

## Predictive Significance of Plasma Levels of Interleukin-6 and High-Sensitivity C-Reactive Protein in Atrial Fibrillation after Coronary Artery Bypass Surgery

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### ABSTRACT

**Background.** Postoperative atrial fibrillation (AF) plays a major role in the determination of hemodynamic deterioration and can be associated with cardiovascular events after coronary artery surgery. Elevated interleukin (IL)-6 and C-reactive protein (CRP) levels in patients with AF suggest a role of inflammation in the pathogenesis of AF. We conducted a study to investigate the correlation between postoperative AF and IL-6 and high-sensitivity CRP (hsCRP).

**Materials and Methods.** Forty-nine patients with a mean age of  $60.3 \pm 10.7$  years were enrolled in this study. Preoperative and postoperative first day blood samples were collected to assess the IL-6 and hsCRP levels. IL-6 levels were measured by enzyme-linked immunosorbent assay, and hsCRP was measured by rate turbidimetry method.

**Results.** Fourteen patients (28.5%) developed AF postoperatively. Patients who developed AF showed elevated serum concentrations of postoperative first day IL-6 ( $P < .001$ ), preoperative hsCRP ( $P < .005$ ), and postoperative first day hsCRP ( $P < 0.001$ ). Preoperative hsCRP levels ( $P < .002$ ) and postoperative first day IL-6 ( $P < .001$ ) and hsCRP ( $P < 0.001$ ) levels were associated with prolonged endotracheal intubation time. Prolonged intensive care unit stay showed significant correlations with elevated levels of preoperative hsCRP ( $P < 0.002$ ) and postoperative first day IL-6 ( $P < 0.001$ ) and hsCRP ( $P < 0.001$ ). There was also statistical significance between the AF+ and AF- groups regarding intensive care unit stay and endotracheal intubation times ( $P = .001$  and  $P = .001$ , respectively). Cut-off points for postoperative first day IL-6, preoperative hsCRP, and postoperative first day hsCRP were 46.4 pg/mL (sensitivity = 92.9% and specificity = 80%), 0.46 mg/L (sensitivity = 71% and specificity = 75%), and 17.9 mg/L (sensitivity = 92.9% and specificity = 78%), respectively.

**Conclusions.** Elevated IL-6 and hsCRP levels in patients with postoperative AF suggest inflammatory components have a role of in the pathogenesis of AF.

### INTRODUCTION

Open heart surgery with cardiopulmonary bypass (CPB) and cardioplegic arrest of the heart is known to cause inflammatory response, which can lead to end-organ dysfunction that may affect the postoperative course of the patients and may limit surgical success [Wan 1996; Gu 1998; Czerny 2000]. CPB induces complex changes in blood proteins and cells that culminate in the activation of diverse inflammatory and coagulation pathways [Rubens 2005]. The inflammatory response after conventional coronary artery bypass grafting (CABG) is primarily associated with low blood pressure, temperature changes, leukocytosis, and tissue edema [Cremer 1996; Taylor 1996]. The contribution of these factors to abnormalities of hemostasis, fibrinolysis, endothelium, and platelets has been described in patients with atrial fibrillation (AF). Such abnormalities may increase the risk of stroke and thromboembolism, which may lead to a prolonged hospital stay after coronary artery surgery for this common cardiac arrhythmia [Lip 1995; Gu 1998; Czerny 2000; Roldan 2003]. The reported incidence of postoperative AF ranges from 5% to 40% and is associated with significant morbidity and a considerable increase of in-hospital costs [Aranki 1996; Ducceschi 1999; Stamou 2000]. Although several studies have analyzed the risk factors for postoperative AF and its possible preventive strategies, the exact pathophysiology of this complication has not yet been clarified. Many investigators have shown that these changes are accompanied by an increased release of inflammatory mediators such as interleukin (IL)-6 and C-reactive protein (CRP). IL-6 is a multifunctional proinflammatory cytokine, which also plays an important role in ischemia-reperfusion injury [Sawa 1998; Czerny 2000; Gaudino 2003].

The aim of this study was to evaluate the correlation between the preoperative and postoperative levels of inflammatory markers IL-6 and high-sensitivity CRP (hsCRP) and the possible effect on postoperative AF and clinical outcomes of the patients after CABG.

Received October 20, 2006; accepted January 4, 2007.

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Table 1. Baseline Characteristics of the Patients\*

	AF+	AF-	P
Age, y	64.3 ± 6.6	58.8 ± 11.6	NS
Sex, male/female	2/12	5/30	NS
Current smoker, n	8/6	21/14	NS
Hypertension, n	3/11	11/24	NS
Diabetes mellitus, n	5/9	10/25	NS
Hypercholesterolemia, n	11/3	24/11	NS
Body mass index, kg/m <sup>2</sup>	28.0 ± 4.1	27.5 ± 3.1	NS
Statins, n	12/2	28/7	NS
Ace inhibitors, n	11/3	25/10	NS
Beta-blocker, n	14/14	35/35	NS
Left coronary disease, n	14/14	35/35	NS
Right coronary disease, n	6/8	23/12	NS
Circumflex coronary disease, n	9/5	23/12	NS
Inotropes, n	5/9	11/24	NS
Intensive care unit stay, d	2.5 ± 0.7	1.9 ± 0.4	.001
Endotracheal intubation time, h	14.5 ± 3.9	10.1 ± 3.7	.001
Total	14	35	49

\*AF indicates atrial fibrillation; NS, not significant.

## MATERIALS AND METHODS

A total of 49 consecutive patients were enrolled in the study. The study protocol was approved by the Hacettepe University Hospital ethics committee, and informed consent was obtained from each patient. Smoking, obesity, hypertension, duration of diabetes, preoperative myocardial infarction, and prior usage of medications were documented before the operation. We excluded patients with an ejection fraction below 40%, chronic pulmonary obstructive disease, severe systemic noncardiac disease, severe renal or liver impairment, infectious disease before the operation, malignancy, and those receiving hormone replacement therapy, oral anticoagulation, corticosteroid, or other immunosuppressive treatment. We also excluded patients with recent (<3 months) venous or systemic thromboembolism, stroke or acute coronary syndrome, inflammatory disease and/or surgery, and valvular heart disease. Cardiac medication, including beta-adrenergic blocking agents, calcium-channel blockers, and nitrates, was continued until the morning of surgery.

### Operative Technique and Anesthesia

The same general anesthetic drugs were used in all patients. Intravenous pentothal sodium (5 to 7 mg/kg) was administered for induction. Anesthesia was continued with sevoflurane or isoflurane. Vecuronium bromide (0.1 mg/kg) was used as the myorelaxant drug. Cefazolin sodium and gentamycin sulphate were administered in the preoperative period for all patients. Standard median sternotomy incision was used for the exposure of the heart. The internal mammary artery and saphenous

vein grafts were used for coronary anastomosis. In each group, routine operations were performed using a membrane oxygenator (Edwards Vital; Edwards Lifesciences, Irvine, CA, USA), a 3 mg/kg dose of heparin sodium, 2000 mL of Ringer's lactate priming, and a roller pump. Nasopharyngeal temperature was kept at 28°C. CPB was instituted via the ascending aorta and single 2-stage venous cannulation (maintained at 2.2–2.4 Lmin<sup>-1</sup> per m<sup>2</sup>). Following cross clamping of the aorta, myocardial protection was accomplished by 10 to 15 cc/kg antegrade intermittent cold blood cardioplegia through the aortic root and topical ice slush, continued every 20 minutes. Heparin was neutralized with protamine hydrochlorur (Protamin 1000; Roche, Istanbul, Turkey).

### Samples Collection and Laboratory Assays

Venopuncture was performed in the morning on the patients, all of whom had been fasting for >12 hours. Blood samples were drawn atraumatically and collected into commercially available tubes containing 0.129 M sodium citrate, which contains 9 parts blood to 1 part trisodium citrate (Becton Dickinson vacutainer systems; Plymouth, UK). Platelet-poor plasma fractions were obtained by centrifugation at 4°C for 20 minutes at 4000g, and soluble IL-6 was measured by an enzyme-linked immunosorbent assay Biosource immunoassay kit (Camarillo, CA, USA). hsCRP levels were assayed in serum samples by rate turbidimetry (Image 800 Immunochemistry System CRPH; Beckman Coulter, Brea, CA, USA) and following the manufacturer's instructions.

### Postoperative Arrhythmia Evaluation and Management

Heart rate and rhythm were continuously monitored for the first 36 to 48 hours, and daily 12-lead electrocardiograms were performed from the first postoperative day until discharge and in instances of clinical suspicion of arrhythmia in the postoperative period. AF was the only documented rhythm abnormality in our study, and amiodarone was able to convert AF to normal sinus rhythm in all cases. All patients had a normal recovery. There was no in-hospital death or perioperative myocardial infarction. Table 1 presents the clinical characteristics of the studied population.

Table 2. Preoperative and Postoperative First Day Serum Interleukin (IL)-6 and High-Sensitivity C-Reactive Protein (hsCRP) Levels and Association with Atrial Fibrillation (AF)\*

	AF+	AF-	P
Preoperative IL-6	7.4 ± 3.6	6.2 ± 2.9	.240
Postoperative first day IL-6	100.7 ± 65.8	36.9 ± 15.9	<.001
Preoperative hsCRP	0.6 ± 0.2	0.3 ± 0.2	.003
Postoperative first day hsCRP	22.4 ± 4.1	16.9 ± 1.9	<.001
Total	14	35	49

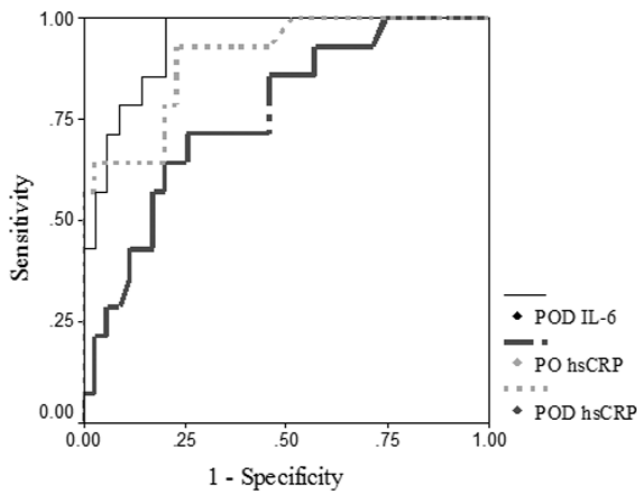


Figure 1. Plot of receiver operating characteristic curves for postoperative first day (POD) interleukin-6 and preoperative (PO) and postoperative first day high-sensitivity C-reactive protein.

### Statistical Analysis

Data were expressed as means  $\pm$  the standard deviation. A 2-tailed  $P$  value less than .05 was considered statistically significant. Correlations between the measured laboratory indices and clinical and demographic data were performed using the Student  $t$  test. Chi-square test was used to compare quantitative data between the groups. Cut-off point analysis using receiver operating characteristic (ROC) curves was applied to evaluate the levels of these markers by which we achieved the best predictive ability regarding the inflammatory status of the AF patients. All statistical analyses were performed with the Statistical Package for Social Sciences (SPSS 11.5 for Windows; SPSS, Chicago, IL, USA).

### RESULTS

A total of 14 patients (28.5%) developed AF postoperatively. Patients with AF showed greater serum concentrations of postoperative first day IL-6 ( $100.7 \pm 65.8$  versus  $36.9 \pm 15.9$ ,  $P < .001$ ), preoperative hsCRP ( $0.6 \pm 0.2$  versus  $0.3 \pm 0.2$ ,  $P < .005$ ), and postoperative first day hsCRP ( $22.4 \pm 4.1$  versus  $16.9 \pm 1.9$ ,  $P < .001$ ). However, no statistical significance was observed between preoperative IL-6 levels and AF ( $7.4 \pm 3.6$  versus  $6.2 \pm 2.9$ ,  $P = .273$ ) (Table 2, Figure 1).

Preoperative hsCRP levels and postoperative first day IL-6 and hsCRP levels were associated with prolonged endotracheal intubation time ( $P < .002$ ,  $P < .001$ , and  $P < .001$ , respectively). Similarly, prolonged stay in the intensive care unit (ICU) was associated with elevated levels of preoperative hsCRP ( $P < .002$ ), postoperative first day IL-6 ( $P < .001$ ), and hsCRP ( $P < .001$ ) levels. There was no statistical significance for preoperative IL-6 levels with endotracheal intubation time ( $P = .480$ ) and ICU stay ( $P = .916$ ). ICU stay ( $P = .001$ ) and endotracheal intubation time ( $P = .001$ ) also showed statistical significance with AF.

There was statistically significant usage of inotropic agents for myocardial support after CPB between the postoperative first day IL-6, preoperative hsCRP, and postoperative first day hsCRP levels ( $P < .001$ ,  $P = .003$ ,  $P < .001$ , respectively) (Table 3). There was no statistical significance for inotropes between the AF+ and AF- groups ( $P = .778$ ).

The number of bypass grafts ( $P = .239$ ), length of aortic cross-clamp time ( $P = .133$ ), length of CPB time ( $P = .077$ ), number of statins ( $P = .649$ ), ace inhibitors ( $P = .618$ ), angiotensin-receptor blockers ( $P = .682$ ), and the occurrence of right coronary artery disease ( $P = .147$ ) did not show any statistical significance with respect to AF (Table 1).

The optimal cut-off points for postoperative first day IL-6, preoperative hsCRP, and postoperative first day hsCRP were 46.4 pg/mL (sensitivity = 92.9% and specificity = 80%), 0.46 mg/L (sensitivity = 71% and specificity = 75%), and 17.9 mg/L (sensitivity = 92.9% and specificity = 78%), respectively. As seen in Figure 2, postoperative first day IL-6 had the largest area under the ROC curves ( $P < .001$ ).

### DISCUSSION

This prospective, randomized study suggests that inflammatory markers IL-6 and hsCRP, which were measured preoperatively and postoperatively, were important predictors of postoperative AF in patients who underwent coronary artery surgery. CABG is one of the most frequent surgical procedures performed. The technical and technological improvements that have occurred in the last decade have rendered this operation safer, reducing to acceptable levels the surgical risk even in very old and sick patients [Gaudino 2002]. However, postoperative AF still has frequent adverse events after CABG procedures and represents one of the most common complications of surgical myocardial revascularization and negatively affects the early clinical outcomes. Although in the last 2 decades several studies have analyzed the risk factors for postoperative AF and its possible preventive strategies, the exact pathophysiology of this complication has not yet been clarified [Gaudino 2002, 2003; Conway 2004].

Many preoperative and postoperative factors have been suggested to increase the incidence of postoperative AF. Age, sex, hypertension, withdrawal of beta-blocker drug therapy, right coronary artery stenosis, respiratory complications, need

Table 3. Inotrope Usage and Association with Inflammatory Markers\*

	Inotropes Used	No Inotropes Used	$P$
Preoperative IL-6	$6.6 \pm 2.5$	$6.4 \pm 3.5$	.482
Postoperative first day IL-6	$78.8 \pm 70.9$	$43.6 \pm 23.0$	.028
Preoperative hsCRP	$0.6 \pm 0.2$	$0.3 \pm 0.1$	<.001
Postoperative first day hsCRP	$20.3 \pm 4.3$	$17.6 \pm 3.0$	.010
Total	16	33	49

\*IL indicates interleukin; hsCRP, high-sensitivity C-reactive protein.

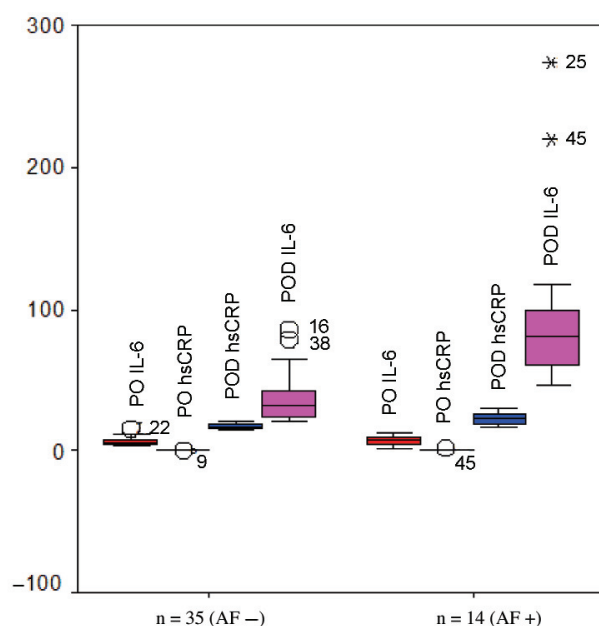


Figure 2. Preoperative and postoperative first day interleukin-6 and high-sensitivity C-reactive protein levels of atrial fibrillation-negative and atrial fibrillation-positive groups. POD indicates postoperative first day; PO, preoperative; IL-6, interleukin 6; hsCRP, high-sensitivity C-reactive protein; AF-, atrial fibrillation-negative group; AF+, atrial fibrillation-positive group.

for intra-aortic balloon support, and excessive bleeding have all been associated with AF in published reports [Crosby 1990; Mendes 1995; Aranki 1996; Moulton 1996; Almassi 1997; Daoud 1997; Gaudino 2003]. In the present study, there was no excessive bleeding and no patient needed intra-aortic balloon support. Additionally, no statistical significance was found between AF occurrence and age, sex, smoking, hypertension, diabetes mellitus, hyperlipidemia, right coronary stenosis, beta-blocking agents, or lipid-lowering drugs (Table 1). The large number and the heterogeneity of these factors is probably the best testimonial of the poor understanding of the mechanisms and pathophysiology of this arrhythmia [Gaudino 2003].

A close relationship between atherosclerosis and inflammation has been reported, and the usefulness of hsCRP as well as inflammatory cytokines in diagnosing and evaluating atherosclerosis has been recognized [Davies 1972; Chamoro 2004; Sata 2004]. On the other hand, little attention has been paid to the relationship between AF and inflammation. It has been thought that most cases of this arrhythmia were caused by fibrosis or degeneration of the atrial muscles, sinus node, conduction pathway, underlying heart disease, or aging [Davies 1972; Sata 2004]. Several reports have suggested that inflammation participates in the pathogenesis of AF [Davies 1972; Frustaci 1997; Chung 2001; Sata 2004]. Frustaci et al found in myocardial biopsies from 12 patients with lone AF that the prevalence of myocarditis was as high as 66% [Frustaci 1997].

Furthermore, Chung et al [2001] suggested that hsCRP is a marker of an inflammatory state and there is an association between AF and CRP levels that is independent of hypertension, structural heart disease, or previous stroke or embolism. They found that hsCRP levels were significantly higher in patients with paroxysmal and chronic AF group than in normal controls, and that the level was higher in the chronic AF than in the paroxysmal AF group [Chung 2001]. Thus, they showed that inflammation is involved in the onset of AF. However, they stated that whether inflammation is a consequence or a cause of AF remained unknown. Our study suggests similar results that show there is a strong correlation between elevated hsCRP and IL-6, which act as markers reflecting an inflammatory state that promotes AF.

IL-6 is an established index of inflammation, which is a circulating cytokine produced by monocytes, macrophages, T-lymphocytes, and endothelial cells. IL-6 can induce a pro-thrombotic state by increasing expression of fibrinogen and several other factors, as well as by activating endothelial cells and increasing platelet production [Kerr 2001; Rodan 2003]. In the present study, our AF patients had higher levels of postoperative first day IL-6, suggesting that it was probably related to the inflammation. Inflammation seems to be the cause of AF rather than the consequence.

The economic and clinical implications of postoperative AF are considerable. Clinically, AF plays a major role in the determination of postoperative neurological events [Hogue 1999] and can be associated with hemodynamic deterioration. Even when AF does not lead to further clinical events, its occurrence lengthens the hospitalization of CABG patients by a mean of 4.9 days, which results in additional cost [Aranki 1996; Gaudino 2003]. Additionally, in our patients, ICU stay and intubation times of the AF+ group were significantly longer than patients in the AF- group. IL-6 and hsCRP play a predictive role for a patient's postoperative course, including length of ICU stay and endotracheal intubation time, which in turn have important economic implications. In view of these considerations, the possibility of predicting the hospital course of a patient by using simple, relatively inexpensive, and readily available markers such as IL-6 and hsCRP would be of obvious interest.

Our findings of elevated hsCRP and IL-6 levels in patients with postoperative AF suggest a role of inflammation in the pathogenesis of this arrhythmia. It has been shown that inflammatory states are not only associated with AF [Bruins 1997; Chung 2001; Gaudino 2003; Roldan 2003; Dernellis 2004; Psychari 2005], but also predict which patients are at risk for future development of this arrhythmia [Aviles 2003; Psychari 2005]. In our series, correlation could be established between the preoperative hsCRP, postoperative hsCRP, and postoperative IL-6 values and the postoperative clinical course: the type and incidence of postoperative AF and complications were significantly different in the high and low groups.

The main limitation of our study was the relatively small number of AF patients. A larger cohort would be desirable to improve the prognostic power of the studied inflammatory markers. In conclusion, our data provide substantial

evidence that elevated postoperative first day hsCRP and IL-6 levels can be considered markers of increased postoperative risk of AF. Among the studied inflammatory markers, postoperative first day IL-6 and hsCRP were the significant predictors for postoperative AF. These findings may have potential implications in better understanding the mechanisms of AF and may offer additional treatment approaches in the future.

## ACKNOWLEDGMENTS

We would like to thank Dr. Yahsi Yazicioglu and Dr. Elif Durukan for their statistical analysis and many helpful suggestions.

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