

Do preoperative C-reactive protein and mean platelet volume levels predict development of postoperative atrial fibrillation in patients undergoing isolated coronary artery bypass grafting?

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Abstract

Introduction: Atrial fibrillation (AF) after coronary artery bypass grafting (CABG) operation is associated with increased risk of prolonged hospitalisation, health expenses and adverse clinical outcomes.

Aim: To investigate the relationship of atrial fibrillation after an isolated coronary artery bypass operation with levels of mean platelet volume and C-reactive protein.

Material and methods: Among 1240 patients who underwent operations for isolated coronary artery bypass grafting with cardiopulmonary bypass between January 2007 and May 2014, 1138 (91.8%) patients with preoperative normal sinus rhythm were enrolled in the study. Patients were assigned to group 1 ($n = 294$) comprising patients who developed atrial fibrillation in the first 72 postoperative hours or group 2 ($n = 844$) comprising patients who remained in normal sinus rhythm in the postoperative period.

Results: The incidence of postoperative atrial fibrillation was 25.8%. The preoperative mean platelet volume (fl) and C-reactive protein (mg/dl) values in group 1 were 9.1 ± 0.5 and 1.1 ± 0.9 respectively, while these values were 8.3 ± 0.6 and 0.5 ± 0.3 respectively in group 2, which was statistically significant ($p = 0.0001$). Length of stay in the hospital ($p = 0.0001$) was higher in group 1. The values of mean platelet volume (fl) and mean C-reactive protein (mg/dl) were 9.9 ± 0.9 and 30.9 ± 3.4 respectively in group 1, while the values of mean platelet volume (fl) and mean C-reactive protein (mg/dl) were 8.8 ± 0.6 and 24.9 ± 4.8 respectively in group 2 ($p = 0.0001$ for mean platelet volume, $p = 0.0001$ for C-reactive protein). The difference between the groups was statistically significant in terms of postoperative neurologic events ($p = 0.0001$) and hospital mortality ($p = 0.001$). Increased C-reactive protein and mean platelet volume levels were found to be independent predictors of postoperative atrial fibrillation.

Conclusions: In our study, elevated preoperative mean platelet volume and C-reactive protein levels were associated with development of postoperative atrial fibrillation.

Key words: coronary artery bypass grafting, mean platelet volume, atrial fibrillation.

Introduction

Despite advances in surgical and anesthetic management of coronary artery bypass grafting (CABG) operation and myocardial protection, a remarkable reduction in the incidence of postoperative cardiac arrhythmias could not be established. In the literature, the incidence of atrial fibrillation (AF) following CABG operations was found to be 30% with extended meta-analysis [1]. Even though well tolerated by the vast majority of patients, AF following cardiac surgery is accepted as an important risk

factor which increases morbidity and mortality, length of hospital stay and health expenses by causing hemodynamic disorder, minor and major thromboembolic events and ventricular arrhythmias [2, 3].

The pathophysiology of AF is complex and not well understood. A correlation between AF and abnormal prothrombotic plasma markers was shown in various studies [4]. Apart from the proven classical risk factors (age, heart failure, hypertension, diabetes, valvular heart disease, etc), new risk factors are recently speculated re-

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garding particularly the role of inflammation in pathophysiology of AF [5, 6]. One of these risk factors is C-reactive protein (CRP), which is an acute phase reactant. The serum CRP level which can be measured by simple methods is a good parameter of inflammatory activation [7]. Atrial fibrillation was frequently observed in myocarditis and pericarditis, which is closely associated with inflammation [8].

One of the recently defined risk factors is mean platelet volume (MPV). Thrombocytes, which used to be accepted as rather ineffective intracellular fragments of hemostasis in the past, are now accepted to play important roles in inflammatory processes. Mean platelet volume is a parameter that is routinely measured in complete blood count devices, and which is an important marker of thrombocyte activation [9]. Although there have been a few studies in which the relationship between MPV and cardiac arrhythmia was observed, these studies particularly focused on the issue of AF [10, 11]. Mean platelet volume levels were found to be high in patients with paroxysmal AF [10].

Aim

In this study, we aimed to investigate the relationship between atrial fibrillation in the early postoperative period (first 72 h) following isolated CABG operation and levels of MPV and CRP in the preoperative and early postoperative periods.

Material and methods

In the study, the medical records of 1240 patients who underwent isolated CABG for coronary artery disease performed by the same surgical team in the Cardiovascular Surgery Clinic of Kocaeli Acibadem Hospital between January 2007 and May 2014 were investigated retrospectively. One thousand one hundred and thirty-eight (91.8%) patients with preoperative normal sinus rhythm who underwent isolated CABG with cardiopulmonary bypass (CPB) were enrolled in the study, while 102 (8.2%) patients were excluded. The number of female patients was 233 (20.5%) and the average age was 60.1 ± 8.2 years (median: 61 years, ranging: 32 to 75 years). Two different populations were created: group 1 ($n = 294$), including patients who developed AF in the first 72 postoperative hours; and group 2 ($n = 844$), including patients who remained in normal sinus rhythm in the postoperative period.

The patients who had formerly known peripheral arterial disease, preoperative AF rhythm, valvular cardiac disease, congenital cardiac disease, left ventricular systolic function disorder (left ventricular ejection fraction ≤ 30%), cerebrovascular disease, advanced age (> 75 years), renal impairment (serum creatinine > 2 mg/dl), chronic obstructive pulmonary disease, malignancy, endocrinologic disorders (hypothyroidism, hyperthyroid-

ism), systemic inflammatory diseases, hematologic diseases, low hemoglobin (Hgb) levels (≤ 10 g/dl); patients who are severely overweight (body mass index > 30 kg/m²), patients with a left atrium diameter > 4.5 cm in echocardiography, patients with acute infections, atrial and ventricular arrhythmia, who had undergone emergency operations, patients who were reoperated on due to hemodynamic instability or bleeding, patients who required intraaortic balloon pump (IABP), patients who died or had a neurologic event in the first 72 postoperative hours, patients who underwent beating heart or redo CABG were excluded from the study.

Fasting venous blood samples on admission were obtained from all patients to determine their plasma fasting glucose, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride, serum creatinine, fasting glucose, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and lipid profiles, which were measured using an autoanalyzer (Roche Diagnostics Modular Systems, Japan). Fasting blood samples of the patients were collected preoperatively and on the first postoperative day for complete blood count (CBC) and CRP analysis. A total of 2–3 ml of venous blood was collected in an EDTA-K2 tube (BD Vacutainer, Becton, Dickinson and Company, Plymouth, UK), and MPV and platelet counts were analyzed using the Advia 2120i Hematology System (Siemens, Germany) within 1 h of sample collection. Timing of MPV measurement must be completed within 120 min to avoid MPV increase caused by EDTA. Levels of CRP were determined using immune-enhanced nephelometry.

The demographic and clinical data of the patients were obtained using the software system of the hospital for records and archives to investigate the patient files, epicrisis, operation notes and laboratory results. Age, gender, smoking history, diabetes, hypertension, hyperlipidemia, left ventricular ejection fraction (LVEF), left atrium diameter, preoperative and postoperative laboratory parameters (hemoglobin, hematocrit, thrombocyte count, CRP, MPV), operation information, the number of grafts used, duration of cardiopulmonary bypass and aortic cross clamp, amount of blood products used and length of stay in the intensive care unit and hospital were recorded. The preoperative basal heart rates of the patients were obtained by analysing 12-lead electrocardiography (ECG) records. Hypertension was accepted as a blood pressure ≥ 140/90 mm Hg or use of antihypertensive drugs; smoking was accepted positive if the patient had not quitted smoking for the last one year. Diabetes was accepted as fasting blood glucose ≥ 126 mg/dl or use of antidiabetic drugs. Hyperlipidemia was accepted as total cholesterol > 220 mg/dl and LDL cholesterol > 130 mg/dl or use of antihyperlipidemic drugs.

The patients were followed up by continuous ECG monitoring during the entire length of stay in the intensive care unit (ICU) and the first 48 h of stay in the inpa-

tient room. If there was no contraindication, 50 mg/day of metoprolol was started orally in all patients following the first postoperative day. The patients were followed up by rhythm ECG once a day, and pulse and arterial blood pressure measurements at maximum intervals of 4 h in the inpatient room. Detection of cardiac arrhythmia or palpitation as a complaint of the patient was managed with standard 12 derivation ECG recording. Diagnosis of AF was made with ECG recording. If required to control heart rate in treatment of AF, intravenous (IV) metoprolol (5–10 mg) was administered. To all patients who required it, a bolus intravenous dose of 300 mg amiodarone was given in 1 hour's time with a maintenance dose of intravenous 900 mg amiodarone continued in the next 24 h followed by 200 mg amiodarone orally three times daily. During the whole AF period, low molecular weight heparin was given based on patient weight (enoxaparin (0.1 mg/kg) twice daily). Patients for whom normal cardiac sinus rhythm could not be established were discharged with oral warfarin therapy.

This study complied with the Declaration of Helsinki and was carried out following approval of the Ethics Committee for Clinical Trials of the Medical Faculty of Kocaeli University.

Operative technique

All of the patients were operated on with median sternotomy under general anesthesia and cardiopulmonary bypass (CPB) with aortic and venous cannulations following systemic heparin administration (300 IU/kg). Activated clotting time (ACT) was maintained over 480 s during the operations. Standard CPB circuit and surgical management were used. Antegrade hypothermic and hyperkalemic blood cardioplegia was applied to all patients. Surgery was performed under moderate systemic hypothermia (30°C). Cardiopulmonary bypass flow was maintained at 2.2–2.5 l/min/m², mean perfusion pressure was maintained between 50 and 80 mm Hg, and hematocrit level was maintained at 20% to 25% during CPB. For the coronary bypass operations, the left internal mammary artery (LIMA) was preferred for the arterial graft for left anterior descending artery (LAD) revascularization, whereas saphenous venous grafts were used for the other bypasses. Distal anastomoses were done during the aortic cross clamp period and proximal anastomoses were done on the beating heart onto the ascending aorta using a lateral clamp.

All of the patients were transferred to the intensive care unit intubated. They were extubated following onset of spontaneous breathing and normalization of orientation and cooperation if the hemodynamic and respiratory functions were appropriate. Meanwhile, the respiratory functions were frequently evaluated by spirometry and blood gas analysis. Electrolyte imbalances, arterial oxygen and lactic acid levels were followed up closely with

arterial blood gas analysis. Postoperative cardiac arrhythmias were detected with daily ECG recording and telemetric ECG monitorization. Potassium replacement or diuretic therapy was given to maintain serum potassium levels between 3.8 and 4.5 mEq/l. Drugs such as statins or β -blockers, which the patients had been using preoperatively, were also continued in the postoperative period depending on the condition of the patients.

Statistical analysis

Statistical analysis was performed using the SPSS software version 12.0 (SPSS Inc, Chicago, IL, USA). Among the data measured, the ones showing normal distribution were presented as mean \pm standard deviation, and the ones not showing normal distribution were presented as median (minimum–maximum). The data obtained by counting were shown as the percentage (%). Among the data measured, the normality of distribution was evaluated by histogram or Kolmogorov-Smirnov test, and the homogeneity of distribution was evaluated by Levene's test for equality of variance. Among the data measured, the difference between the groups was evaluated by Student's *t* test in the case of a normal and homogeneous distribution and by the Mann-Whitney *U* test in the case of a distribution which is not normal and homogeneous. The Spearman correlation test was used to detect the relation between all data. Among the data obtained by counting, the differences between the groups were evaluated by the parametric or non-parametric Pearson χ^2 test or Fisher's exact test depending on the distribution being parametric or not. Forward stepwise multivariate logistic regression models were created to identify the independent predictors of postoperative AF. Variables with a *p* value less than 0.10 in univariate analyses were included in the multivariate model. As preoperative and postoperative laboratory parameters were highly correlated, preoperative and postoperative parameters were entered to the multivariable regression model separately. The sensitivity and specificity of the independent risk factors to predict postoperative atrial fibrillation were determined by receiver operating curve (ROC) analysis. For a *p* value less than 0.05 among the groups, the difference was accepted as significant.

Results

The demographic characteristics and clinical features of patients undergoing isolated CABG who developed AF in the first 72 postoperative hours (group 1) and who did not develop AF (group 2) are summarized in Table I. There were no differences between the groups regarding demographic and clinical features.

The preoperative MPV (fl) and average CRP (mg/dl) values in group 1 were 9.03 \pm 0.74 (median: 8.90, range: 7.60–12.60) and 1.03 \pm 0.83 (median: 0.76, range: 0.23–4.94), respectively. The same values in group 2 were 8.32

Table I. Clinical and demographic properties of the patients

Characteristics	Group 1 with atrial fibrillation (n = 294)	Group 2 without atrial fibrillation (n = 844)	P-value
Age	60.5 ±7.8 (median: 62, range: 32–75)	60.0 ±8.4 (median: 60, range: 36–75)	0.21**
Male	227 (25.1%)	678 (74.9%)	0.25*
Female	67 (28.8%)	166 (71.2%)	0.25*
Hypertension	171 (58.2%)	515 (61.0%)	0.39*
Diabetes mellitus	95 (32.3%)	316 (37.4%)	0.12*
Smoking	117 (39.8%)	340 (40.3%)	0.88*
Hyperlipidemia	154 (52.4%)	444 (52.6%)	0.95*
Preoperative heart rate [bpm]	66.3 ±6.0 (median: 66.5, range: 54–85)	66.2 ±7.8 (median: 65, range: 52–89)	0.41**
Left ventricle ejection fraction (%)	55.1 ±8.5 (median: 55, range: 34–72)	55.9 ±8.8 (median: 56, range: 30–72)	0.17**
Left atrium diameter [cm]	3.76 ±0.17 (median: 3.77, range: 3.32–4.33)	3.75 ±0.19 (median: 3.76, range: 3.37–4.27)	0.33**

*Pearson χ^2 test or Fisher's exact test, **Mann-Whitney U test.

±0.60 (median: 8.25, range: 7.20–11.30) and 0.54 ±0.29 (median: 0.48, range: 0.12–4.97), respectively. When the two groups were compared, the difference was statistically significant ($p = 0.0001$ for MPV, $p = 0.0001$ for CRP). In the preoperative period, the average hemoglobin (Hgb) (g/dl) and hematocrit (Hct) (%) levels in group 1 were 13.3 ±1.4 (median: 13.6, range: 10.4–16.5) and 40.7 ±4.0 (median: 41.6, range: 30.3–48.9) respectively, while these values in group 2 were 13.4 ±1.5 (median: 13.8, range: 10.2–16.7) and 40.6 ±4.1 (median: 41.2, range: 30.5–49.8) respectively. There was no statistically significant difference between the groups ($p = 0.56$ for Hct, $p = 0.46$ for Hgb). Preoperative thrombocyte counts were not significantly difference between group 1 and group 2; 262 ±59 (median: 254, range: 147–443) × 10³/ml vs. 266 ±62 (median: 256.5, range: 121–452) × 10³/ml ($p = 0.39$). Preoperative average creatinine levels (mg/dl) in group 1 and group 2 were 0.74 ±0.34 (median: 0.66, range: 0.36–1.94) and 0.72 ±0.32 (median: 0.62, range:

0.26–1.94) respectively, for which the difference was not statistically significant ($p = 0.51$).

The mean average number of grafts used in group 1 patients who developed AF and in group 2 patients who did not develop AF were 3.39 ±0.92 (median: 3, range: 1–6) and 3.28 ±0.97 (median: 3, range: 1–7) respectively, which was not statistically significantly different between the groups ($p = 0.10$). Among the patients, 264 (89.8%) of the patients in group 1 and 730 (86.5%) of the patients in group 2 underwent a bypass to the right coronary artery (RCA), which did not show a statistically significant difference between the groups ($p = 0.14$).

The time of occurrence of AF was in the first 8 postoperative hours in 67 (22.8%) patients, between the 9th and 24th h in 84 (28.6%) patients, and between the 25th and 72nd h in 143 (48.6%) patients.

The intraoperative and postoperative data of the patients are summarized in Table II. There were no differences in terms of aortic cross clamp time, total CPB time,

Table II. Intraoperative and postoperative data of the patients

Characteristics	Group 1 with atrial fibrillation (n = 294)	Group 2 without atrial fibrillation (n = 844)	P-value
Aortic cross clamp time [min]	52.8 ±12.1 (median: 53, range: 23–82)	51.5 ±12.8 (median: 51, range: 18–91)	0.18**
Cardiopulmonary bypass time [min]	83.9 ±15.3 (median: 85.5, range: 45–123)	82.6 ±16.2 (median: 85, range: 42–126)	0.45**
Use of blood products	109 (37.1%)	316 (37.2%)	0.97*
Amount of drainage [ml]	358 ±177 (median: 300, range: 150–1250)	340 ±151 (median: 300, range: 150–1200)	0.12**
Intubation time [h]	6.0 ±2.1 (median: 6, range: 3–18)	5.8 ±1.9 (median: 6, range: 3–22)	0.13**
Stay in the intensive care unit [h]	23.3 ±9.9 (median: 21, range: 17–86)	22.3 ±8.6 (median: 21, range: 17–88)	0.83**

*Pearson χ^2 test or Fisher's exact test, **Mann-Whitney U test.

amount of drainage, amount of blood products used, duration of intubation and stay in the intensive care unit ($p > 0.05$). Twenty-four (8.2%) patients in group 1 and 48 (5.7%) patients in group 2 required inotropic support in the postoperative period ($p = 0.13$).

The first postoperative day MPV (fl) levels were 9.9 ± 0.9 (median: 9.8, range: 7.9–13.7) in group 1 and 8.8 ± 0.6 (median: 8.7, range: 7.5–11.4) in group 2 ($p = 0.0001$). The first postoperative day CRP (mg/dl) levels were 30.9 ± 3.4 (median: 31.2, range: 7.5–40.1) in group 1 and 24.9 ± 4.8 (median: 25.1, range: 12.2–37.1) in group 2 ($p = 0.0001$). The first postoperative day Hct (mg/dl) levels were 28.7 ± 3.2 (median: 28.1, range: 24.3–39.0) in group 1 and 29.1 ± 3.1 (median: 28.6, range: 24.3–39.3) in group 2 ($p = 0.052$). The first postoperative day Hgb (mg/dl) levels were 9.1 ± 1.2 (median: 8.9, range: 7.4–12.7) in group 1 and 9.2 ± 1.1 (median: 9.0, range: 7.4–13.1) in group 2 ($p = 0.085$).

The neurologic event rate (transient ischemic event, speech disorder, hemiplegia or hemiparesia) within the first 72 h postoperatively was significantly higher in group 1 compared to group 2 (13 (4.4%) patients vs. 6 (0.7%) patients; $p = 0.0001$). Likewise, in-hospital mortality following the first 72 postoperative hours occurred in 8 (2.7%) patients in group 1 and in 3 (0.4%) patients in group 2, which showed a statistically highly significant difference between the groups ($p = 0.001$).

In this study, which included a total of 1138 patients who were evaluated retrospectively and in which AF occurred in 294 (25.8%) patients in the first 72 postoper-

ative hours, 267 (90.8%) patients who developed AF returned to normal sinus rhythm with amiodarone therapy, but 9 (3.1%) patients were discharged following conversion to sinus rhythm with electrical cardioversion. Eighteen (6.1%) patients, for whom appropriate rate control could not be established, were discharged with AF rhythm and oral anticoagulant (warfarin sodium) therapy.

The mean durations of stay in the hospital (days) were 6.7 ± 1.5 (median: 7, range: 5–19) in group 1 with AF and 5.3 ± 1.1 (median: 5, range: 5–18) in group 2 without AF. There was a statistically significant difference in terms of stay in the hospital between the groups ($p = 0.0001$).

Univariate and multivariate regression analyses, by which the possible predictors of postoperative atrial fibrillation in the study population were detected, are shown in Table III. In univariate regression analysis, increased duration of cardiopulmonary bypass duration and aortic cross clamp time, increased preoperative and early postoperative MPV and CRP levels were associated with postoperative AF. In multivariate regression analysis, only increased preoperative MPV (OR = 3.51, 95% CI: 2.64–4.69, $p = 0.0001$) and CRP (OR = 5.61, 95% CI: 3.41–9.24, $p = 0.007$) levels and early postoperative MPV (OR = 5.77, 95% CI: 4.21–7.91, $p = 0.0001$) and CRP (OR = 1.23, 95% CI: 1.17–1.30, $p = 0.0001$) levels remained as independent predictors of postoperative AF.

In multivariate logistic regression analysis, the preoperative and postoperative MPV and CRP levels to predict AF were determined by ROC curve analysis (Fig-

Table III. Univariate and multivariate regression analysis for the possible predictors of postoperative atrial fibrillation in the study population

Variables	Unadjusted OR (95% CI)	P-value	Adjusted OR (95% CI)*	P-value
Age, 1-SD increase	1.01 (0.99–1.02)	0.34	–	–
Gender	0.83 (0.60–1.14)	0.25	–	–
Hypertension	0.89 (0.68–1.16)	0.39	–	–
Diabetes mellitus	0.80 (0.60–1.06)	0.12	–	–
Hyperlipidemia	0.99 (0.76–1.29)	0.95	–	–
Smoking	0.98 (0.75–1.29)	0.88	–	–
Left ventricular EF, 1 – SD decrease	0.99 (0.98–1.01)	0.19	–	–
Left atrial diameter, 1 – SD increase	1.27 (0.62–2.59)	0.51	–	–
CPB duration, 1 – SD increase	1.01 (0.99–1.03)	0.20	–	–
Aortic cross clamp time, 1 – SD increase	1.01 (1.00–1.02)	0.14	–	–
Use of blood products	0.99 (0.76–1.31)	0.97	–	–
Preoperative hemoglobin, 1 – SD decrease	0.96 (0.88–1.06)	0.41	–	–
Preoperative creatinine 1 – SD increase	1.19 (0.79–1.80)	0.40	–	–
Preoperative MPV, 1 – SD increase	5.33 (4.10–6.93)	0.0001	3.51 (2.64–4.69)	0.0001
Preoperative CRP, 1 – SD increase	14.46 (9.29–22.50)	0.0001	5.61 (3.41–9.24)	0.007
Postoperative MPV, 1 – SD increase	9.28 (6.76–12.05)	0.0001	5.77 (4.21–7.91)	0.0001
Postoperative CRP, 1 – SD increase	1.41 (1.35–1.48)	0.0001	1.23 (1.17–1.30)	0.0001

EF – ejection fraction, CPB – cardiopulmonary bypass, CRP – C-reactive protein, MPV – mean platelet volume, SD – standard deviation, *Preoperative and postoperative parameters were entered to the multivariable regression model separately in order to prevent multicollinearity.

ures 1, 2). Cut-off levels for CRP and MPV were 0.58 mg/dl and 8.65 fl respectively. Area under the curve values for CRP and MPV were 0.77 (95% CI: 0.72–0.80, $p = 0.0001$) and 0.78 (95% CI: 0.75–0.81, $p = 0.0001$) respectively. The sensitivity and specificity of the preoperative CRP cut-off value were 70.1% and 68.2% respectively. The sensitivity and specificity of the preoperative MPV cut-off value were 74.1% and 68.4% respectively. The postoperative first day CRP and MPV levels to predict postoperative AF were determined by ROC curve analysis (Figure 2). Cut-off levels for CRP and MPV were 28.45 mg/dl and 9.25 fl respectively. Area under the curve values for postoperative CRP and MPV were 0.83 and 0.88 respectively (95% CI for postoperative CRP: 0.81–0.86, $p = 0.0001$, 95% CI for postoperative MPV: 0.85–0.91, $p = 0.0001$). The sensitivity and specificity of the postoperative CRP cut-off value were 75.2% and 74.6% respectively. The sensitivity and specificity of the preoperative MPV cut-off value were 81.6% and 72.2% respectively.

Discussion

Our results suggested that elevated levels of MPV and CRP were associated with the development of postoperative atrial fibrillation. Elevated MPV and CRP levels in patients with atrial fibrillation support the theory that inflammation may play a role in pathogenesis of this arrhythmia. Postoperative AF is a complex process which is associated with multiple risk factors. The most reliable among these are advanced age, history of AF, increased left atrium diameter, low LVEF, chronic obstructive pul-

monary disease, chronic kidney failure, diabetes mellitus, obesity and valvular heart disease [12, 13]. Exclusion of patients with risk factors in our study may enable us to investigate other risk factors. On the other hand, the absence of a significant correlation between AF and risk factors known to effect the development of AF such as diabetes mellitus, hypertension, hyperlipidemia, history of smoking and low hemoglobin levels strengthens our thesis.

In our study, we found that the measured levels of preoperative and postoperative MPV and CRP were significantly higher in group 1 than group 2. Exclusion of patients with risk factors which may increase levels of MPV and CRP such as advanced age, low hemoglobin and hematocrit levels, infection, obesity, low LVEF (< 30%), hematologic disorders, COPD, reoperation, liver and kidney dysfunctions, acute myocardial infarction, increased left atrium diameter (> 4.5 cm), inflammatory diseases and malignancy suggests that elevated levels of MPV and CRP are significant in the group of patients with AF. We also suggest that preoperative levels of MPV, which were not correlated with age, gender, diabetes mellitus, hypertension, LVEF, history of smoking or hyperlipidemia, increase the significance of elevated MPV values in patients with AF.

It is our opinion that elevated CRP levels in the preoperative period were highly significant together with elevated MPV levels in patients with ischemic cardiac disease who underwent CABG operation with CPB who developed AF in the early postoperative period.

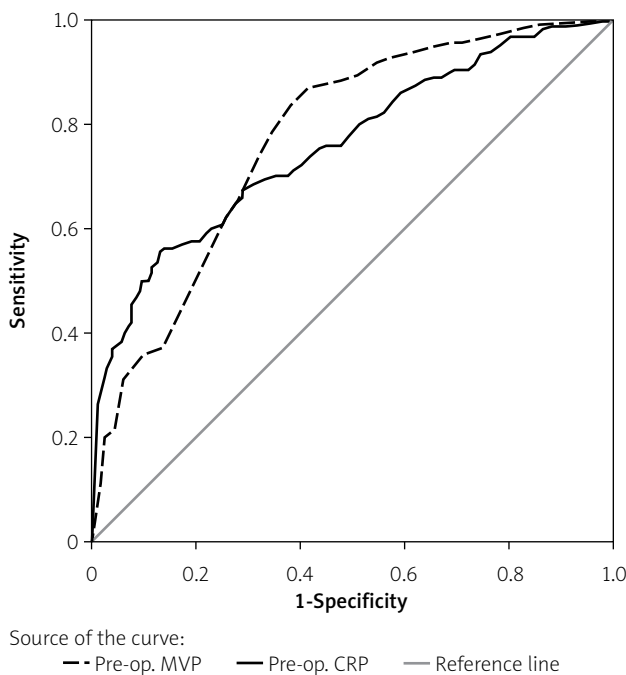


Figure 1. ROC analysis of preoperative MPV and CRP levels to predict postoperative AF

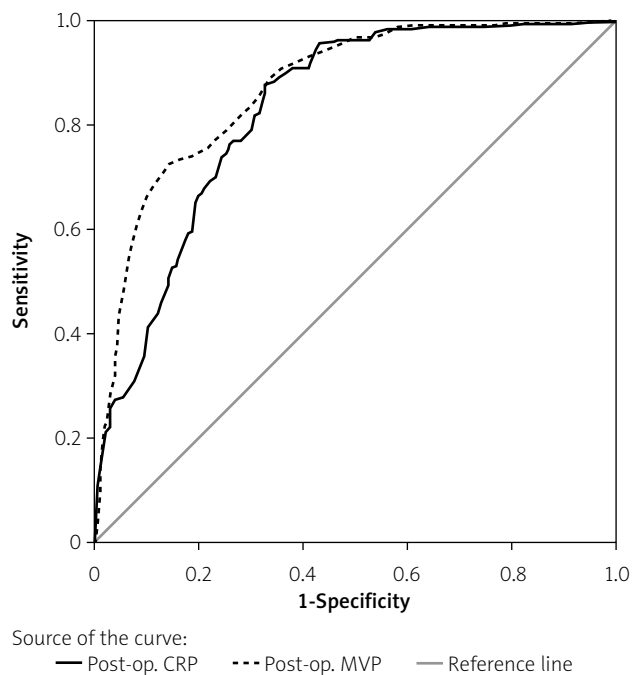


Figure 2. ROC analysis of postoperative MPV and CRP levels to predict postoperative AF

The incidence of atrial fibrillation following CABG operations has been reported as 10% to 50%. The most frequent period for postoperative AF to occur is the early postoperative period. In various studies, AF has been shown to occur frequently in the first postoperative week and mostly on the 2nd and 3rd postoperative days [14]. In a prospective study Ceyran *et al.* [15] observed that atrial fibrillation most commonly occurred between postoperative 12 and 24 h. In parallel with the literature, the incidence of postoperative AF was found to be 25.8% in our study, which occurred in 51.4% of cases in the first 24 h and in 48.6% of them between the 24th and 72nd postoperative hours.

Postoperative AF was associated with hemodynamic instability, increased risk of stroke and mortality, prolonged hospitalization, increased requirement of antiarrhythmic drugs, pacemakers and increased treatment costs [16]. In our study, the length of stay in hospital was found to be higher in patients with AF. Occurrence of in-hospital neurologic events and mortality following the first 72 postoperative hours was significantly higher in the group of patients with AF. There were no differences between the two groups regarding requirement of inotropic support due to postoperative hemodynamic instability.

Although the reasons for postoperative AF in patients following the CABG operation are not fully understood, multiple risk factors and triggering events have been linked to its development. The CPB has been claimed as an important risk factor. The CPB is known to result in oxidative stress and inflammatory processes shown to be related to AF [17]. An isolated CABG operation with CPB was performed in all of the patients included in our study. Therefore, determining predictors for AF in this type of patient population is important.

C-reactive protein is a prototype marker of inflammation controlled by various cytokines, particularly interleukin-6 (IL-6), and it is an acute phase reactant mainly produced in hepatocytes [18]. Lo *et al.* [19] were the first to show the relationship between AF and inflammation in CABG patients. More recent studies showed an increase in CRP and IL-6 levels in occurrence and presence of AF [20]. Dernellis *et al.* [21] showed that elevated CRP levels as a marker of inflammation increased the risk of AF. In a cross sectional study by Aviles *et al.* [22] on 6000 patients, the incidence of AF was found to be higher in patients with a CRP level higher than 3.41 mg/l than in patients with a CRP level lower than 0.97 mg/l (7.4% and 3.7% respectively).

It is not clear whether AF activates the inflammatory response or the systemic inflammatory response results in AF. Even though the direction of causality between CRP levels and occurrence of AF cannot be determined, CRP levels measured before the onset of AF in the majority of patients may predict the effect of a high basal level of systemic inflammation [23]. In parallel with the liter-

ature, postoperative AF occurred more often in patients with high preoperative and early postoperative CRP levels in our study.

Narducci *et al.* [24] reported in their prospective and nonrandomized study that myocardial ischemia also played a role in occurrence of postoperative AF. The incidence of postoperative AF was shown to be related to preoperative CRP levels in patients undergoing off-pump CABG [25].

Thrombocytes have different properties according to their activity, density and size. Bigger thrombocytes contain more secretion granules and mitochondria, known to be more effective than smaller ones [26]. The physical and chemical properties of thrombocytes depend on their size. The MPV is an increasing matter of interest as a new and independent cardiovascular risk factor. The MPV is a parameter of thrombocyte function and activation which plays an important role in the pathophysiology of cardiovascular complications. It is a great advantage for such a parameter to be available for routine measurement together with whole blood count in automatic devices [27].

Changes in MPV in patients with AF have not been investigated until the recent years. Although there have been a few studies which investigated the relationship between MPV and cardiac arrhythmia, these studies particularly concentrated on the issue of AF. More recently, Çölkesen *et al.* [10] reported higher MPV levels in patients with paroxysmal AF. Choudhury *et al.* [28] reported in their study that thrombocyte activation and levels of MPV were higher in patients with AF than the control group which consisted of patients with sinus rhythm. Likewise, the levels of MPV in patients with AF were found to be significantly higher than in patients without AF in our study.

In the recent studies, presence of an association between AF and specific thrombocyte markers has been emphasized. In a study by Erdem *et al.* [11], the risk of AF following the CABG operation was found to be related to the preoperative MPV levels. Both our study and their study examined the relationship between MPV and CRP levels and postoperative AF. In both studies, MPV and CRP levels were higher in the group of patients with AF. However, the number of patients enrolled (208 patients) in their study was much lower than in ours. Ha *et al.* [29] observed elevated MPV levels as a marker of thrombocyte activation and higher levels of MPV in patients with AF.

Our study has some limitations. Firstly, even though the number of individuals enrolled in the study, at over 1000, ensured statistical power of the study, the most important limitation was the study not being designed as a prospective follow-up study. This is a retrospective study in which the causal relationship could not be observed. Some of the drugs, especially statins and antiplatelets, may have an effect on levels of MPV [30, 31]. Besides MPV, which is accepted as a crude marker of thrombocyte function, measurement of more expensive and uncommon

advanced markers of thrombocyte functions may provide more information about pathogenesis and risks.

Conclusions

We suggest that elevated levels of MPV and CRP were related to postoperative AF, according to the findings of our study. Levels of MPV and CRP in the preoperative and early postoperative period may be used as a risk factor in development of early term AF as one of the postoperative complications. Easily measurable MPV and CRP levels in the preoperative and early postoperative periods may contribute to taking precautions against postoperative AF, as well as reducing the length of stay in the hospital and treatment costs.

Conflict of interest

The authors declare no conflict of interest.

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