

The relationship between postoperative atrial fibrillation after coronary artery bypass surgery and inflammation

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ABSTRACT

Objectives: Postoperative atrial fibrillation (PoAF) may occur up to 50% after coronary artery bypass grafting (CABG) operations. The most important problems related to this are prolonged hospitalizations, thromboembolic cerebrovascular events and new onset heart failure. In this study, we aimed to investigate the relation of high sensitivity C-reactive protein (hsCRP) and heat shock protein 70 (HSP70) levels and occurrence of PoAF in patients undergoing isolated CABG.

Methods: Patients who underwent elective isolated coronary artery bypass surgery between November 2008 and April 2009 in the Cardiovascular Surgery Clinic of Dışkapı Yıldırım Beyazıt Training and Research Hospital were prospectively included in the study.

Results: A total of 40 patients (20 Off-pump CABG (OPCABG), mean age: 59.3 ± 5.56 years) and 20 On-pump CABG (mean age: 60.7 ± 5.3 years) were included in the study. PoAF ratio was 25% in on-pump CABG patients and 15% in OPCABG group ($p = 0.356$). Age and diameters of the heart cavities were statistically significantly higher in patients with POAF in both surgical groups. Left ventricular ejection fraction was significantly lower in patients with PoAF. Preoperative hsCRP, postoperative hsCRP, preoperative HSP70 and postoperative HSP70 levels were significantly higher in patients with PoAF who underwent OPCABG ($p = 0.018$, $p = 0.044$, $p < 0.001$ and $p = 0.047$; respectively).

Conclusions: As a result, PoAF is undesirable for CABG operations. PoAF can be predicted by evaluating HSP70 and hsCRP values before coronary bypass operations.

Keywords: Coronary artery bypass grafting, postoperative atrial fibrillation, inflammation, heat shock protein 70

Coronary artery disease (CAD) is the leading cause of mortality worldwide. Although technological advances in endovascular interventions have increased treatment options in recent years, coronary artery bypass grafting (CABG) surgery is still an effective and important treatment modality [1, 2]. CABG is a major surgical procedure and it is important to predict the possible morbid and mortal

conditions after surgical approach and to take the necessary precautions. Cardiac rhythm problems after these operations are important and the most common one is atrial fibrillation. Postoperative atrial fibrillation (PoAF) may occur up to 50% after CABG operations [3]. The most important problems related to this are prolonged hospitalizations, thromboembolic cerebrovascular events and new onset heart failure. The

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risk factors for PoAF development includes advanced age, history of cerebrovascular event, existence of preoperative heart failure, and chronic pulmonary disease [4].

The role of inflammatory parameters in the development and prognosis of cardiovascular diseases has been the subject of research. One of those, high sensitivity C-reactive protein (hsCRP), is a valuable parameter that is safe and easily detectable [5]. Blood hsCRP levels is found to be higher in patients suffering from atrial fibrillation (AF) than normal individuals in several studies [6, 7].

Heat Shock Protein 70 (HSP70), which is one of the heat shock protein family, can limit the damage in the cells exposed to stress. A study revealed that, intracellular HSP70 levels in the right atrial tissue were shown to be negatively correlated with PoAF [8].

In this study, we aimed to investigate the relation of hsCRP and HSP70 levels and occurrence of PoAF in patients undergoing isolated CABG.

METHODS

Patients

After obtaining local ethical committee approval, 40 patients who underwent elective isolated coronary artery bypass surgery between November 2008 and April 2009 in the Cardiovascular Surgery Clinic of Dışkapı Yıldırım Beyazıt Training and Research Hospital were prospectively included in the study.

Patients who were scheduled forelective CABG between the ages of 40-70 years, left ventricular functions were not depressed (ejection fraction [EF] > 45%), had no cardiac valve pathology, left atrial and right atrial diameters were not increased, had no chronic obstructive pulmonary disease, had no preoperative arrhythmia and did not have a history of any antiarrhythmic drug usage were included in the study.

Patients with previous history of arrhythmia, advanced age (> 70) patients, heart failure patients, patients who suffered from an acute coronary syndrome attack in the last 60 days, patients who were operated under emergency conditions, patients with temporary or permanent pacemaker, patients who had proximal right coronary artery lesions, patients with inotropic need for more than 24 hours postoperatively and/or intra-aortic balloon pump implanted, patients

whose preoperative echocardiogram revealed grade 2 or more mitral insufficiency or moderate and severe mitral stenosis or greater than 2 degree aortic insufficiency or with moderate and severe aortic stenosis or grade 2 or higher tricuspid regurgitation or moderate to severe tricuspid stenosis, patients of impaired renal function (serum creatine levels > 2mg / dl), patients who were diagnosed with pulmonary embolism in the last 60 days prior to CABG, and severe lung disease that may lead to right heart failure was excluded from the study group.

Age, gender, presence of diabetes mellitus, hypertension, hypercholesterolemia, preoperative EF, left ventricular end-systolic diameter (LVESD), left ventricular end-diastolic diameter (LVEDD), left atrial diameter (LAD), right atrial diameter (RAD), right ventricular diameter (RVD), duration of total anesthesia time, postoperative inotropic drug support (5-15 µg / kg / min dobutamine infusion if low flow or hypotension persists noradrenaline infusion) and PoAF development were recorded for all patients. Also for On-pump patients, cross-clamp (CC) time and cardiopulmonary bypass (CPB) time were recorded.

Laboratory Test Analysis

Blood samples were collected on the day before the operation and on the postoperative 3rd day to measure hsCRP and HSP70 levels. Blood samples were taken after a fasting period longer than 12 hours. Platelet-poor plasma samples were obtained by centrifugation at 3500 rpm for 5 minutes at + 4 ° C. Samples were stored at -80 ° C. After all samples were prepared, HSP70 levels were measured in the HSP70 ELISA Kit test system. In the study, the unit for HSP70 was taken as ng / ml. The lower limit of the Hsp 70 level that the test can detect is 0.039 ng / ml. Serum levels of hsCRP (Dade Behring, CardioPhase hsCRP) were studied by immunonephelometer (Dade Behring, Marburg GmbH, Germany). The normal value of hsCRP was < 3.19mg / dl.

Postoperative Cardiac Rhythm Analysis

All patients were fully monitored including electrocardiography (ECG) monitoring during intensive care follow-up and 12-lead ECG recordings were recorded daily during the postoperative hospital stay. In addition, 12-lead ECG was performed in patients with palpitation, sweating, dyspnea and chest

pain during the follow-up.

PoAF was defined as the absence of p wave and development of irregular ventricular rhythm before QRS complex in all of the ECG derivations.

Statistical Analysis

In this study, statistical analyzes were performed using SPSS 16.0 statistical package program. The p values obtained in the test results were evaluated at significance level below 0.05. Mean and standard deviations were calculated using descriptive methods for continuous and ordinal data. The distribution of normality were tested by “Kolmogorov-Smirnov test” and “Shapiro-Wilk test”. “Student ‘s t test” was used for the data showing normal distribution and “Mann-Whitney U test” was used for the data that did not fit the normal distribution. Frequency and percentage analysis was performed for nominal data and Chi Square test was used to compare these data.

RESULTS

A total of 40 patients (20 OPCABG (mean age:

59.3 ± 5.56 years) and 20 On-pump CABG (mean age: 60.7 ± 5.3 years) were included in the study. There were no statistically significant difference between the two surgical groups in terms of hypertension, diabetes mellitus, hyperlipdemia, preoperative echocardiography findings, distal anastomosis numbers, total anesthesia duration and inotropic requirements. PoAF ratio was 25% in on-pump CABG patients and 15% in OPCABG group ($p = 0.356$). Demographic characteristics and peroperative data of both surgical groups are given in Table 1.

The parameters affecting the development of PoAF were evaluated separately for both surgical groups and the data are given in Table 2. Age, LVESD, LVEDD, LAD, RAD and RVD were statistically significantly higher in patients with PoAF in both surgical groups. Left ventricular ejection fraction was significantly lower in patients with PoAF. When the surgical groups were individually evaluated and PoAF and the rest were compared, there was no difference between the groups in terms of the number of distal anastomosis, inotropic requirement, and total anesthesia duration times. There were no significant difference between the patients of PoAF and the rest

Table 1. Demographic characteristics and peroperative features of the patients

Characteristics	Off-Pump (n = 20)	On-Pump (n = 20)	p value
Age (years)	59.3 ± 5.56	60.7 ± 5.3	0.424
Hypertension, n (%)	16 (80)	18 (90)	0.661
Diabetes mellitus, n (%)	10 (50)	13 (65)	0.523
Hiperlipdemia, n (%)	18 (90)	18 (90)	1.000
EF (%)	49.2 ± 2.6	50.2 ± 3.5	0.292
LVEDD (cm)	4.8 ± 0.5	4.7 ± 0.6	0.726
LVESD (cm)	3 ± 0.3	3.1 ± 0.4	0.404
LAD (cm)	3 ± 0.5	3.2 ± 0.5	0.135
RAD (cm)	3.54 ± 0.58	3.56 ± 0.59	0.893
RVD (cm)	2.2 ± 0.18	2.13 ± 0.21	0.273
Distal anastomosis number > 2, n (%)	10 (50)	15 (75)	0.102
Inotropic support, n (%)	9 (45)	12 (60)	0.342
Anesthesia time (min)	216.4 ± 26.8	241.8 ± 40.7	0.026
PoAF, n (%)	3 (15)	5 (25)	0.356

Data are shown as mean ± standard deviation or number (%). EF = Ejection fraction, LVESD = Left ventricular end-systolic diameter, LVEDD = Left ventricular end-diastolic diameter, LAD = Left atrial diameter, RAD = Right atrial diameter, RVD = Right ventricular diameter, PoAF = Postoperative atrial fibrillation

Table 2. Comparison of demographic and peroperative characteristics of patients in two surgical groups according to PoAF status

Characteristics		Off-Pump (n = 20)	On-Pump (n = 20)	p value
Age (years)	PoAF (-)	58.2 ± 5.3 ^a	59 ± 4.9 ^b	^a 0.038
	PoAF (+)	65.3 ± 2.3 ^a	65.8 ± 2.8 ^b	^b 0.010
EF (%)	PoAF (-)	49.8 ± 2.2 ^a	51.5 ± 3 ^b	^a 0.007
	PoAF (+)	45.6 ± 0.57 ^a	46.4 ± 1.5 ^b	^b 0.002
LVESD (cm)	PoAF (-)	3 ± 0.36 ^a	3 ± 0.38 ^b	^a < 0.001
	PoAF (+)	3.5 ± 0.1 ^a	3.5 ± 0.15 ^b	^b 0.011
LVEDD (cm)	PoAF (-)	4.77 ± 0.55 ^a	4.59 ± 0.58 ^b	^a 0.009
	PoAF (+)	5.26 ± 0.15 ^a	5.36 ± 0.2 ^b	^b 0.012
LAD (cm)	PoAF (-)	2.9 ± 0.45 ^a	3.1 ± 0.45 ^b	^a < 0.001
	PoAF (+)	3.73 ± 0.11 ^a	3.78 ± 0.13 ^b	^b 0.005
RAD (cm)	PoAF (-)	3.44 ± 0.56 ^a	3.36 ± 0.52 ^b	^a 0.002
	PoAF (+)	4.1 ± 0.17 ^a	4.18 ± 0.18 ^b	^b 0.003
RVD (cm)	PoAF (-)	2.15 ± 0.15 ^a	2 ± 0.15 ^b	^a 0.003
	PoAF (+)	2.47 ± 0.05 ^a	2.4 ± 0.07 ^b	^b < 0.001
Distal anostmosis > 2, n(%)	PoAF (-)	9 (52.9) ^a	11 (73.3) ^b	^a 1.000
	PoAF (+)	1 (33.3) ^a	4 (80) ^b	^b 1.000
Inotropic support, n(%)	PoAF (-)	8 (47) ^a	9 (60) ^b	^a 1.000
	PoAF (+)	1 (33.3) ^a	3 (60) ^b	^b 1.000
CC time (min)	PoAF (-)		58.9 ± 22.5 ^b	^b 0.668
	PoAF (+)		54.2 ± 14.2 ^b	
CPB time (min)	PoAF (-)		109.2 ± 42 ^b	
	PoAF (+)		96.4 ± 23.9 ^b	^b 0.517
Anesthesia time (min)	PoAF (-)	216 ± 27.2 ^a	243.6 ± 43.8 ^b	^a 0.879
	PoAF (+)	218.6 ± 29.9 ^a	236.4 ± 33.2 ^b	^b 0.740

Data are shown as mean ± standard deviation or number (%). EF = Ejection fraction, LVESD = Left ventricular end-systolic diameter, LVEDD = Left ventricular end-diastolic diameter, LAD = Left atrial diameter, RAD = Right atrial diameter, RVD = Right ventricular diameter, CC = Cross-clamp, CPB = Cardiopulmonary bypass, PoAF = Postoperative atrial fibrillation. Evaluating patients with and without PoAF among OPCABG patients ^a, Evaluating patients with and without PoAF among On-pump CABG patients ^b

in terms of CC time, CPB time in the On-pump CABG group.

Preoperative hsCRP, postoperative hsCRP, preoperative HSP70 and postoperative HSP70 levels were significantly higher in patients with PoAF who underwent OPCABG ($p = 0.018$, $p = 0.044$, $p < 0.001$ and $p = 0.047$; respectively). (Table 3).

Preoperative hsCRP, postoperative hsCRP, preoperative HSP70 and postoperative HSP70 values were significantly higher in patients with PoAF who underwent CABG with cardiopulmonary bypass ($p = 0.013$,

$p = 0.009$, $p = 0.011$ and $p < 0.001$; respectively) (Table 3).

DISCUSSION

Atrial fibrillation is an atrial activation and rhythm disorder in which the atrium loses its mechanical functions. This is often accompanied by a rapid and irregular ventricular rhythm. This occurs frequently after CABG operations, and in several studies the inci-

Table 3. Preoperative and postoperative change of HSP70 and hsCRP values between patients with and without PoAF in two surgical groups

Characteristics		Off-Pump (n = 20)	On-Pump (n = 20)	p value
Preoperative hsCRP (mg/dL)	PoAF (-)	72.6 ± 10.6 ^a	52.5 ± 25.8 ^b	^a 0.018
	PoAF (+)	89.5 ± 7.5 ^a	92.9 ± 36 ^b	^b 0.013
Postoperative hsCRP (mg/dL)	PoAF (-)	97.4 ± 15.7 ^a	125.6 ± 36.8 ^b	^a 0.044
	PoAF (+)	122.9 ± 34.6 ^a	176.8 ± 21.6 ^b	^b 0.009
Preoperative HSP70 (ng/dL)	PoAF (-)	1.37 ± 0.2 ^a	1.69 ± 0.58 ^b	^a < 0.001
	PoAF (+)	2.08 ± 0.1 ^a	2.52 ± 0.55 ^b	^b 0.011
Postoperative HSP70 (ng/dL)	PoAF (-)	1.73 ± 0.35 ^a	2.13 ± 0.71 ^b	^a 0.047
	PoAF (+)	2.23 ± 0.51 ^a	3.91 ± 0.6 ^b	^b < 0.001

Data are shown as mean ± standard deviation. hsCRP = High-sensitivity C-reactive protein, HSP70 = Heat shock protein 70, PoAF = Postoperative atrial fibrillation. Evaluating patients with and without PoAF among OPCABG patients ^a, Evaluating patients with and without PoAF among On-pump CABG patients ^b

dence rates are given in the range of 20-50% [9]. According to data from the United States, PoAF can increase hospital costs [10]. The occurrence after coronary bypass surgery increases postoperative mortality and morbidity. In this study, we demonstrated that preoperative and postoperative elevated hsCRP and HSP70 levels were associated with the occurrence of PoAF in on pump CABG and OPCABG patients.

Although CABG operations using cardiopulmonary bypass are proved to be safe and effective, side effects can be occurred due to blood and foreign surface contact. Additionally, ischemia-reperfusion injury due to cross-clamping of the ascending aorta may also adversely affect other vital organs such as kidney, intestines and brain [11]. In OPCABG these CPB-related effects have been avoided, and postoperative complications have been shown to be less [12]. One of the undesirable and common problems after these operations is PoAF.

After on pump CABG, the inflammatory response increases due to the CPB system, posing a risk for the development of PoAF [13]. However, in a study conducted by Lin *et al.* [14] OPCABG and on pump CABG PoAF rates were found to be similar. In our study, PoAF rates were similar between the two surgical groups.

The relationship of C-reactive protein (CRP) levels, that predicts the inflammation and tissue damage, and cardiovascular diseases has been extensively investigated in recent years. However, hsCRP values

have become more prominent since more sensitive measurements are needed for the cardiovascular system. Plasma CRP shows a proinflammatory effect by clustering with blood lipids and activating the complement pathway [15].

Inflammation also poses a risk for AF and also plays a role in prolonging AF periods [16]. Because arrhythmia occurs as a result of fibrosis in atrial muscle structures and conduction pathways [7]. The most important reason for this is inflammatory processes. Accordingly, in a study by Ucar *et al.* [17] 49 patients who underwent on pump CABG were prospectively examined and the relationship between PoAF and inflammatory markers was investigated. In this study, the authors reported PoAF rates as 28.5% and found that hsCRP values collected preoperatively and postoperatively on the first day were significantly higher in the group developing PoAF [17]. In our study, we studied preoperative and postoperative 3rd day hsCRP values and found significantly higher in patients who developed PoAF in both surgical groups.

Heat shock proteins (HSPs) are heat-permeable gene products that protect cells against stress. HSP90, HSP70 and HSP60 belong to the first group family of these proteins [18]. HSP70 plays important intracellular roles in facilitating protein transport, preventing misfolding of newly synthesized polypeptide chains and preserving protein denaturation [19]. Many studies have shown increased HSP levels in atrial tissue in patients with paroxysmal or persistent AF [20, 21]. In

a study by Mandal *et al.* [8], HSP 70 levels obtained from atrial tissue with AF found to be negatively correlated with PoAF development. In our study, HSP70 peripheral blood levels were found to be high in patients with PoAF in both surgical groups.

Although advanced age generally poses a risk in all surgeries, it is one of the most important risk factors for PoAF in patients undergoing CABG. Myocardial fibrosis and accumulating amyloid stores with increasing age lead to AF by causing reentries between the atria [22]. Studies have shown that advanced age is a risk factor for PoAF after cardiac surgery [23, 24]. In our study, patients over 70 years of age were excluded, but age was higher in the PoAF group in both surgical groups.

Increased left atrial diameter and low ejection fraction are also risk factors for PoAF. This means increased fibrosis in the heart muscle and therefore increased inflammation. As a result, the risk for AF increases [25, 26]. In our study, left atrial diameters, LVESD, LVESD and RVD were significantly higher and EF was significantly lower in patients with PoAF in both surgical groups.

Limitations

The most important limitations of our study includes small number of the patients and single-centeredness. Another limitation is the fact that holter recording could not be used in rhythm follow-ups during the follow-up of the patients.

CONCLUSION

As a result, PoAF is undesirable for CABG operations. PoAF can be predicted by evaluating HSP70 and hsCRP values before coronary bypass operations. The importance of these blood parameters should be investigated by prospective and multicenter studies with high number of patients.

Conflict of interest

The author disclosed no conflict of interest during the preparation or publication of this manuscript.

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