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RESEARCH ARTICLE

# Effects of Cardiopulmonary Bypass on Systemic Inflammatory Response and Organ Dysfunction in Patients Who Had Low Left Ventricular Ejection Fraction Underwent Coronary Artery Surgery

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## ABSTRACT

**Objectives:** Cardiac surgery with cardiopulmonary bypass (CPB) causes systemic inflammatory response and multiple organ dysfunction. The release of cytokines including tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-10 (IL-10) and interferon-gamma (IFN-γ) was reported to be the main reason of multiorgan failure after CPB. The aim of this study is to investigate the effects of cardiopulmonary bypass on the systemic inflammatory response and the relationship between cytokine responses and organ dysfunction in patients with poor left ventricles underwent coronary revascularization with cardiopulmonary bypass.

**Methods:** Thirty patients who had depressed left ventricular function (EF≤35%) and underwent CABG surgery were included in this prospective observational study. The maintenance of anesthesia and CPB was performed in accordance with institutional standards. After induction of anesthesia, a thermodilution pulmonary artery catheter was placed via the right internal jugular vein. Peripheral blood samples for the assessment of TNF-α, IL-6, IL-8 and IL-10 levels were taken immediately after the induction of anesthesia (T0), at 30$^{th}$ minute (T1) after the beginning of CPB and at the 1$^{st}$ (T2), 3$^{rd}$ (T3), 6$^{th}$ (T4), and 24$^{th}$ (T5) hours after CPB. Hemodynamic parameters including mean arterial pressure (MAP), heart rate (HR), central venous pressure (CVP), left ventricular end diastolic pressure (LVEDP) and cardiac index (CI) were also recorded in these time intervals. Multiorgan dysfunction score (MODS) was recorded daily for 3 days after the surgery.

**Results:** IL-6 and IL-8 peaked at the 3$^{rd}$ hour after CPB and returned to the level of the first half hour at the 24$^{th}$ hour. IL-10 peaked at the 1$^{st}$ hour after CPB. TNF-α increased in the first half hour after the beginning of CPB, and this level was maintained. A significant positive correlation was found between IL-6 levels at the 3$^{rd}$ hour and pulmonary, cardiopulmonary and renal dysfunction (r=0.3, p=0.04; r=0.4, p=0.003; r=0.3, p=0.04, respectively). Also, there was a correlation between IL-10 levels at the 6$^{th}$ hour and renal dysfunction (r=0.5, p=0.001) and between IL-6 levels at the 6$^{th}$ hour (r=0.3, p=0.05) and IL-8 levels at the 3$^{rd}$ hour (r=0.3, p=0.03) and hematological dysfunction.

**Conclusion:** IL-6 and IL-8 peaked at the 3$^{rd}$ hour after CPB; IL-10 peaked at the 1$^{st}$ hour after CPB. TNF-α reached its highest level in the first half hour. A positive significant correlation was found between IL-6 levels and pulmonary, cardiopulmonary and renal dysfunction in the early postoperative period. Also, there was a relationship between IL-8 levels and hematological dysfunction. The development of these studies may be valuable in developing medical treatment protocols that will prevent inflammatory systemic responses.

**Keywords:** Cardiopulmonary bypass, cytokines, multiple organ dysfunction syndrome, systemic inflammatory response

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## Introduction

Ischemic attacks can impair left ventricular function in patients with coronary artery disease, resulting in low ejection fraction (LVEF). The pathophysiology of this condition involves not only the presence of chronic atheromatous plaques but also proinflammatory cytokines such as interleukin-6 (IL-6), interleukin-1 beta (IL-1β) and tümör necrotising factor-alpha (TNF-α) originating from the vascular bed.[1–3] IL-6 plays a critical role in the development

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of heart failure following myocardial infarction (MI).[4] Studies have reported an inverse relationship between patients' left ventricular ejection fraction (LVEF) values and IL-6 levels.[5] Samples obtained from the coronary sinus have confirmed that IL-6 and IL-1β are cardiac in origin.[6] Furthermore, reperfusion of ischemic areas following bypass surgery induces cytokine responses through ischemia-reperfusion (I/R) injury. TNF-α and IL-6 are the primary proinflammatory cytokines involved in early reperfusion injury.[7]

The systemic inflammatory response caused by cardiopulmonary bypass procedures leads to multiple organ dysfunctions affecting the cardiac, pulmonary, hepatic, neurological, renal systems, and coagulation functions. As a result, morbidity and mortality rates increase following cardiopulmonary bypass.[8–12] Cytokines such as TNF-α, IL-1, IL-6, interleukin-8 (IL-8), interleukin-10 (IL-10) and interferon-gamma (IFN-γ) are primarily implicated in organ dysfunctions observed after open-heart surgery.[9,13–15] A higher proinflammatory response is observed in patients with low ejection fraction (EF) compared to those with normal EF. These patients are associated with increased perioperative hemodynamic instability and complications.[16]

The aim of this prospective observational study was to investigate the effects of cardiopulmonary bypass on the systemic inflammatory response and the relationship between cytokine responses and organ dysfunction in patients with coronary artery disease and poor left ventricles who underwent coronary revascularization with cardiopulmonary bypass.

## Methods

This observational and prospective study was completed in 2010 at the Department of Anesthesiology and Reanimation of Celal Bayar University Hospital with the approval of the Celal Bayar University Scientific Research Ethics Committee (135/27.10.2008). The study adhered to the ethical principles outlined in the Declaration of Helsinki. Thirty patients who were undergoing elective coronary revascularization due to coronary artery occlusion, aged between 45 and 80 years, and had low left ventricular ejection fraction were included in the study. Based on Simpson's echocardiography method, patients whose ejection fraction (EF) is measured below 35% by a cardiologist before surgery are categorized as having low EF. Patients with neoplastic or chronic inflammatory disease (n=2), those receiving immunotherapy and those receiving aprotinin, anticoagulant and non-steroidal anti-inflammatory treatment (n=3) were excluded from the study. Three patients with high initial biochemical cytokine values were excluded from the study. Patients included in the study were informed about the study, and patient consent forms were obtained. The study was supported by the Celal Bayar University Scientific Research Projects Committee (Project No: 2008/093).

### Anaesthesia and Cardiopulmonary Bypass Management

A similar anaesthesia management was applied to all cases. Induction was achieved by 2 mg IV midazolam, 3–5 $\mu g.kg^{-1}$ IV fentanyl and titrating etomidate. 0.1 $mg.kg^{-1}$ vecuronium was given for muscle relaxation. Maintenance was continued with 5–10 $\mu g.kg^{-1}.hour^{-1}$ IV fentanyl infusion, 0.03 $mg.kg^{-1}$ IV midazolam at one-hour intervals and sevoflurane inhaled at a concentration of 0.5–2% in 50% air. Routine monitoring (electrocardiogram, pulse oximetry, end-tidal carbon dioxide) was applied to the cases, and a radial artery catheter, oropharyngeal temperature probe and urinary catheter were placed. After induction of anaesthesia, an 8F Introducer (Arrow Corporation) and a 7F thermodilution pulmonary artery catheter (Baxter Healthcare Corporation, Irvine, CA) were placed via the right internal jugular vein.

Cardiopulmonary bypass (CPB) management was performed using moderate hypothermia (32–34°C) and a continuous flow membrane oxygenator with a roller pump. After cross-clamping (CC) was placed on the aorta, myocardial protection was achieved with cold blood cardioplegia administered anterogradely at a dose of 10 $ml.kg^{-1}$. Cardioplegia solution was maintained with boluses at a dose of 5 $ml.kg^{-1}$ at 20-minute intervals throughout the cross-clamping. Topical hypothermia was also applied.

During CPB, mean arterial pressure was maintained between 60–80 mmHg. When mean arterial pressure (MAP) was ≤60 mmHg, ephedrine was applied to the pump at a dose of 5 mg to provide the desired MAP. If MAP was >80 mmHg, the depth of anesthesia was increased and nitroglycerin infusion (0.1 $\mu g.kg^{-1}.min^{-1}$, to the pump) was started. Just before the cross-clamp was removed (3–5 minutes before), dopamine infusion was started at a dose of 2 $\mu g.kg^{-1}.min^{-1}$ in all appropriate cases according to the clinic's protocol. At the same time, levosimendan was administered as a 10-minute bolus at a dose of 12 $\mu g.kg^{-1}$ to all cases with a cardiac index less than 1.5 L/min/$m^2$ in hemodynamic measurements. Following this, maintenance infusion was started at a rate of 0.1 $\mu g.kg^{-1}.min^{-1}$. During weaning from CPB, if MAP was ≤60 mmHg, pulmonary capillary wedge pressure (PCWP) was ≥18 mmHg and central venous pressure (CVP) was >15 mmHg within the sufficient reperfusion period, dobutamine and/or adrenaline infusion was added.

In cases where the cross-clamp was removed, 100 mg lidocaine was routinely given as an intravenous bolus. In cases where ventricular tachycardia or fibrillation developed, it was repeated twice with 50 mg doses. In resistant tachyarrhythmias, a 24-hour amiodarone infusion was started at a dose of 8 $mg.kg^{-1}.h^{-1}$ following a 300 mg loading. In the postoperative period, when hemodynamic stability was achieved, the doses of inotropic agents were reduced and stopped.

### Hemodynamic Measurements and Biochemical Analysis

The age, gender, body surface area (BSA), preoperative characteristics, ejection fractions, operation time (time from incision to skin closure), cross-clamp time (time between application and removal) and CPB time (time to enter the pump and exit the pump), number of grafts used, amount of antiarrhythmic and inotropic agents used during weaning from CPB were recorded. The intervals of taking peripheral blood samples from the cases were; after induction (T0), at the 30$^{th}$ minute after the beginning of CPB (T1), at the 1$^{st}$ hour (T2), 3$^{rd}$ hour (T3), 6$^{th}$ hour (T4) and 24$^{th}$ hour (T5) after CPB (after exit from the CPB). Tubes (plain blood tubes) were sent to the biochemistry laboratory to measure TNF-α, IL-6, IL-8 and IL-10 levels. At the same time intervals, hemodynamic data of the cases; mean arterial pressure (MAP), central venous pressure (CVP), left ventricular end-diastolic pressure (LVEDP) and cardiac index (CI) values were recorded using the thermodilution method.

Patient blood samples were centrifuged at 3500 rpm for 10 minutes at +4°C to separate the serum. Serum samples were frozen at -20°C and all analyses were run collectively. IL-6, IL-8, IL-10 and TNF-α were analyzed by enzyme-linked immunoassay method (ELISA) using commercial kits (DIACLONE HUMAN ELISA KIT, Besancon Cedex, France) according to the procedure recommended by the manufacturer. While the intra-assay coefficient of variation (CV) of the IL-6 kit was 4.2%, the inter-assay coefficient of variation CV was 7.7%. While the intra-assay coefficient of variation (CV) of the IL-8 kit was 3.1%, the inter-assay coefficient of variation CV was 9.7%. The intra-assay coefficient of variation (CV) of the IL-10 kit was determined as 3.2%, while the inter-assay coefficient of variation CV was determined as 7.3%. The intra-assay coefficient of variation (CV) of the TNF-α kit was determined as 3.3%, while the inter-assay coefficient of variation CV was determined as 9%.

### Recording of Multiple Organ Dysfunction Score (MODS)

Daily organ dysfunction scores were evaluated using the multiple organ dysfunction score (MODS) at the same time every day for three days after the operation. According to this scoring system, cardiac functions (pressure values compatible with heart rate), pulmonary performance ($PaO_2/FiO_2$), renal functions (creatinine level), hepatic functions (bilirubin), haematological functions (platelet count) and neurological functions (Glasgow coma scale) of the cases were scored with values between 0 and 4. A score of 0 is related to less than 5% intensive care mortality and indicates normal or minimally impaired organ functions. A score of 4 indicates 50% and above intensive care mortality and significantly impaired organ function.[17] MOD score values were recorded in the first 3 consecutive days after the operation. The arithmetic average of these scores was given. This mean MOD score was included in the statistical evaluation for every patient.

### Statistical Analysis

Data were evaluated using the Statistica for Windows® v6.0 (StatSoft Inc., Tulsa, USA) statistical program. The distribution properties of the variables were investigated with the Kolmogorov-Smirnov test. Normally distributed data were given as mean±SD, others as either frequency percentages or median±interquartile range. Comparisons of independent variables were made with Student-t for normally distributed data, Mann-Whitney for non-normally distributed data and chi-square for categorical variables. Hemodynamic parameters measured at different times were compared with ANOVA, and circulating cytokine values were compared with Friedman repeated-measures analysis of variance. In the correlation analysis between independent variables, the "Pearson product-moment" method was used for normally distributed continuous variables, and the "Spearman rank-order" tests were used for non-normally distributed continuous data and categorical variables. For variables found to be correlated with the primary outcome of the study when univariate analysis was applied, the statistical significance of these correlations was then tested with multiple regression analysis. The statistical significance limit of the "p" value was accepted as 0.05.

## Results

The clinical and demographic characteristics of 27 patients who underwent CPB are summarised in Table 1. The mean age included in the study was 61.3±9.8 years. Of 27 participants, 21 were male, and the rest were female (n=6). The patients who had a history of myocardial infarction were 5. The mean EuroSCORE of the patients was 7.1±2.1. Surgical characteristics of the patients, mean perioperative blood and blood product requirements, and mean inotropic agent consumption are given in Table 2. The mean time of operation was 227.6±61.7 minutes, and the

**Table 1.** The characteristics of patients undergoing coronary artery bypass greft surgery

| Clinical specialities | Mean±SD |
|---|---|
| Age | 61.3±9.8 |
| Gender (M/F) | (21/6) |
| Body surface area | 1.9±0.3 |
| Euro skore | 7.1±2.1 |
| Ejection fraction (%) | 29.4±4.0 |
| Story of suffered myocardial infarction) | 5 |
| Diabetes mellitus (n) | 4 |
| Hipertention (n) | 7 |
| Angiotensin converting enzym inhibitor (n) | 7 |
| Beta blocker (n) | 11 |

SD: Standart deviation.

**Table 2.** The perioperative surgical specialities of patients, perioperative consume proportion of blood and blood product and consume amount of inotropic agents

| | |
|---|---|
| Mean of anastomosis count | 2.2±0.5 |
| Time of operation (minutes) | 227.6±61.7 |
| Time of cardiopulmonary bypass (minutes) | 80.9±3.6 |
| Time of cross clemp (minutes) | 42.9±11.8 |
| Time of stay at postoperative care unit (minutes) | 88.3±34.8 |
| Consumption of erythrocyte suspention (Unit) | 4.7±1.7 |
| Consumption of fresh frosen plasm (Unit) | 1.6±0.7 |
| Dopamine doses ($mg.kg^{-1}$) | 7.6±5 |
| Dobutamine doses ($mg.kg^{-1}$) | 7.5±4.8 |
| Adrenaline consumed patients (n) | 11 |
| Adrenalin doses ($mg.kg^{-1}$) | 0.2±0.2 |
| Levosimendan consumed patients (n) | 14 |

**Table 3.** Haemodynamic date of patients during the perioperative period

| | HR beat/dk | MAP mmHg | CI L/dk/$m^2$ | LVEDP mmHg | CVP mmHg |
|---|---|---|---|---|---|
| T0 | 68±8.0 | 75±10 | 1.4±0.2 | 18±6 | 13±5 |
| T2 | 106±15* | 69±9** | 2.2±0.7** | 20±7 | 14±6 |
| T3 | 114±11* | 70±9** | 2.7±0.9** | 16±5* | 11±5** |
| T4 | 110±9* | 72±6 | 2.7±0.9** | 14±4* | 10±3** |
| T5 | 107±11* | 75±9 | 2.4± 0.9** | 13±3* | 9±3** |

*: p<0.001; **: p<0.05; ANOVA. HR: Heart rate; MAP: Mean arterial pressure; CI: Cardiac index; LVEDP: Left ventricles end-diastolic pressure; CVP: central venous pressure; T0: After induction; T1: At the 30th minutes after the beginning of CPB; T2: At the 1st hour; T3: At the 3rd hour; T4: At the 6th hour; T5: At the 24th hour after CPB; ANOVA: Analysis of variance; CPB: Cardiopulmonary bypass.

mean time of the cross-clamp was 42.9±11.8 minutes. The mean erythrocyte suspension consumption was 4.7±1.7 units per patient, which was higher than those expected for patients with normal ejection fraction. Of 27 patients, fourteen needed levosimendan infusion.

Table 3 shows that hemodynamic data before and after CPB were obtained from all patients. Heart rate increased significantly at all times compared to baseline (p<0.001). Mean arterial pressure decreased significantly at the 3rd and 6th hours of cardiopulmonary bypass compared to baseline (p<0.05). The cardiac index increased significantly at all measurement times compared to baseline (p<0.05). Left ventricular end-diastolic pressure and central venous pressure decreased significantly at the 3rd, 6th, and 24th hours after cardiopulmonary bypass compared to baseline (p<0.05).

Cytokine levels are shown collectively in Figure 1. Initial TNF-α (8 pg/mL), IL-6 (2 pg/mL), IL-8 (29 pg/mL) and IL-10 (5 pg/mL) values of the cases, adjusted according to the variance analysis of the kits, are shown as 0 in the graph. Interleukin-6, IL-8 and IL-10 increased significantly compared to the baseline during and after cardiopulmonary bypass in all cases (p<0.05). IL-6 and IL-8 reached their maximum levels at the 3rd hour of CPB. IL-10 peaked at the 1st hour of CPB. TNF-α did not change significantly during cardiopulmonary bypass.

As a result of univariate analyses applied to the data of the cases, a significant correlation was found between multiple organ dysfunction scores (MODS) and IL-6 levels at the 3rd and 6th hours of cardiopulmonary bypass (r=0.3, p=0.02; r=0.4, p=0.02, respectively). A significant positive correlation was found between IL-6 levels at the 3rd hour and pulmonary, cardiopulmonary and renal dysfunction (r=0.3, p=0.04; r=0.4, p=0.003; r=0.3, p=0.04, respectively). Also, there was a correlation between IL-10 levels at the 6th hour and renal dysfunction (r=0.5, p=0.001) and between IL-6 levels at the 6th hour (r=0.3, p=0.05) and IL-8 levels at the 3rd hour (r=0.3, p=0.03) and haematological dysfunction.

When these significant variables were evaluated with "Multivariate analysis" (Multiple Regression Analysis); none of them were independently associated with MOD mean scores. No significant correlation was found between the studied cytokine levels and neurological dysfunction and cardiac dysfunction.

Two of our patients died 24 and 40 hours after the operation. Both patients did not respond to fluid, inotrope, and intra-aortic balloon pump support.

## Discussion

In this study, we observed the changes in IL-6, IL-8, TNF-α and IL-10 levels during and in the early period after cardiopulmonary bypass in patients with poor left ventricles who underwent cardiopulmonary bypass grafting surgery. We found a relationship between these cytokine changes and postoperative multiorgan failure scores. In our study,

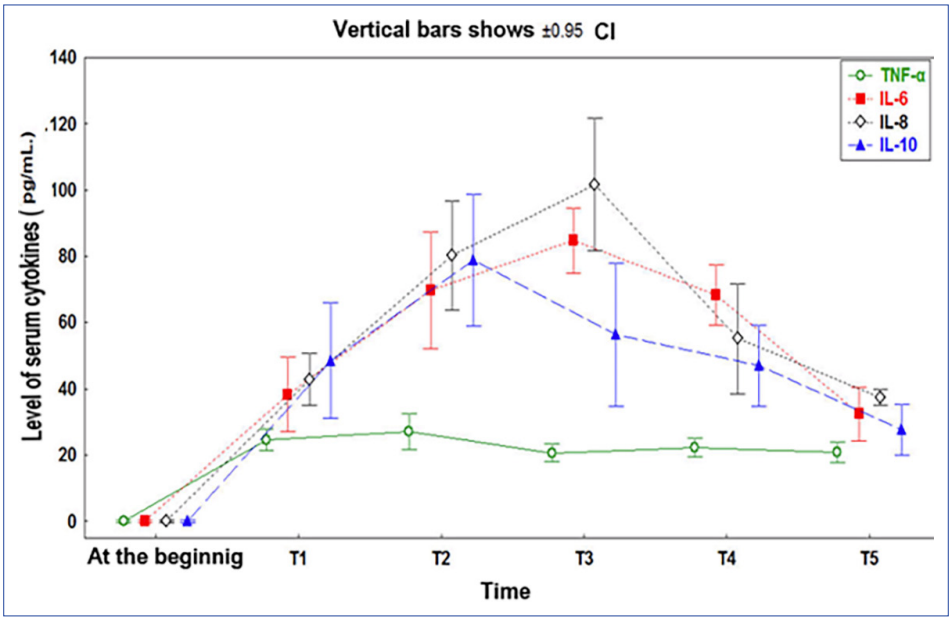


**Figure 1.** The level of TNF-α, IL-6, IL-8 and IL-10 cytokines at the studies times.

*: p<0.05: Friedman test. CI: Confident interval; T1: At the 30th minutes after the beginning of CPB; T2: At the 1st hour; T3: At the 3rd hour; T4: At the 6th hour; T5: At the 24th hour after CPB exit; TNF-α; Tumor necrosis factor-alpha; CPB: Cardiopulmonary bypass.

while IL-6, IL-8 and IL-10 levels increased significantly compared to the baseline at all time intervals, TNF-α levels did not change significantly in the perioperative period. A significant positive correlation was found between IL-6 levels at the 3rd hour after CPB and pulmonary, cardiopulmonary and renal dysfunction. There was a correlation between IL-10 levels at the 6th hour and renal dysfunction as well. Also, there was a correlation between IL-6 levels at the 6th hour and IL-8 levels at the 3rd hour and haematological dysfunction.

In cases where cardiopulmonary bypass is performed, pro-inflammatory cytokines play a significant role in the development of multiple organ failure. The increased production of these cytokines can worsen early clinical outcomes.[8,18] We found a relationship between pulmonary, cardiopulmonary and renal dysfunction and IL-6 levels at the 3rd hour after CPB. Similarly, research has shown that the extent of tissue damage is correlated with levels of interleukin-6.[18–20] Additionally, elevated IL-6 levels are considered a reliable predictor of clinical outcomes following cardiopulmonary bypass.[13] In our study, we also found a significant correlation between IL-6 levels and the onset of multiple organ dysfunction during the early period after the procedure. Furthermore, Wei et al.[19] reported no significant difference in plasma IL-6 levels between on-pump and off-pump surgeries; however, they noted substantial increases in the levels of interleukin-8 and interleukin-10.

In this study, we found that the development of pulmonary dysfunction observed after cardiopulmonary bypass correlated with IL-6 levels. Contrary to our study, it has been reported that IL-8 is responsible for the lung damage observed after CPB by causing pulmonary leukocyte sequestration with its strong neutrophil chemotaxis effect,[14,15,21] while IL-6 has no direct effect on pulmonary dysfunction.[9] This difference in our study may be due to the differences in the characteristics of the cases or the differences in the kits and blood sampling times. The effect of IL-6 on postoperative pulmonary functions in patients with poor left ventricles can be investigated in further studies.

It has been reported that renal dysfunction is closely related to the increase in IL-6 levels in the first 24 hours after cardiopulmonary bypass and that anti-inflammatory IL-10 also increases in parallel with the increase in IL-6 levels.[9] Similarly, in this study, renal dysfunction significantly correlated with the increase in IL-10 levels but not with the increase in IL-6 and other cytokines. Because of the increase in IL-10, the increase of the other cytokines might have been blocked or balanced. IL-10 inhibits the production of IL-2 and INF-γ by inhibiting the production of cytokines by natural killers and macrophages and shifts the immune balance in favour of TH2.[22]

It has been reported that the systemic inflammatory response (IL-6 and IL-8 response) is greater in patients with limited left ventricular function than those with normal heart function.[17,23] Similarly, in our patient group with left ventricular dysfunction, IL-6 and IL-8 levels were significantly higher during and after cardiopulmonary bypass. The common features of our cases were low initial mean cardiac output and high mean left ventricular end-diastolic pressures. Because we have no control group

patients with normal left ventricular function, we couldn't show these differences. The patients included in our study initially had high right heart-filling pressures. It is also a preoperative risk factor for the development of multiple organ dysfunction after cardiopulmonary bypass. In addition to left ventricle dysfunction caused by cytokines, severe ventricular dysfunction limits organ perfusion, and therefore the organs predispose to the development of dysfunction after cardiopulmonary bypass.

## Limitations

First of all, the small number of cases is an important limitation of our study. Secondly, the lack of cases with normal ventricular ejection fraction as a control group in our study is another limitation. Thirdly, although the use of anaesthetic agents in our cases was homogeneous, the use of inotropic agents (especially levosimendan) was not homogeneous. Recently, it has been reported that levosimendan has an anti-inflammatory effect. This may have affected the cytokine responses. Our study team intends to plan new studies in the future to address these deficiencies.

## Conclusion

In conclusion, IL-6 and IL-8 peaked at the 3rd hour after CPB and returned to the level of the first half hour at the 24th hour. IL-10 peaked at the 1st hour after CPB. TNF-α maintained the level of increase in the first half hour for 24 hours in patients with low ejection fraction who underwent coronary artery bypass surgery. We found a positive significant correlation between IL-6 levels and pulmonary, cardiopulmonary and renal dysfunction in the early postoperative period. Also, there was a relationship between IL-8 levels and haematological dysfunction. No significant correlation was found between the studied cytokine levels and neurological dysfunction and cardiac dysfunction. We believe that the development of these studies may be valuable in developing medical treatment protocols that will prevent inflammatory systemic responses.

### Disclosures

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**Ethics Committee Approval:** The study was approved by The Celal Bayar University Scientific Research Ethics Committee (no: 135, date: 27/10/2008).

**Authorship Contributions:** Concept – T.Ö., M.Ö., F.T.; Design – T.Ö., M.Ö., F.T., M.Ç.; Supervision – T.Ö., F.T., M.Ç.; Materials – M.Ö., T.Ö., F.T.; Data collection &/or processing – M.Ö., F.T.; Analysis and/or interpretation – T.Ö., M.Ö., F.T.; Literature search – Ö.T., M.Ö., O.Y., A.Ş.; Writing – Ö.T., M.Ö., O.Y., A.Ş.; Critical review – T.Ö., M.Ö., M.Ç., O.Y., A.Ş., F.T.

**Informed Consent:** Written informed consent was obtained from all patients.

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