

Systemic Inflammatory Response Syndrome after Cardiac Surgery under Cardiopulmonary Bypass

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Objective: This prospective study was designed to elucidate the duration of systemic inflammatory response syndrome (SIRS) and the mechanisms that lead to the protraction of SIRS in patients who are operated on under cardiopulmonary bypass (CPB).

Methods: The duration of SIRS in 13 patients with SIRS was studied. Two groups were divided according to the duration to investigate the meaning of the duration of SIRS. The perioperative parameters which significantly correlated with the duration of SIRS, including the kinetics of cytokines and white blood cells (WBC) counts were investigated.

Results: In patients with SIRS extending for a period greater than 12 hours (group A), the duration of CPB, interleukin-6 (IL-6), interleukin-8 (IL-8) and WBC count after aortic declamping were significantly longer and higher than those in patients with SIRS lasting less than 12 hours (group B). The duration of SIRS significantly correlated with the highest level of IL-6 ($r=0.724$, $p=0.0038$) and the duration of CPB ($r=0.626$, $p=0.0201$).

Conclusions: These results suggest that the duration of CPB and cytokinemia, with high IL-6 levels, during this short time frame until just after cardiac surgery might play an important role in the development of the SIRS. (*Ann Thorac Cardiovasc Surg* 2003; 9: 365–70)

Key words: systemic inflammatory response syndrome (SIRS), cardiac surgery, cardiopulmonary bypass, cytokine

Introduction

Recently, systemic inflammatory response syndrome (SIRS) has become a widely accepted concept to explain the pathophysiology of systemic inflammation of multiple etiologies (i.e., trauma, infection or surgery).^{1,2} SIRS is regarded as a preparatory state of organ dysfunction and the protraction of SIRS is an early warning sign of organ damage.³ In this prospective study, patients whom were operated on under cardiopulmonary bypass (CPB), were studied to elucidate the duration of SIRS and the mechanisms that lead to the progression of SIRS (i.e., severe SIRS), including the role of cytokines.

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Patients and Methods

Thirteen patients (age: 44-78 years old) with SIRS undergoing elective cardiac surgery under CPB at Hiroshima University Hospital (n=13) were studied. Two groups were divided according to the duration to investigate the effect of the duration of SIRS: a group with more than 12 hours of SIRS (group A, n=7) and a group with less than 12 hours of SIRS (group B, n=6). The perioperative parameters were compared between group A and group B and the perioperative parameters which significantly correlated with the duration of SIRS, including the kinetics of cytokines and white blood cells (WBC) counts were investigated.

Venous blood was sampled before sternotomy (BS), just before aortic declamping (BD), three minutes after aortic declamping (AD) and at 1, 3, 24, and 48 hours after aortic declamping (1 h, 3 h, 24 h, 48 h). No adjustment of the cytokine levels was made for hemodilution during the CPB. The blood samples were collected into

Table 1. Clinical characteristics of the 13 patients

Variable	Group A (n=7)	Group B (n=6)	p value
Duration of SIRS (hrs)	19±1.5	7.4±1.3	<0.01
Age (y)	70±2.4	66±4.4	NS
Operation time (min)	419±22.4	351±25.8	NS
CPB time (min)	220±12.4	166±4.22	<0.01
Aorta clamp time (min)	155±13.5	96.0±11.0	0.01
Drainage discharge (ml/8 hrs)	304±29.4	238±53.0	NS
Operation procedure			NS
① CABG	2	2	
② Valve repair/replacement	1	1	
①+②	0	1	
②+③ MAZE procedure	3	2	
①+②+③	1	0	
Major complication (total patients)	0	0	NS

Group A: patients with SIRS extending for a period greater than 12 hours

Group B: patients with SIRS extending for a period less than 12 hours

Data are the mean value ± standard error of the mean.

CPB, cardiopulmonary bypass; CABG, coronary artery bypass grafting; ASD, atrial septal defect.

sterile vacuum tubes containing EDTA, immediately centrifuged and then the plasma was stored at -80°C until the cytokine assays were performed; that is, less than three months. Interleukin-6 (IL-6), interleukin-8 (IL-8), and interleukin-10 (IL-10) levels in the plasma were measured by an enzyme-linked immunosorbent assay using a commercially available kit (IL-6, IL-8, and IL-10; R&D Systems Inc., Minneapolis, MN, USA). The WBC count was corrected for hemodilution.

Each patient was administered 1,000 mg of methylprednisolone sodium succinate, and 2,000 mg of urinastatin just before starting CPB and just after stopping the CPB. In addition, the patients were also administered nafamostat mesilate at an initial dose of 20 mg at the beginning of the CPB, and then at 40 mg/h during the CPB. The patients were cooled down to a rectal temperature of 32°C . Patients with acute infection, acute or chronic respiratory failure, renal or hepatic failure, acute cardiogenic shock, and emergency patients were excluded.

SIRS is manifested by two or more of the following conditions : temperature $>38^{\circ}\text{C}$, heart rate >90 beat/min, respiratory rate >20 breath/min or PaCO_2 (carbon dioxide) <32 mmHg, WBC count $>12,000/\text{mm}^3$ or $<4,000/\text{mm}^3$ or $>10\%$ immature (band) neutrophils of the total number of neutrophils. Of course, respiratory rate and PaCO_2 during forced mechanical ventilation and postoperative pacing rate by the external pacemaker were excluded from the SIRS definition.

Informed consent was obtained from all the patients to obtain blood samples for the purpose of this study.

Statistical analysis

Data were expressed as the mean value ± standard error of the mean. The Mann-Whitney U test was used to evaluate differences of perioperative parameters without time running between group A and group B. The repeated-measured ANOVA technique was used to evaluate differences of the cytokine and WBC data between group A and group B at each time point. Pearson's correlation coefficient test was used to explore the correlation between the duration of SIRS and clinical data. A p value of less than 0.05 was considered to be statistically significant.

Results

Patient's data are summarized in Table 1. The duration of SIRS ranged from 2 to 24 hours: that is from 1 to less than 12 hours in six patients, from 12 to less than 24 hours in seven. Therefore, those with SIRS extending for a period greater than 12 hours were allocated to group A (n=7) and those with SIRS lasting less than 12 hours were allocated to group B (n=6). Compared to group B in group A, the duration of CPB and aortic clamping were significantly longer. However, there were no statistically significant differences between the two groups regarding age, operation time, drainage discharge, operative procedures, or major complication.

The plasma levels of proinflammatory (IL-6, IL-8) and antiinflammatory (IL-10) cytokines were significantly elevated in all patients from the time just before aortic

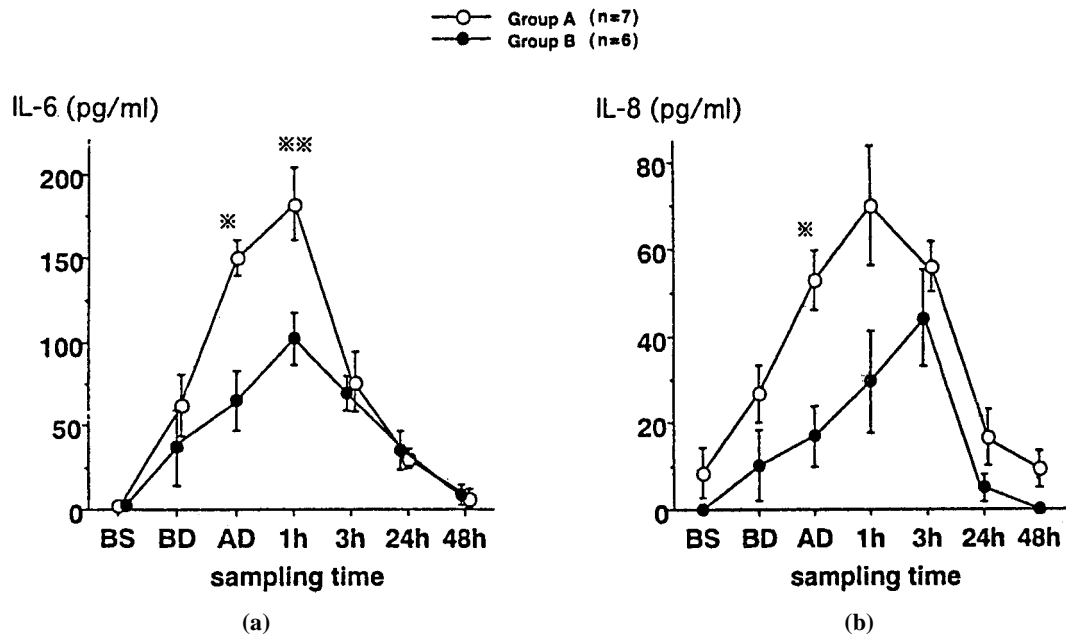


Fig. 1. Plasma levels of IL-6 (a) and IL-8 (b) in groups A and B.

Data are the mean value \pm standard error of the mean.

(a) * indicates $p=0.0015$ versus group B. ** indicates $p=0.0139$ versus group B.

(b) * indicates $p=0.0035$ versus group B.

BS, before sternotomy; BD, just before aortic declamping; AD, 3 minutes after aortic declamping; 1 h, 3 h, 24 h, 48 h, time points after aortic declamping.

declamping in both groups. At three minutes and at one hour after aortic declamping, IL-6 levels in group A ($n=7$) were significantly higher than in group B ($n=6$) (AD, $p=0.0015$; 1 h, $p=0.0139$), as shown in Fig. 1a. At three minutes after aortic declamping, IL-8 levels in group A ($n=7$) were also significantly higher than in group B ($n=6$, $p=0.0035$), as shown in Fig. 1b. IL-10 levels in group A ($n=7$) tended to be lower than in group B ($n=6$), but the difference was not significant, as shown in Fig. 2a. The WBC count rose in all the patients before removal of the aortic cross-clamp, and remained elevated until one hour after removal of the aortic cross-clamp in both groups. The WBC count of group A ($n=7$) was significantly higher than that of group B ($n=6$) at one hour after aortic declamping (1 h, $p=0.0453$), as shown in Fig. 2b. Interestingly, at three hours after aortic declamping, the WBC count dropped once in both groups. Thereafter the WBC count remained elevated.

The perioperative parameters which significantly correlated with the duration of SIRS are the highest plasma level of IL-6 ($r=0.724$, $p=0.0038$) and the duration of CPB ($r=0.626$, $p=0.0201$), as shown in Fig. 3. Furthermore, the highest plasma level of IL-6 significantly correlated

with the duration of CPB ($r=0.600$, $r=0.0284$), the highest plasma level of IL-8 significantly correlated with the highest level of WBC count ($r=0.760$, $r=0.0016$), as shown in Fig. 4.

Discussion

Recently, the members of the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) Consensus Conference proposed precise definitions for the terms sepsis, severe sepsis and septic shock.¹⁾ The term SIRS was proposed to describe any inflammatory process independently of its cause since it can be seen after a wide variety of insults. SIRS can be considered as an extension of physiologic self-defense mechanisms, and the protraction of SIRS implies deterioration of the patient status.^{4,5)}

Cardiac surgery under CPB causes SIRS due to surgical trauma, contact of blood with foreign materials, abnormal shear stress, ischemia, reperfusion, hypothermia, and unphysiological situations. It is said that SIRS occurring after cardiac surgery is associated with a massive, unbalanced induction of cytokines. In particular, in-

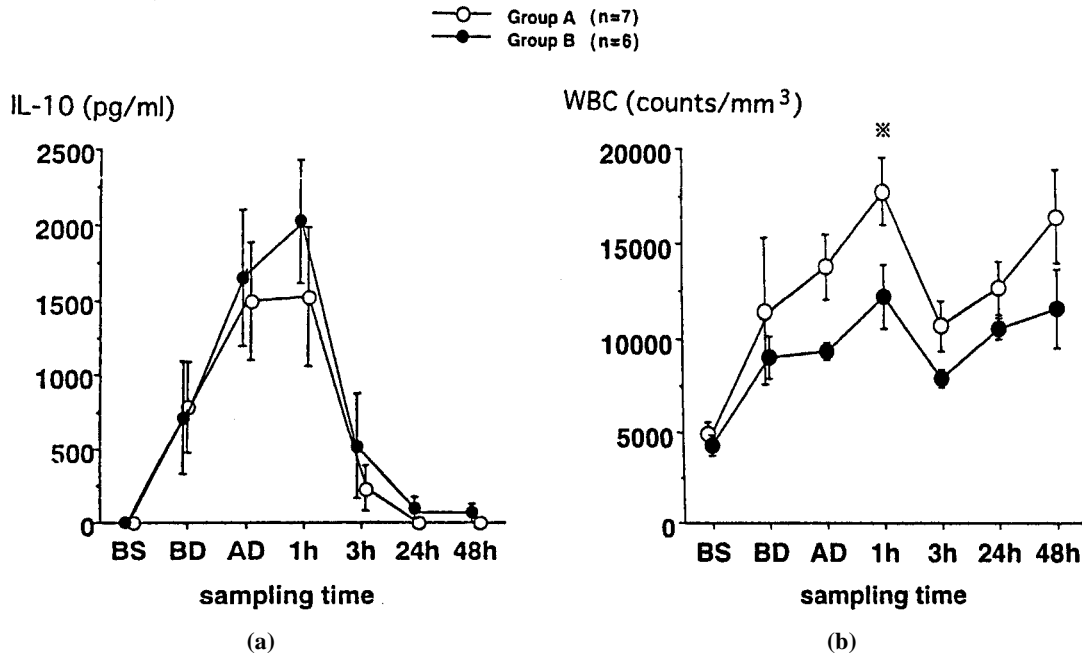


Fig. 2. Plasma levels of IL-10 (a) and WBC (b) count in groups A and B. Data are the mean value \pm standard error of the mean. * indicates $p=0.0453$ versus group B.

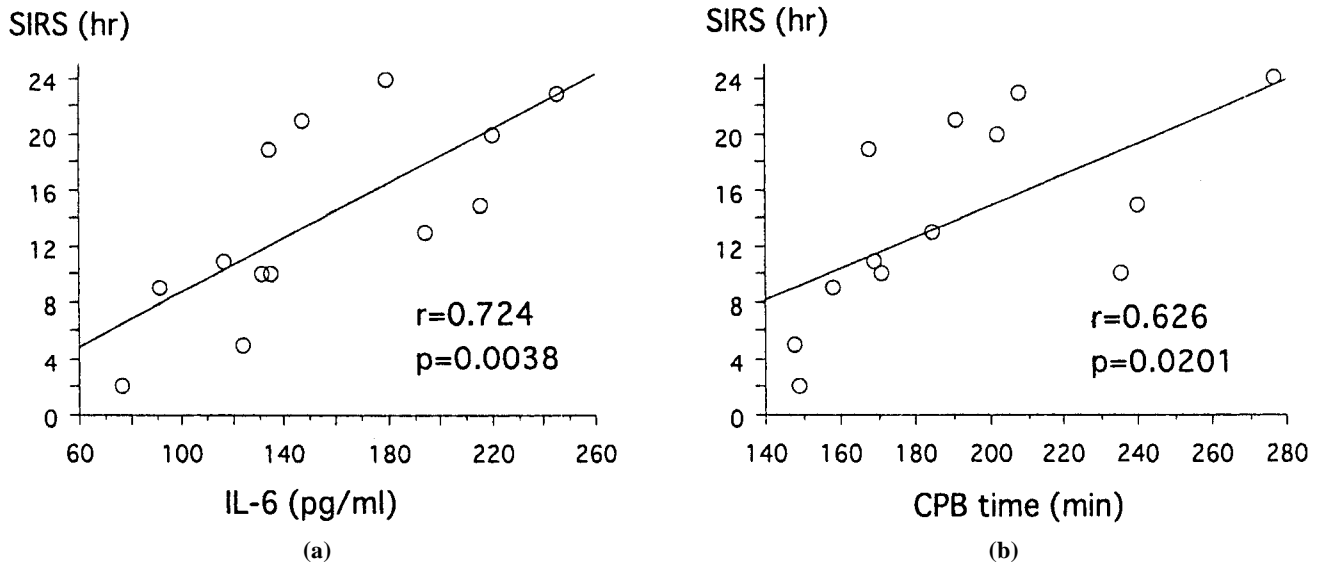


Fig. 3. a: Correlation between the duration of SIRS and the highest level of IL-6. b: Correlation between the duration of SIRS and the duration of CPB.

teraction of the blood components with artificial surfaces and ischemia-reperfusion injury upon aortic declamping cause a significant elevation in plasma cytokine levels during and after cardiac surgery under CPB. This study also showed that the highest circulating levels of the in-

flammatory cytokines IL-6 and IL-8, and the antiinflammatory cytokine IL-10 were observed from at one hour to at three hours after the removal of the cross-clamp and that the duration of SIRS correlated with an extended and/or more invasive operation (i.e., longer CPB time) which

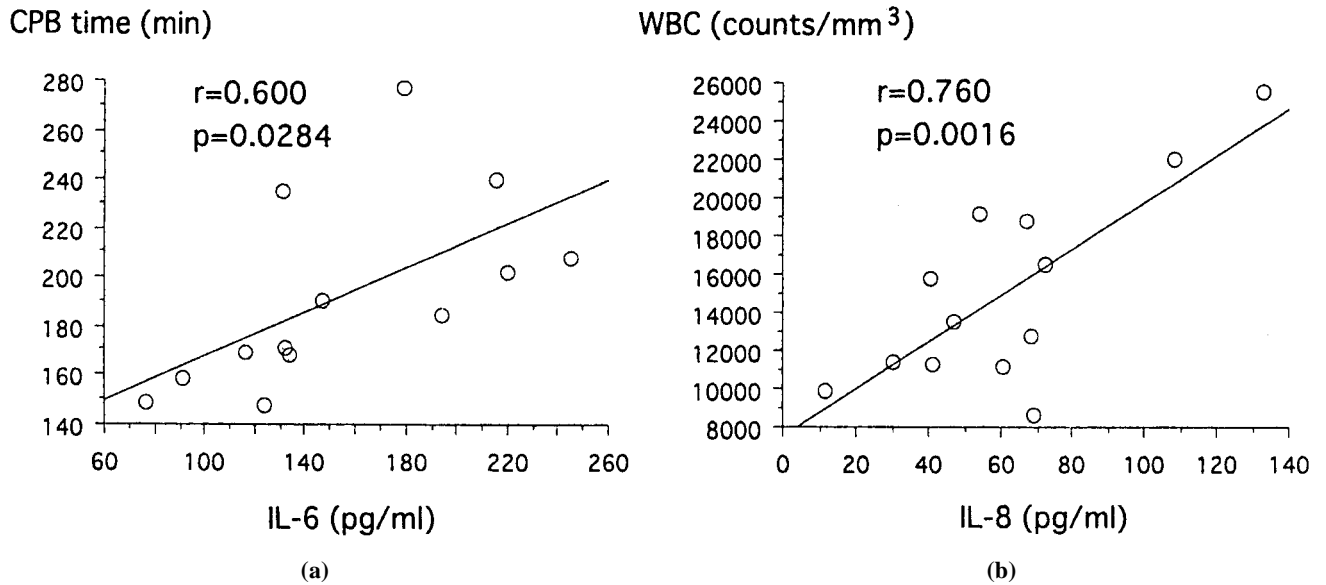


Fig. 4.

- a: Correlation between the duration of CPB and the highest level of IL-6.
 b: Correlation between the highest level of WBC count and the highest level of IL-8.

caused a significant elevation of plasma cytokine levels.

IL-6 is produced by monocytes, lymphocytes, and endothelial cells. It is thought that IL-6 stimulates an adhesive neutrophil-cardiac myocyte interaction and induces myocardial damage following CPB surgery.⁶⁾ This study showed that the highest plasma level of IL-6 significantly correlated with the duration of SIRS and CPB. Hence, we guessed that IL-6 would be one of the key mediators of the acute phase response in patients subjected to cardiac surgery under CPB.

IL-8 is produced by monocytes, polymorphonuclear (PMN) leukocytes, macrophages, fibroblasts, and vascular endothelial cells. It is thought that IL-8 induces the amplification of neutrophils and macrophages.⁷⁾ This study also showed that the highest plasma level of IL-8 correlated with the highest level of WBC count which included neutrophils and macrophages. Furthermore, as IL-8 has been also reported to regulate neutrophil transendothelial migration, and potentially to control neutrophil-mediated tissue injury, it was guessed that the acute drop in leukocytes count seen at three hours after aortic declamping, just after the highest plasma level of IL-8, would be due to the state of so-called priming in the second attack theory. This results in local inflammation, in addition to migration and accumulation of leukocytes in the vascular endothelial cells and thus led to the development of postoperative organ damage at a later time.⁸⁻¹⁰⁾

Recently, the existence of antiinflammatory responses which compensate for SIRS have been considered and the concept of a counter antiinflammatory response syndrome (CARS) has been proposed.^{11,12)} This study also indicated an enhanced production of the antiinflammatory cytokine IL-10, which may represent an attempt of the host to counteract the excessive activity of the proinflammatory cytokines IL-6 and IL-8. The relative balance between SIRS and CARS determines the prognosis after an insult; if the balance between SIRS and CARS is optimal, the body recovers from the insult. Patients in group A had significantly higher levels of inflammatory cytokines after aortic declamping when compared to those in group B. The level of IL-10, however, tended to be lower in group A than in group B. It can be speculated that the balance between SIRS and CARS was disrupted and SIRS became relatively dominant and was protracted in group A. The protraction of SIRS by the excessive production of inflammatory cytokines causes an increase in the potential of the organs to be stimulated (i.e., attacked and triggered, as proposed in the second attack theory)¹³⁾ and raises the possibility that neutrophils release excessive quantities of free radicals and proteases, which damage the microcirculation and lead to postoperative organ dysfunction.^{6,14)}

These results suggest that the duration of CPB and cytokinemia, with high IL-6 levels after aortic declamping

are highly valuable indices of the duration 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 [i.e., reducing the duration of CPB and administration of antiinflammatory drugs (steroids) to enhance the production of antiinflammatory cytokines and/or a monoclonal antibody against the overproduction of these inflammatory cytokines], may be useful in patients undergoing elective cardiac surgery under CPB.

Conclusions

This study suggests that the duration of CPB and cytokinemia, with high IL-6 levels, during the short time frame just after cardiac surgery, might play an important role in the development of the SIRS.

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