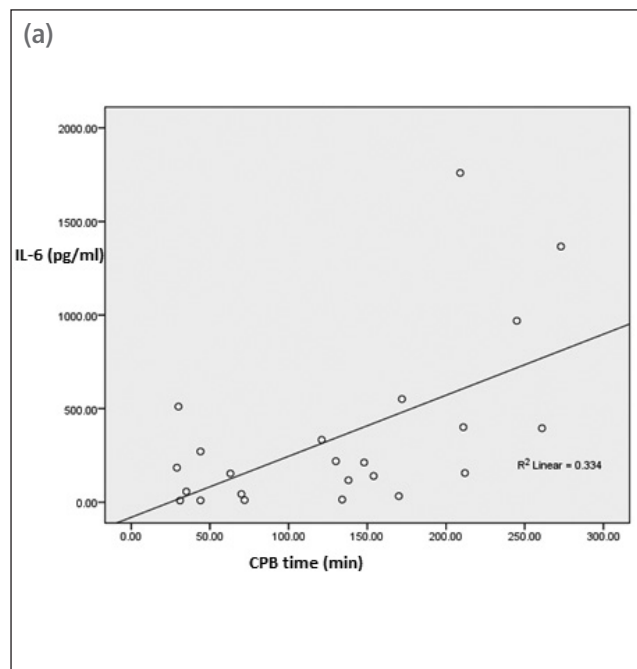


Figure 3.

- a: Correlation between the duration of CPB time and the highest recorded level of IL-6.
- b: Correlation between the duration of ACC time and the highest recorded level of IL-6.

It is thought that IL-6 stimulates an adhesive neutrophil-cardiac myocyte interaction that induces myocardial damage following CPB surgery [23]. This study shows that the highest plasma level

Table 2. Logistic regression for SIRS.

Variables	OR	95% CI	p-value
Highest level of IL-6	1.01	1.00-1.01	<0.05
WBC	1.05	0.96-1.15	0.226

Table 3. Univariable and multivariable linear regression for the highest recorded level of IL-6.

Variables	Univariable regression			Multivariable regression		
	B coeff.	95% CI	p-value	B coeff.	95% CI	p-value
Age	12.4	-4.74 to 29.6	0.147			
Diagnosis	-147	-245 to -49	<0.01			
CPB time	3.26	1.17 to 5.35	<0.01			
ACC time	4.37	1.78 to 6.96	<0.01	4.37	1.78 to 6.96	<0.01
Operation time	1.69	-0.07 to 3.46				

of IL-6 is significantly correlated with the occurrence of SIRS and duration of CPB. Hence, this suggests that IL-6 is one of the key mediators of the acute phase response in patients subjected to cardiac surgery under CPB. Our data was similar to previously published work, which demonstrated a marked increase in IL-6, reaching maximum levels 1-2 hours after aortic declamping [24,25].

Our study showed patients in group A had significantly higher levels of inflammatory cytokines after aortic declamping when compared to those patients in group B. The protraction of SIRS by the excessive production of inflammatory cytokines causes an increase in the potential stimulation organs and raises the possibility of neutrophils releasing excessive quantities of free radicals and proteases, damaging microcirculation and leading to postoperative organ dysfunction [25-27].

These results suggest that the duration of CPB and cytokinemia with high IL-6 levels after aortic declamping are highly valuable indices of the occurrence of SIRS after cardiac surgery under CPB. As the protraction of SIRS is an early warning sign of organ damage, treatment to prevent the excess production of inflammatory cytokines immediately after the aortic declamping may be useful in patients undergoing elective cardiac surgery under CPB.

A limitation of our study was the small number of patients due to cost of supplies. Future study goals include (1) correlation of complications after open-heart surgery and inflammatory biomarkers, (2) procedures to balance inflammatory and anti-inflammatory cytokines during cardiac surgery.

In conclusion, our study results suggest that the duration

of CPB and cytokinemia with high IL-6 levels might play an important role in the development of the SIRS.

Conflict of Interest

The authors state no conflict of interest.

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