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Changes in Interleukin-6 and Highly Sensitive C-Reactive Protein in Patients who Underwent Redo Coronary Artery Bypass Grafting

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Abstract

Background: Determination of biomarkers can assess cardiac injury induced by cardiopulmonary bypass (CPB) during coronary artery bypass grafting (CABG). Open heart surgery initiates inflammatory reaction. Aim of this study was to compare the inflammatory response in patients undergoing first- and CABG-reoperation.

Methods: Fifty-four patients (16% female, 84% male; 60.5 ± 6.5 *vs.* 66.2 ± 7.3 years) scheduled for elective cardiac surgery were divided into: Group 1, CABG primo-operation, and Group 2, CABG re-operation (redo CABG). The extent of inflammation was estimated by measuring interleukin (IL)-6 and highly sensitive C-reactive protein (hs-CRP) in plasma. Blood samples were collected: 24 hours prior, 6, and 24 hours after initiation of CPB. Demographic data, preoperative risk assessment Euro-score, laboratory values and clinical outcomes: atrial fibrillation rate, tracheal intubation time, revisions, blood loss, length of Intensive Care Unit (ICU) and hospital stay were analyzed.

Results: Baseline levels of IL-6 ($p < 0.001$) were significantly higher in re-operated patients. IL-6 increased significantly 6 hours after initiation of CPB in both groups ($p < 0.0001$). Day after surgery IL-6 ($p = 0.472$) and hs-CRP ($p = 0.248$) levels were similar in both groups. Although hs-CRP was higher in Group 1 (90.45 ± 46.67 *vs.* 72.91 ± 57.31 mg/L) this had no statistical significance. Clinical outcomes have been in positive correlations with inflammation, but statistically insignificant in both groups.

Conclusion: Monitoring of IL-6 and hs-CRP during redo CABG has shown that CPB cause inflammatory reaction but repeated use does not cause extensive reaction potentially harmful for myocardium.

Keywords: Cardiovascular surgery; Coronary disease; Cytokines; Immunology; Inflammation

Introduction

Ischemic events affecting arteries due to partial or complete blood vessel lumen occlusion are among leading causes of mortality. Atherothrombosis and platelets have the key role in these conditions and antiplatelet agents are very important for prevention and control of thrombosis. Two basic medicines are aspirin and clopidogrel, which are used in ischemic heart disease therapy, alone or as combination [1]. In some of these patients open heart surgery with cardiopulmonary bypass (CPB) is necessity. During the operation they received an anticoagulant, nonfractioned heparin [2]. At the same time, the patient`s immune system is in contact with foreign materials which makes part of the CPB, the circuit. Biocompatibile materials of the circuit are thinly coated tubes which provide similar enviroment like endothelial cells [3]. Operative wound is exposed to heparinized blood, and synthetic surfaces of the circuit partially activated protein coagulation system, fibrinolysis, complement cascade, platelets and white blood cells (PMN), which in turn compromises hemostasis [4]. Of particular interest is the subgroup of patients scheduled for repeated intervention on CPB.

Primary cardiac intervention patient`s immune system is sensibilized to foreign substances and ingredients of the circuit, establishing immunological memory [5]. After repeated surgery, immune system can react excessively, but in most patients such reaction is based on the secondary impact of the memory pool of lymphocytes [5]. An inappropriate immune response may lead to harmful, potentialy life threatening consequences due to severe inflammatory tissue destruction [4]. During the passage of blood through circuit, PMN and espetialy monocytes produces various cytokines involved in the inflammatory response, in particular, interleukin-1β (IL-1β), and tumor necrosis factor-alpha (TNF-α) [6]. These in turn lead to the release of interleukin-6 (IL-6), the cytokine that is primarily responsible for the induction of acute phase protein production by the liver [6]. The concentration of IL-6 gradually increases and reaches a peak 4 hours after the inclusion of protamine infusion [7]. IL-6 initiates the synthesis of other cytokines, dozens of proteins, including a large increase in the production and release of the C-reactive protein (CRP). Cascade of proinflammatory cytokines TNF-α, IL-6, and interleukin-8 (IL-8), are soon followed by an assembly of anti-inflammatory cytokines, intreleukin-10 (IL-10) and other cell-to-cell mediators [6,8].

CRP as acute-phase reactant indicates the presence of the inflammation in the body [9]. CRP has pro- and anti-inflammatory properties and is involved in the removal of necrotic and apoptotic cells. In addition to inducing inflammatory cytokines in monocytes, CRP also appears to buffer against inflammatory damage [10]. High CRP level is considered to be a risk factor for heart disease [11]. Several reports have confirmed that CRP present in circulation is a reliable

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marker of risk for cardiovascular disease and stroke prior to cardiac operations [12,13]. A more sensitive CRP test, called a highly-sensitive CRP (hs-CRP) assay, is available to determine a person's risk for heart disease [14].

PMN's in contact with biocompatible materials releases mediators that are partially responsible for inflammatory reaction [15]. Blood collected by suction during cardiac surgery and the erythrocytes remaining in the CPB could be washed with the machine, cell saver, which in turn reduces the inflammatory response [16]. This approach helps in preparing patients for open heart surgery with an increased risk of bleeding to prevent postponing the surgical procedures and unnecessary blood transfusions.

The aims of this study was to measure the concentrations of the IL-6 and hsCRP during and after CPB usage, in patients undergoing primo-operation and re-operation on coronary arteries, and to determine the impact of the biocompatible materials on the plasma concentration in re-operated patients. At the end of the surgery, we have measured IL-6 in buffy coat after blood processing with cell salvage procedure, before erythrocyte reinfusing to the patient's blood stream.

Patients and Methods

Patients

After ethical committee approval and written informed consent, 54 patients with impaired left ventricle ejection fraction (LVEF<35%), scheduled for elective cardiac surgery, were included in this non-randomized prospective study. Patients were identified from daily surgical programme from November 2010 until May of 2011 at the Cardiovascular Institute Dedinje, Belgrade, Serbia. There were 2 patients with changed indications throughout surgery, and they were excluded from further observation.

Fifty-two consecutive patients were classified into two groups: Group 1, the first coronary artery bypass grafting (CABG) and Group 2, re-operation on the coronary arteries (redo CABG). Patients from Group 1 were on the list for the first time in their life. On the contrary, the patients in Group 2 already have undergone primo-operation on coronary arteries several years before. They required the second-operation CABG, in some cases accomplished with valve reconstruction or replacement. The inclusion criteria fulfil the patients who needed simultaneous operation on carotid arteries (EAC, Carotid Artery Endarterectomy) also. Patients having indication for urgent intervention, as well as patients planned for valve procedure only, were excluded from this study. Final confirmation was obtained at the operating room during surgical procedure.

Patients were monitored daily until they leave the hospital. Any change in clinical status and course of disease was registered in the patient`s record. Care of the patients was not different from the usual standard care in the experimental groups.

Determination of routine blood test parameters

The basic tests include routine laboratory blood tests and clinical data. The number of leukocytes, erythrocytes, platelets, haemoglobin and other haematological parameters were determined on an automatic haematology analyzer Coulter HMX counter (Beckman Coulter Electronics, USA). In our hospital, Cell Salvage device (Dideco Sorin, Italy) is in routine usage, for collecting, filtrating, washing and reinfusing autologous concentrated red blood cells. Thus, the need for transfusion of alloganeic blood products is significantly reduced [16].

Serum concentrations of IL-6 and hs-CRP were measured 24 hours before surgery, 6 hours and 24 hours after the surgery. Blood samples were taken from peripheral vein and immediately centrifuged for 20 minutes. Serum was divided into two aliquots for biochemical analysis and for determination of immunological parameters. For the quantitative determination of IL-6 we have used chemiluminiscent immunoassay IL-6 in human serum (Beckman Coulter Inc, CA). The recommended serum concentration of IL-6 in healthy individuals is less than 6.4 pg/mL. At the end of the surgery we measured IL-6 in buffy coat after blood processing with cell saver procedure in those patients where autotransfusion was done. Immuno-turbidimetric method Biokit (Barcelona, Spain) was applied for quantitative measurement of hs-CRP levels in serum. According to the American Heart Association the recommended limit for hs-CRP healthy people is up to 3.0 mg/L [14].

Clinical outcomes

The primary objective of this study was to determine the concentrations of IL-6 and hs-CRP *in vitro* and to compare obtained values. We have analyzed the factors related to inflammation and clinical outcomes: the incidence of atrial fibrillation (AF, Atrial Fibrillation), tracheal intubation time, revision, length of stay in the Intensive Care Unit (ICU), and length of hospital stay. In addition, we correlated inflammatory markers with preoperative risk assessment Euro-score. In the patient`s record all the data on blood loss, the volume of erythrocytes saved, washed and returned to patient's circulation were recorded.

Statistical anayses

Statistical analyses were done by using SPSS 11.0 software (SPSS, Chicago, IL). Data are expressed as mean values ± standard deviations. Intragroup and intergroup differences for hematological, biochemical and other clinical data were assessed by two-way analysis of variance (ANOVA) with Fisher`s least significant difference procedure for post hoc repeated measurements. When continuous data had no normal distribution, the Kruskal-Wallis test was used. Proportions were compared by the Chi-square and by Fisher`s exact test when the expected frequency was less than five. Baseline patient characteristics were adjusted for analyses by using Multivariate General Linear Modeling. All analysis was 2-sided and based on an intention-to-treat principle. A value of $p<0.05$ was considered statistically significant.

Results

Study population and study design

In this study, the patient population consisted of 44 males (84%) and 8 females (16%), mean age 61.5 ± 7.8 (range, 50-80 years). Isolated CABG surgery and first open heart surgery was performed in 30 patients (55%), re-operation on coronary arteries in 10 patients (19%), re-operation on coronary arteries with simultaneous carotid surgery in 2 patients (4%), while other 22% of patients underwent combined re-operation CABG and valve procedure.

Baseline characteristics of patients in both groups were similar for the most part (Table 1). Sex and body weight of the patients in two groups were uniform. In Group 2 only 4/22 (18%) of the patients were treated with clopidogrel before open heart surgery.

Prior to surgery, patients in Group 1 had low levels of IL-6 (4.49 ± 2.98 pg/mL, range 0.92-11.34 pg/mL), while in Group 2 the mean value was above the recommended value for healthy subjects (10.29 ±

8.07 pg/mL, range 2.5-32.8 pg/mL) ($p < 0.001$). In addition, in Group 1, only 7/30 (23%) of the patients with IL-6 plasma concentrations were above the limit, while in Group 2 there were 13/22 (59%) patients. If the peripheral circulation increased, IL-6 levels were recorded 6 hours after the inclusion of CPB in both groups (Table 2), where the mean value in Group 1 (253.35 ± 158.52 pg/mL) was not significantly different compared to Group 2 (320.58 ± 427.19 pg/mL) ($p = 0.489$). Faster downward trend in IL-6 levels were recorded 24 hours after surgery in Group 2 (247.36 ± 31 *vs.* 204.12 ± 33 pg/mL), without statistical significance ($p = 0.472$). In both groups, peak of IL-6 levels were recorded 6 hours after initiation of the CPB. In serial samples taken from the same patient at regular intervals, a significant increase was seen compared to the preoperative results ($p < 0.0001$) (Figure 1). There was no difference in mean values of the IL-6 measured in aspirated blood

Variable	**CABG** (n = 30)	**redo CABG** (n = 22)	**P-Value**
Sex (male %)	23 (83.3%)	18 (81.8 %)	0.887
Age (years)	61.50 ± 7.700	65.95 ± 7.352	0.041
Euroscore	4.67 ± 1.373	8.00 ± 2.390	0.000
LVEF %	26.00 ± 4.807	35.64 ± 10.817	0.001
Body waight (kg)	79.89 ± 11.188	79.52 ± 14.542	0.922
Aspirin therapy (%)	28 (93.3%)	17 (77.3 %)	0.094
Hemoglobin (g/L)	241.48 ± 67.551	186.86 ± 45.327	0.002
Leukocytes x10^9/L	8.05 ± 2.199	7.39 ± 3.233	0.390
Platelets x10^9/L	241.48 ± 67.551	186.86 ± 45.327	0.002
IL-6 (pg/mL)	4.49 ± 2.981	10.29 ± 8.073	0.001
hs-CRP (mg/L)	3.255 (2.012-5.266)	4.159 (2.066-8.371)	0.553

Data are mean ± standard deviation for continue variables or n (%) for categorical variables
hs-CRP = highly sensitive C-reactive protein; IL-6 = interleukin-6; LVEF = left ventricle ejection fraction

Table 1: Demographic characteristics of patients, preoperative and laboratory data.

Variable	**CABG** (n = 30)	**redo CABG** (n = 22)	**P-Value**
IL-6 (pg/mL) after 6 h	253.35±158.525	320.58±427.193	0.489
IL-6 (pg/mL) after 24 h	247.369 (196.229-311.836)	204.126 (124.190-335.552)	0.472
hs-CRP (mg/L) after 24 h	90.45±46.67	72.91±57.31	0.248
Hemoglobin (g/L) after 24 h	133.38±16.108	114.00±13.438	0.000
Leukocytes x10^9/L after 24 h	17.07±3.726	16.35±4.711	0.000
Platelets x10^9/L after 24 h	155.043 (126.839-189.519)	131.002 (113.571-151.109)	0.165
AF (%)	5 (16.7%)	3 (13.6%)	0.765
Tracheal intubation time (hours)	16.073 (13.998-18.456)	19.120 (12.138-30.118)	0.453
Revision (%)	3 (10.0%)	2 (9.1%)	0.913
Blood loss (ml)	868.52±587.555	1088.33±819.517	0.285
Length of stay at ICU (days)	3.032 (2.327-3.951)	4.555 (2.762-7.513)	0.145
Length of stay at hospital (days)	9.141 (7.973-10.479)	14.606 (10.226-20.863)	0.017

Data are mean ± standard deviation for continue variables or n (%) for categorical variables
AF = atrial fibrillation rate; CABG = coronary artery bypass grafting; hs-CRP = highly sensitive C-reactive protein; ICU = Intensive Care Unit; IL-6 = interleukin-6

Table 2: Laboratory findings and clinical outcomes after first CABG and re-operation.

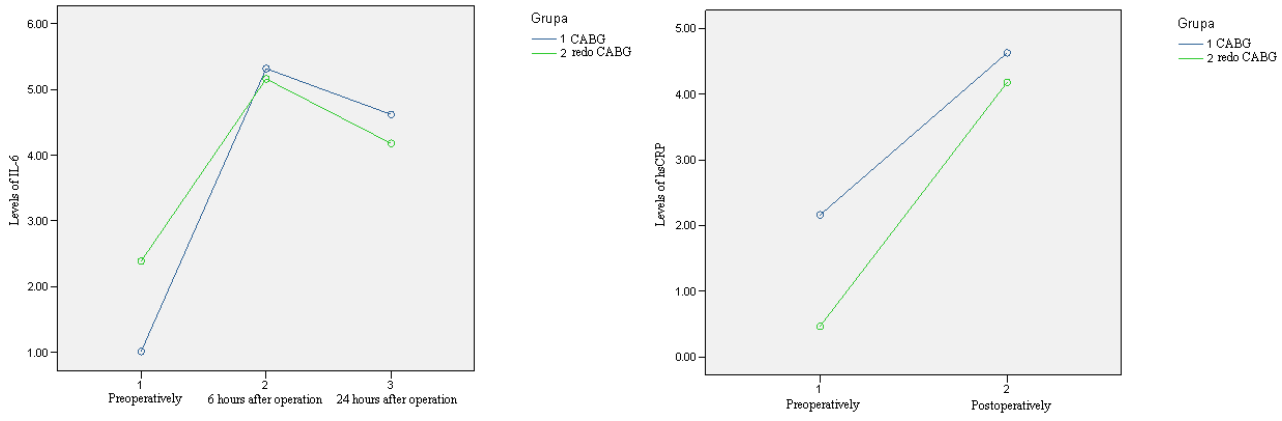

Figure 1: Mean values of interleukin-6 (IL-6; A) and highly sensitive C-reactive protein (hsCRP; B) in CABG and redo CABG groups. Sampling points are 24 hours before surgery, 6 and 24 hours postoperatively.
(Mixed Model ANOVA)

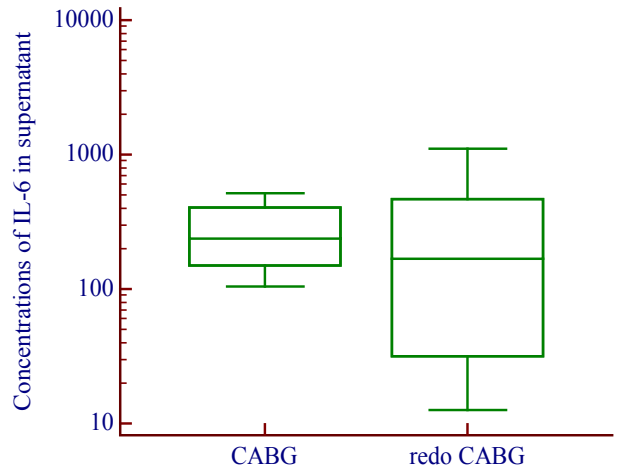

Figure 2: Graphical representation of the IL-6 levels measured in supernatant during autotransfusion of the erythrocytes returned to patient's peripheral circulation after cell-saver procedure during primo- and re-operation coronary artery bypass grafting.

after cell-saver procedures between two groups (p = 0.147). Actually, just in 4 patients we measured highly elevated concentration during autologous blood component transfusion in re-operation (Figure 2), but without high levels of the IL-6 in peripheral circulation.

Basic values of hs-CRP levels were above the recommended value for healthy individuals in both groups (3.25 ± 2-5.2 *vs.* 4.15 ± 2-8.37 mg/L) (p = 0.553). No signs of inflammation were found in 13/30 (43%) patients in Group 1, while in Group 2 were only 6/22 (27%).

Clinical endpoints

As shown in Table 2 there was no difference between Group 1 and Group 2 in the measured postoperative laboratory parameters, except for the content of haemoglobin and white blood cell count. IL-6 measured preoperatively was in positive correlation with Euroscore in Group 1, (r = 0.05, p = 0.78), while in Group 2 correlation was negative (r = - 0.21, p = 0.36). Day after surgery in both groups, IL-6 levels were positively correlated with Euroscore (r = 0.10, p = 0.58 *vs.* r = 0.06, p = 0.81) and drainaged blood content (r = 0.17, p = 0.41 *vs.* r = 0.002, p = 0.99). The hs-CRP was in good correlation with ICU before (r = 0.24, p = 0.30 *vs.* r = 0.23, p = 0.26) and after operation (r = 0.07, p = 0.72 *vs.* r = 0.06, p = 0.78), as well as IL-6 (r = 0.08, p = 0.69). Relations between inflammatory markers and other clinical outcomes followed in this study were without significance. Looking precisely in re-operated patients, IL-6 content in autologous blood returned to the patient's circulation after cell-saver procedures was in positive correlation with ICU stay (r = 0.30 p = 0.28) but did not reach the level of significance.

Preoperative laboratory data: haemoglobin, leukocytes, platelets, IL-6 and hsCRP were adjusted by group with age, LVEF, Euroscore, platelets, and IL-6. Repeated Measures procedure was used to measure the effect of each variable accounting effect of time. Adjustment for multiple comparisons was above 0.05 for all covariate observed except for IL-6 preoperatively. Preoperative and postoperative laboratory data: haemoglobin, leukocytes, platelets, IL-6 and hsCRP adjusted by group with age, LVEF, Euroscore, platelets, IL-6, and length of hospital stay. The significance values for platelets count measured preoperatively and IL-6 measured 24 hours pre-, 6 and 24 hours post-operatively were both less than 0.05, so we concluded that they contribute to the model (p=0.048, p=0.026, p=0.033).

Discussion

Open-heart surgery is associated with the inflammatory response, which occurs as a result of the contact of blood and artificial surfaces of the circuit, ischemia-reperfusion damage, surgical trauma, changes in body temperature and release of endotoxin [17,18]. The purpose of this study was to clarify whether the inflammatory markers in the blood become more intensive in patients with re-operation by using CPB, after second impact on the immune system. Thus, we have decided to measure the level of IL-6 as an early marker and hs-CRP as a late indicator of CPB-induced systemic inflammatory response.

Literature data have shown that IL-6 is a major proinflammatory cytokine known to be produced in excessive amounts after CPB, and IL-6 is one of the earliest endogenous mediators released as a result of the inflammatory response [19,20]. IL-6 plasma level started to rise during CPB and peaked 4 h after protamine infusion [7]. Previous studies reported a similar pattern for TNF-α and IL-6 evolution during CPB surgery [21]. In this study levels of CRP were measured, because CRP is a generally considered as a non-specific marker of inflammation, and is associated with the diffuse inflammatory response after CPB [15]. CRP indicates underlying inflammation, and has repeatedly been shown to influence the risk of cardiovascular disease, particularly stroke and transient ischemic attack in the elderly [11-13,22].

IL-6 is a multifunctional protein that regulates the immune response, acute phase reaction and haematopoiesis [23]. IL-6 is produced by lymphoid and nonlymphoid cells, T and B lymphocytes, monocytes, fibroblasts, endothelial cells and transformed cells of many tumours [23]. Induction of the acute phase reactant production of CRP in hepatocytes is promoted through synergistic action of proinflammatory cytokines IL-6 and IL-1β [23]. Of particular importance is the discovery that there is an interaction between IL-6 and CRP at the level of their gene expression, with their genetic correlation and is an important determinant of the risk of stroke after cardiac surgery. Therefore, genetic variants modulating IL-6 levels and CRP expression may contribute to perioperative pro-inflammatory phenotype that is seen in cardiac patients [24].

Re-operation with CPB is considered as a high-risk surgery [25,26]. Due to the re-exploration of chest these patients are at higher risk of perioperative bleeding [27], complications that are often found in the re-operation and requires consequential substitution of blood products. For complicated cardiac surgery, such as re-operation with repeated use of CPB (Group 2), as a control group in this study we choose the patients with poor left ventricular ejection fraction (26% *vs.* 35%, p = 0.001). Patients in these groups did not differ by sex and weight, but the basic preoperative characteristics shown some differences. Patients in Group 2 belonged to an older age (65.9 ± 7.35 years), since the re-operation was proceeded by a period of one year or more, from the first surgery. They had a higher estimated risk for cardiac intervention, calculated with the Euroscor system (p < 0.0001) due to numerous comorbidities.

When analyzing laboratory parameters measured preoperatively, there were no significant differences in haematological values, except for haemoglobin and platelet count (p = 0.002). It did not affect the clinical course and outcome because the platelets were in the range of reference values for the adult population in both groups, although with lower values in re-operated patients at the start of the study.

Low concentrations of IL-6 indicates a complete absence of immune activation in first-operated [28], whereas in re-operated there was some degree of immunoreactivity (p = 0.001) preoperatively. This is also reflected in a slightly elevated hs-CRP values, but not significant (p = 0.553). Nevertheless, in patients undergoing reoperation we have not perceived any extensiveness of immune activation intraoperatively, after the reunion of the memory-pool cells with biocompatible materials. We believe that in this subpopulation of patients, scheduled for redo CABG, preoperative IL-6 measurement could distinguish patients with early infection from those with systemic inflammatory response syndrome but without infection, as it was reported by Sander et al. [29].

Observed postoperatively, immune response was even lower in patients with re-operation, in relation to the first operated subjects. The increase in IL-6 levels was almost the same in observed groups (p = 0.489) 6 hours after the surgery. Paradoxically, IL-6 had a faster downward trend towards the initial values within 24 hours in re-operated patients, although insignificant (p = 0.472). When observing the increase in hs-CRP levels, this raise was more slowly in Group 2 than in Group 1 (p = 0.248). Such inertia of the immune response in re-operated patients could be explained by the fact that these patients belong to an older age [10]. These changes are independent on blood transfusions [17], and indicate the depression of the immune response [4]. However, we have not found excessive increase of the inflammatory parameters in peripheral circulation patients during re-operation, and this observation is in orchestra with findings of Klein and co-workers [18]. In addition, other authors suggested that the reperfusion of heart and lungs rather than CPB itself is the main trigger for systemic inflammatory response. Moreover, blood stagnation can facilitate PMN adhesion and activation [7]. Riter and co-workers referred that PMN could be trapped in the coronary and the pulmonary vascular bed during cardiac arrest [30].

When we have analysed the clinical course immediately after the operation, we have found no difference in the number of revisions, length of stay on mechanical ventilation and incidence of atrial fibrillation in patients in the both groups. From the literature data it is well known that postoperative levels of C4d-CRP, which are the specific marker of the CRP-mediated complement activation, correlates with the incidence of postoperative arrhythmias occurring after coronary artery bypass surgery [31]. Lafey et al. reported that a strategy that improves biocompatible materials of the circuit reduces the incidence of complement activation, which reduces post-operative complications, especially in high-risk patients [15]. Furthermore, Edmunds and Stenach stated that contemporary biocompatible materials result in significant reduction of myocardial injury, blood loss, and the patient's cognitive sequels initiated by the CPB [4], while Car and Siverman concluded that inflammation and coagulation should perhaps be considered as the different facets of the host response to injury [32]. Elmistekawy et al. [16] have shown that cellular debris collected during surgery in the cell saver machine could change the amount of proinflammatory cytokines by washing and reinfusing red blood cells. Therefore, we believe that the degree of inflammation caused by the CPB could be attenuated with cell salvage procedure, which followed in this study.

Study limitations: this study was not randomised, controlled study with perfectly matched patients in two groups. This is prospective, observational investigation where control group and study group were chosen in consecutive manner, to compare biomarkers in uncomplicated and complicated open heart surgery.

In conclusion, our data demonstrates that the plasma levels of the inflammatory markers were not altered during repeated use of the CPB. IL-6 levels also remain essentially unchanged in blood after cell salvage procedures. Preoperative and early perioperative monitoring of biomarkers could help in identification of patients at risk from altered immune function prior to surgery. This small study was, however, observational in nature, and further investigations on large number of patients are needed.

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