The Heart Surgery Forum #2006-1012
9 (4), 2006 [Epub June 2006]
doi:10.1532/HSF98.20061012

Online address: http://cardenjennings.metapress.com/link.asp?id=112496

The Changes and Effects of the Plasma Levels of Tumor Necrosis Factor after Coronary Artery Bypass Surgery with Cardiopulmonary Bypass

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ABSTRACT

Background. Systemic inflammatory response after cardiopulmonary bypass (CPB) is thought to result from contact of cellular and humoral blood components with the synthetic material of the extracorporeal circulation system, leukocyte and endothelial activation caused by ischemia and reperfusion or endotoxins, or by surgical trauma. Proinflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-6, and IL-8, play an important role in the inflammatory processes after CPB and may induce cardiac and lung dysfunction. This study examined the association of the increased release of TNF-α with increased myocardial and lung injury after CPB and its effect on postoperative morbidity.

Methods. Twenty patients undergoing elective coronary artery bypass grafting (CABG) were included in the study. Four intervals of blood samples were obtained and assayed for TNF-α, white blood cells, C-reactive protein, and erythrocyte sedimentation rate.

Results. All patients were similar with regards to preoperative and intraoperative characteristics, and clinical outcomes were comparable. Plasma levels of TNF-α rose more than 20 pg/mL during and after standard CPB in 13 patients (group 1), whereas the plasma levels were less than 20 pg/mL in the remaining 7 patients (group 2) after CPB. The patients of the first group had increased mediastinal bleeding and prolonged intubation time compared to the other group.

Conclusion. Cardiac surgery and CPB stimulate systemic inflammatory processes characterized clinically by changes in cardiovascular and pulmonary function. Significant morbidity is rare, but most patients undergoing CPB exhibit some degree of organ dysfunction due to activation of the inflammatory response. This study showed that there were no major clinical results of TNF-α and white blood cell level, C-reactive protein, and erythrocyte sedimentation rate after the operation, but in patients with a high level of TNF-α (more than 20 pg/mL), increased mediastinal bleeding and longer orotracheal intubation time was observed. A number of studies have shown the increase of TNF-α after open heart surgery; however, the specific level of TNF-α was first described as 20 pg/mL in this study.

INTRODUCTION

Cardiac surgery with cardiopulmonary bypass (CPB) may cause a systemic inflammatory response, which can lead to end-organ dysfunction and postoperative mortality and morbidity. Surgical trauma, the contact of blood with the extracorporeal circuit, endothelial toxin release, increase of vascular permeability, and lung reperfusion injury on discontinuing bypass are all reported causes [Butler 1992, 1993b; Miller 1997; Wan 1997a, 1997b; Mikko 2001]. The relationship between TNF-α and postoperative hemodynamic disturbances and morbidity has been previously reported [Hill 1997]. In addition, it has been reported that high levels of TNF-α have a negative effect in older patients and/or in patients with poor left ventricular functions [Deng 1996; Te Velthius 1996]. The aim of this study was to investigate the release of TNF-α and its possible effect after open-heart surgery in patients who underwent coronary artery bypass grafting (CABG) and extracorporeal circulation (ECC).

METHODS

Because of the cost of the assays, only 20 patients, 18 male and 2 female, undergoing elective CABG surgery with CPB were randomized for this study. The study was approved by the hospital ethics committee and all patients gave their informed consent. We excluded patients with severely impaired left ventricular function, chronic pulmonary obstructive disease, severe systemic noncardiac disease, renal or liver impairment, insulin-dependent diabetes, infectious disease before operation, and those receiving corticosteroid or other immunosuppressive treatment. Cardiac medication, including beta-adrenergic blocking agents, calcium-channel blocking agents, and nitrates, was continued until the morning of surgery.

The same general anesthetic drugs were used in all patients. Intravenous penthotal sodium was administered 5 to 7 mg/kg for induction. Anesthesia was continued with sevoflouran or

Received February 28, 2006; accepted May 4, 2006.

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Table 1. Patients' Preoperative, Intraoperative, and Postoperative Characteristics*

	Group 1		Group 2		
	Mean Value	Standard Deviation	Mean Value	Standard Deviation	*P*
Preoperative period					
Sex, M/F	12/1		6/1		
Age, y	57.8	8.6	60.7	13.1	.562
Weight, kg	73.8	9.6	77.0	10.3	.467
Height, cm	170.0	6.4	169.0	8.7	.750
Body area, m^2	1.85	0.12	1.86	0.18	.428
Cleveland Clinic score	2.07	2	1.1	1	.734
Intraoperative					
Cardiopulmonary bypass time, min	79.8	20.3	83.0	19.1	.750
Aortic cross-clamp time, min	44.0	15.0	44.0	8.2	.810
Number of grafts	3.0	0.9	3.0	0.8	.736
Postoperative					
Mediastinal bleeding, mL	901	283	678	115	.026
Hospitalization, d	8.3	2.4	8.2	2.9	.935
Orotracheal intubation time, h	9.7	4.8	6.2	1.1	.049

*There was no statistical significance between the patients' preoperative, intraoperative, and postoperative characteristics including Cleveland Clinic score.

isoflouran. Vecuronium bromide 0.1 mg/kg was used as the myorelaxan drug. Cefazelin sodium and gentamycin sulphate were administered in the preoperative period in all patients.

The surgical procedure was median sternotomy and placement of the internal mammary artery or saphenous vein grafts. The radial artery was used in 2 patients. In each group, routine operations were performed using a membrane oxygenator (Dideco 708 Simplex III; Dideco, Mirandola Italy), a 3 mg/kg dose of heparin sodium, 2000 mL of Ringer's lactate priming, a roller pump, a body temperature of 28°C, and antegrade crystalloid cardioplegic solution (Plegisol; Abbott Laboratories, Abbott Park, IL, USA). Heparin was neutralized with pretamine hydroclorur (Protamin 1000; Roche, Istanbul, Turkey). The circuit was primed with 2000 mL. The CPB flow was maintained at 2.2 to 2.4 liter/min^{-1} per m^{-2}, and mild hypothermia of 32°C was accomplished. Cold cardioplegic solution was given after cross clamping for myocardial protection (1000 mL through the aortic root). After completion of surgery, patients were transferred to the intensive care unit (ICU), where standard care and processes were followed until discharge. Patients were weaned from mechanical ventilation when they were hemodynamically stable, responded to verbal stimulation, were completely rewarmed, and when blood loss did not exceed 100 mL/h^{-1}. Cardiovascular and respiratory values and temperature were recorded every 15 minutes before extubation and then hourly until discharge from the ICU. Length of stay in the ICU was also recorded. Patients were discharged from the ICU on the first morning if they were hemodynamically stable, had normal blood gases during spontaneous breathing, and had satisfactory renal function. We reviewed each patient's records after discharge from the ICU and noted the minimum and maximum values of mean arterial pressure, heart rate, respiratory rate, and body temperature.

Samples Collection

Four serial blood samples were obtained from each patient via an arterial line. Blood was sampled for measurement of TNF-α, white blood cells (WBC), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) at the following times: before induction of anesthesia (T-I), after induction of anesthesia and 1 hour after aortic cross clamping (T-II), in ICU (T-III), and 24 hours after skin closure (T-IV). Samples were collected in tubes containing lithium heparin (Dio-Tube). The samples were immediately centrifuged at 1000*g*, and the plasma was stored at –70°C until assays were performed. Enzyme-linked immunosorbent assays (ELISA) (Immulite; DPC, Los Angeles, CA, USA) were used to measure TNF-α. All assays were performed according to the manufacturers' instructions. Blood samples were put in a vacutainer tube (BD Medical Systems, Franklin Lakes, NJ, USA), for complete blood count, and into the Bio-tube (Diamond, Silikon, Turkey). WBC, hemoglobin, and hematocrit values were measured in a Coulter counter (STUR; Coulter, Hialeah, FL, USA). A Dade Behring (Deerfield, IL, USA) machine was used for the detection of CRP levels.

The samples for TNF quantification were immediately centrifuged (1000 cycles for 10 minutes at 28°C), and the plasma was separated and frozen at –70°C until use. An h-TNF kit was used for measuring the level of TNF (BioSource International, Camarillo, CA, USA).

Laboratory Tests

The presence of the circulating TNF was measured using an ELISA. Test sensitivity was 1.7 pg/mL. The WBC count, CRP, and ESR were also measured. Mean systolic blood pressure, body temperature, heart rate, orotracheal intubation time, postoperative bleeding, and inotropic agent requirement during the postoperative period were recorded and compared. No inotropic agent was required in the early postoperative period for any patient.

Statistical Analysis

Statistical analysis was performed with the use of an SPSS for Windows 10.0 computer program (SPSS, Chicago, IL, USA). Nonparametric tests for data comparison, Mann-Whitney *U*, Friedman, and Bonferroni-corrected Wilcoxon 2-sample test were also used. Significance was accepted when *P* was .05 or less.

RESULTS

There was no hospital mortality in either group. The two groups appeared similar in physical and preoperative clinical characteristics (Table 1). The patients in groups 1 and 2 did not differ significantly in respect to age, sex, body weight, body mass index, or number of grafts. No patient required a positive inotropic agent after surgery. The levels of ESR,

Table 2. Changes in the Levels of White Blood Cells, Erythrocyte Sedimentation Rate, and C-Reactive Protein

No.	Hospitalization Time, d	WBC 1	WBC 2	WBC 3	WBC 4	ESR 1	ESR 2	ESR 3	ESR 4	CRP 1	CRP 2	CRP 3	CRP 4
1	7	4.800	6.400	8.400	6.400	11	03	05	68	0.40	0.34	0.34	16.50
2	6	8.800	13.900	16.800	10.400	18	11	11	57	0.60	0.53	0.73	18.40
3	15	12.500	22.100	15.000	15.000	36	25	64	28	2.22	1.43	1.83	18.30
4	14	6.700	13.600	22.600	17.700	02	05	18	13	0.34	0.34	0.34	19.20
5	8	2.900	3.400	4.100	8.800	29	15	80	115	0.86	0.34	0.50	18.50
6	7	13.300	7.600	22.100	15.100	34	36	38	50	0.52	0.34	0.34	18.10
7	10	7.900	15.300	20.600	7.300	18	11	06	100	1.51	0.89	0.89	17.80
8	8	8.600	10.000	12.200	12.100	08	11	11	30	0.94	0.42	0.40	17.10
9	7	6.000	9.900	11.200	9.200	22	11	10	09	0.53	0.34	0.34	14.40
10	9	4.900	10.100	10.700	14.200	03	11	11	22	0.34	0.34	0.34	15.80
11	8	7.800	14.000	12.200	13.900	28	11	11	36	1.00	0.61	0.72	17.10
12	7	7.700	8.900	10.900	8.800	44	30	47	95	2.86	1.74	1.91	21.80
13	5	3.600	5.500	8.400	8.100	08	08	11	25	0.34	0.34	0.34	19.30
14	7	4.100	5.600	9.600	11.100	20	21	24	42	0.65	0.84	0.52	18.80
15	7	6.000	6.800	11.800	13.900	19	24	11	24	0.19	0.10	0.10	16.30
16	7	6.300	4.200	8.000	8.600	11	11	23	27	0.34	0.34	0.34	14.90
17	6	5.600	11.300	18.300	11.100	02	03	02	27	0.34	0.34	0.34	15.30
18	10	12.300	12.100	14.100	11.900	20	20	18	31	1.64	0.91	1.06	18.00
19	11	7.900	11.400	14.500	14.900	11	25	09	25	0.34	0.34	0.34	17.70
20	7	7.900	13.000	12.800	10.100	08	23	45	102	1.15	2.29	2.15	16.10

*The postoperative white blood cells (WBC) were significantly increased in almost all patients and, in addition, the relationship between the WBC, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) values were increased. There was no significant difference when considering the hospitalization time in relation to the WBC, ESR, and CRP values. Only 4 cases needed hospitalization longer than 10 days after surgery. We also observed an increment of leukocyte counts, ESR, and CRP values in almost all patients in the postoperative period. Similar findings were observed after comparison to ESR-I and ESR-IV and ESR-II and ESR-III. There were significant differences between the value of CRP-I and CRP-IV and CRP-II and CRP-III when compared to the individual change in the level of CRP.

CRP, and WBC were not different between the 2 groups, and the operation time was not significantly different when compared to these data. Mean arterial pressure and body temperature were similar in both groups.

The postoperative leukocyte counts were significantly increased in all patients (Table 2). We detected an increase in leukocyte counts, ESR, and CRP in almost all patients in the postoperative period. The patients in group 1 and 2 did not differ significantly with respect to age, sex, body weight, or number of grafts. ESR, CRP, and leukocyte counts were significantly different between some of the patients. Bonferroni-corrected Wilcoxon 2-sample test showed that there was a statistically significant difference between the level of WBC-1 and WBC-2 and also between WBC-1 and WBC-3. In addition, we observed a statistically significant difference between the level of WBC-4 and WBC-1 and between the level of WBC-3 and WBC-2 (chi-square = 31.561 and P = .000). When compared to ESR, it was seen that there was a statistical difference between the level of ESR-4 and ESR and also between the ESR-2 level and ESR-3 level (chi-square = 23.1 and P = .000). There was a significant difference between the level of CRP-4 and CRP-1 and between CRP-2 and CRP-3, additionally (chi-square = 47.526 and P = .000).

These cases were divided into 2 groups according to the lower and higher TNF-α levels, and we compared preoperative, intraoperative, and postoperative patient characteristics including age, blood oxygen saturation, CPB time, number of grafts, orotracheal intubation and hospitalization time, complications, mortality, and Cleveland Clinic scoring.

In the first group, consisting of 13 patients, TNF-α level was detected as 20 pg/mL and more than 20 pg/mL during and after the induction of anesthesia, whereas in the second group, consisting of 7 patients, the TNF-α level was less than 20 pg/mL during and after the induction of anesthesia. There was no statistical difference between the basal level of TNF-α in our 2 groups (t: 0.590, P = .555). However, in the first group during CPB and 1 day after surgery (24 h), the level of TNF-α was statistically significant (t: 0.001, P = .0001). In the first group, TNF-α counts were more than 20 pg/mL in the early postoperative period (24 h), whereas their levels were less than 20 pg/mL in both groups, but in 7 patients its level was lower than 20 pg/mL in all periods.

The intraoperative course was uneventful. The serum TNF-α levels for all measurement times are shown in Table 3 (for group 1) and Table 4 (for group 2). The mean levels of TNF-α in groups 1 and 2 are shown in Table 5, and its levels are displayed as a graph in the Figure.

TNF-α was more than 20 pg/mL in group 1. However, in group 2 at T-II, T-III, and T-IV levels were changed from 21.56 to 65.64, from 20.41 to 144.57, and from 20.12 to 157.22 pg/mL^{-1}, respectively. The increase of TNF-α levels in both groups above the preinduction values started at T-I and peaked at T-IV (P <.05), but the concentrations were significantly lower in group 2 than in group 1 at T-II, T-III, and T-IV (t: 0.0001, P = .0001). The level of T-I was not significantly different between the 2 groups (t: 0.590, P = .555).

The extubation time was longer in group 1 when compared to group 2 (15.1 ± 2.7 versus 8.8 ± 2 hours) (U = 21,

Table 3. The Value of Tumor Necrosis Factor (TNF)-α (pg/mL) in Group 1*

Patient No.	TNF-1	TNF-2	TNF-3	TNF-4
1	8.91	25.46	39.31	36.99
2	10.31	23.89	25.69	25.69
3	19.10	64.69	144.57	27.75
6	11.00	65.64	26.84	20.12
7	13.90	27.52	21.56	20.95
8	19.27	27.07	41.92	27.52
10	10.50	25.00	32.93	22.02
12	9.12	25.69	24.77	32.96
14	16.51	25.92	45.69	22.51
15	13.90	51.19	88.56	21.79
16	19.85	30.97	23.85	157.22
19	6.70	21.56	20.41	22.48
20	6.70	25.46	29.82	25.46

*All measured TNF-α levels were more than 20 pg/mL after the operations in this group.

P = .049) and mediastinal bleeding was statistically higher in group 1 than group 2 (U = 17.5, *P* = .026) (Tables 6 and 7). No significant difference in length of ICU or hospital stay was observed between groups. No postoperative major complications occurred in either group up to discharge from the hospital, and no patients had adverse events such as mediastinitis.

DISCUSSION

The use of CPB during CABG is associated with a severe systemic inflammatory response due to the contact of blood with artificial surfaces. Surgical trauma, reperfusion injury in the lungs, changes in body temperature, and the release of endothelial toxins play an important role in these pathologic conditions. The clinical relevance of CPB-related systemic inflammation varies with the patient, and such inflammation may be accompanied by intermittent organ dysfunction and finally multi-organ failure may increase catecholamine requirement [Butler 1992, 1993b; Miller 1997; Wan 1997a, 1997b; Mikko 2001]. Jansen et al have reported on the relationship between the level of TNF-α and postoperative hemodynamic disturbances in their study [Jansen 1992]. Also, it has been clearly demonstrated that the release of TNF-α during CPB has negative effects on myocardial performance in patients with poor left ventricular functions [Deng 1996; Te Velthius 1996].

Table 4. The Value of Tumor Necrosis Factor (TNF)-α (pg/mL) in Group 2*

Patient No.	TNF-1	TNF-2	TNF-3	TNF-4
4	13.30	16.74	17.87	19.87
5	16.51	19.00	15.40	17.30
9	16.05	17.20	19.13	15.46
11	18.81	17.30	19.49	18.58
13	11.00	19.41	17.21	18.35
17	11.00	18.58	19.27	11.30
18	11.00	16.74	16.28	17.66

*In all periods after the surgery, the level of TNF-α was lower than 20 pg/mL for all patients. When compared to the basal TNF-α level there was no statistical difference between group 1 and group 2 (t: 0.590, *P* = .555). But statistical difference was noted between the level of TNF-II, TNF-III, and TNF-IV counts when compared to group 1 and group 2 (t: 0.001, *P* = .0001).

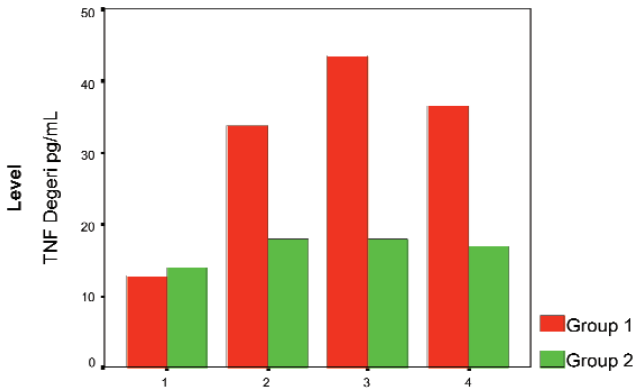
Table 5. The Mean Plasma Levels of Tumor Necrosis Factor (TNF)-α*

	TNF-1	TNF-2	TNF-3	TNF-4
Group 1 (n = 13)	12.75	33.85	43.53	36.65
Group 2 (n = 7)	13.95	17.85	17.80	16.93

*The plasma TNF-α levels of group 2 were less than 20 pg/mL in all periods, whereas the patients in group 1 had a higher level of TNF-α (more than 20 pg/mL) after open heart surgery.

The aim of this study was to investigate the release of TNF-α and its clinical importance, as we know that it is an important part of the mediation of inflammatory response, and its effect on myocardial performance after open heart surgery in patients undergoing CABG. In addition, we observed the change of WBC, ESR, and CRP values and their effects on postoperative mortality and morbidity after surgery.

Several studies have shown that inflammatory processes have increased including TNF-α after open heart surgery [Chenoweth 1981; Starnes 1988; Bellomo 1992; Jansen 1992; Gu 1993; Hennein 1994; Gu 1999]. Also, a number of studies have demonstrated that there was a positive correlation between the postoperative mortality and the increase of inflammatory agents [Schindler 1990; Kawamura 1993; Steinberg 1993; Hennein 1994; Menasche 1994; Ashraf 1999]. According to the literature, our study demonstrated that the increment of the TNF-α level is associated with more mediastinal drainage and the need for more blood and product transfusion in the postoperative period, resulting from increased bleeding and prolonged orotracheal intubation time after CABG. However, to date, the critical value of TNF-α has not yet been reported in the English literature. A critical TNF-α level was determined as 20 pg/mL in our study. In this study, the patients were separated into 2 groups



The mean level of tumor necrosis factor-α in group 1 and group 2 patients.

Table 6. Intraoperative and Postoperative Characteristics of Group 1*

Patient No.	ACC Time, min	CPB Time, min	Number of Grafts	CCS	Postoperative Bleeding	Orotracheal Intubation Time, h	Hospitalization Time, d
1	35	80	3	00	850	7	7
2	45	70	4	00	1.000	8	6
3	27	63	2	03	1.125	15	15
6	50	85	4	02	1.025	9	7
7	40	70	3	00	850	9	10
8	70	110	4	00	1.575	18	8
10	60	85	3	08	475	8	9
12	40	105	4	00	475	6	7
14	20	40	1	05	900	20	7
15	40	80	3	05	950	5	7
16	40	60	2	04	925	6	7
19	70	110	4	00	925	10	11
20	35	80	3	00	650	6	7

*ACC indicates aortic cross clamp; CPB, cardiopulmonary bypass; CCS, Cleveland Clinic score.

Table 7. Intraoperative and Postoperative Characteristics of Group 2*

Patient No.	ACC Time, min	CPB Time, min	Number of Grafts	CCS	Postoperative Mediastinal Bleeding	Orotracheal Intubation Time, h	Hospitalization Time, d
4	50	110	3	03	700	7	14
5	45	95	4	00	750	7	8
9	35	59	2	03	750	6	7
11	55	95	4	01	600	5	8
13	40	60	2	01	825	5	5
17	50	87	3	00	650	8	6
18	33	75	3	00	475	6	10

*ACC indicates aortic cross clamp; CPB, cardiopulmonary bypass; CCS, Cleveland Clinic score.

according to the level of TNF-α. The first group of patients had more than 20 pg/mL of TNF-α, and the other had a lower level of TNF-α (below of 20 pg/mL). In the first group, orotracheal intubation time was longer than in the second group, and also mediastinal bleeding increased in the first group of patients. Our results have shown that the indicated TNF-α value was at a critical level in our patients. But there was no mortality and were no statistical differences in Cleveland Clinic score, aortic cross clamp time, CPB and hospitalization time, and number of bypass grafts between the 2 groups. In addition, we noted that there was no statistical difference between the patients' systemic blood pressure, heart rate, or body temperature in the preoperative and postoperative periods for the 2 groups.

Previous studies have suggested that the activation and release of cytokines, especially TNF-α, plays an important role in the pathogenesis of the inflammatory response syndrome induced by ECC [Jansen 1992; Gu 1993; Hennein 1994]. A number of studies have demonstrated that TNF-α has increased vascular permeability, caused endothelial dysfunction, and increased peripheric vascular resistance and leucopenia [Starnes 1988; Bellomo 1992]. However, in contrast to previous studies, we did not see a decrease in WBC; rather, WBC counts increased in almost all patients after the operation. In some studies, the complement system and other systemic inflammatory cytokines have been investigated and the authors proposed that all inflammatory products are responsible for the metabolic, hemodynamic, and end-organ dysfunction in the postoperative period [Kawamura 1993; Hennein 1994; Menasche 1994; Te Velthius 1996; Wan 1996, 1997a; Hill 1997; Ashraf 1999; Wan 1999].

Jansen and colleagues have suggested that there is a positive correlation between the levels of TNF-α and postoperative hemodynamic dysfunctions [Jansen 1992]. However, we have not seen any correlation between the levels of TNF-α and hemodynamic disturbances in our patients. It has been reported in another comparative study [Deng 1996] that excessive release of TNF-α and common postoperative morbidity in patients with poor left ventricular functions are due to this effect. Barnes et al have reported on a positive correlation between the high level of TNF-α and prolonged CPB time [Barnes 1998]. In our two groups, comparisons of CPB time and TNF-α levels indicated no statistical difference. But in our first group of patients, the TNF-α level was greater than in the second group of patients. We believe that an individual effect may also play an important role in the level of TNF-α.

Frequently, the levels of TNF-α are variable because technical sensitivity varies in the analysis of TNF-α, because release of TNF-α may be inhibited from some plasma proteins, and because there is individual differentiation of cases during CPB. Also, the plasma cytokine level does not always reflect the local cytokine release in all patients, and circulatory TNF-α levels rapidly breakdown [Fong 1990]. Therefore, TNF-α levels were not generally correlated between the studies. The levels of TNF-α have been reported from 14.3 pg/mL to 155.7 pg/mL by Brasil et al in their 20 patients [Brasil 1998]; however, the change of levels of TNF-α were detected from 11 pg/mL to 144.57 pg/mL in our patients.

The release of cytokines is stimulated from ischemia reperfusion, complement activation, and the release of endotoxin and the other cytokines [Schindler 1990]. Some reports demonstrated an increase of TNF-α [Journois 1994; Menasche 1994; Teoh 1995], IL-1 [Haeffner-Cavaillon 1989; Kawamura 1995], IL-6 [Kawamura 1993; Oz 1995; Teoh 1995; Liebold 1999], IL-8 [Teoh 1995; Liebold 1999] and IL-10 [Kawamura 1995] during CBP. However, excessive postoperative TNF-α levels have been reported after open heart surgery and, in a limited number of studies, surgeons have found that TNF-α levels have changed minimally [Haeffner-Cavaillon 1989; Mikko 2001]. Beutler and colleagues have shown that the release of TNF-α has reached peak level by the activation of monocyte and macrophage after 60 to 90 minutes in their in vivo study [Beutler 1985].

We detected the alteration of WBC, ESR, and CRP levels at the same time in these patients. We noted that the levels of WBC, ESR, and CRP had no significant effect on the postoperative morbidity in our groups after surgery. Although the levels have not been associated with clinical importance, the levels

of the parameters showed significant differentiation when compared to the preoperative and postoperative periods. According to the study findings, Butler et al have shown that the levels of CRP and WBC increased within 4 hours and these high levels of CRP and WBC continued during the 48 hours after surgery [Butler 1993a]. They have also detected high levels of TNF-α in the 10 patients in the same study, but they have not demonstrated statistically significant alteration in this study.

Many studies have proposed that the high level of TNF-α was caused by persistent and severe systemic vascular resistance, hypertension, low cardiac output, or tachycardia after open heart surgery with the use of CPB [Gomes 1994; Speziale 1996]. It has been reported that patients with these conditions have required a positive inotropic agent to obtain hemodynamic stability after surgery in these studies. We did not detect any hemodynamic disturbances in our patients, although some patients (especially in group 1) had high levels of TNF-α postoperatively.

For the systemic inflammatory mediators that contribute to the morbidity of ECC, limitation of the intensity of the response should be possible with treatment including high-dose corticosteroids and aprotinin [Dietrich 1990; Kim 1993; Royston 1996], estrogen [Rosano 1993], adenosine [Lee 1995; Mentzer 1999; Belhomme 2000], oxygen radical scavengers, neutrophil granule stabilizers, and specific monoclonal antibodies. Adenozin anti-cytokine monoclonal antibody was a new agent for the introduction of the treatment for the decrease of the effect of proinflammatory cytokines, and its use is continued in experimental models. TNF-α was successfully blocked with the specific use of this agent in animal models [Hendrik 1995]. Inhibition of TNF-α from the left ventricle has been shown with the use of sodium nitroprussid and amrinon and milrinon as phosphodiesterase inhibitor in a limited number of studies [Bergman 1996; Marina 1996]. The increase of plasma levels of IL-10 have been demonstrated with the use of alprinon, which is known as a new phosphodiesterase-III inhibitor, and clearance of IL-6 has been increased by this agent. In addition, it has been demonstrated that the production of TNF-α and IL-6 have been decreased from mononuclear cells by amiodarone in an experimental study [Matsumori 1997]. The heparin-coated circuit systems and ultrafiltration have been used for avoidance of the inflammatory effects of open heart surgery in some studies [Tè Velthius 1996]. It has been demonstrated that thrombocyte adhesions and leukocyte activation have been additionally decreased with the help of these systems [Gu 1993; Elliot 1993; Hatori 1994; Journois 1994]. Schulz et al have reported a phospholipid-coated circulatory system that has significantly reduced the systemic increase in proinflammatory and anti-inflammatory cytokines [Schulz 2002]. They suggested that the observed significant reduction in systemic inflammatory parameters might provide an improved biocompatibility of ECC materials when they were coated with phospholipids [Schulz 2002].

We conclude that CPB induces a whole-body inflammatory response through the release of TNF-α among other possible mediators, resulting in adverse systemic effects. It is possible that TNF-α plays a role in the clinical pathologic conditions of the alterations observed after open heart surgery in this study, although no major clinical findings were found in the present study. We detected prolonged intubation time and postoperative increased mediastinal bleeding was observed in the first group of patients who had an excessive increase of the level of TNF-α after CABG operation when compared to the other group. Interestingly, these patients had TNF-α levels greater than 20 pg/mL. To our knowledge, the critical level of TNF-α has not been clearly explained by any study, but we propose that all cytokines are responsible including individual patients' characteristics as well as TNF-α, a key factor in the inflammatory cascade, and future studies may exhibit additional important factors in these particular cases.

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