



The Effect of the Presence and Degree of Mitral Regurgitation Before Isolated Coronary Artery Bypass Grafting Surgery on the Development of Postoperative Atrial Fibrillation

İzole Koroner Arter Bypass Greftleme Operasyonu Öncesi Mitral Yetersizliğinin Varlığı ve Derecesinin Postoperatif Atriyal Fibrilasyon Gelişimine Etkisi

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ABSTRACT

Objectives: Postoperative atrial fibrillation (POAF) is a common complication following coronary artery bypass grafting (CABG). Mitral regurgitation (MR) is associated with left atrial (LA) structural changes that may play a role in the development of AF. However, the relationship between MR without significant LA enlargement and POAF has not been adequately studied. In this study, we aimed to investigate the relationship between the degree of MR and the development of POAF in patients who underwent isolated CABG without significant LA dilation.

Methods: A total of 262 patients (51 with POAF and 211 without POAF), aged 26-85 years, who underwent CABG between January 2016 and March 2017, were included in the study retrospectively. Patients' data were obtained from hospital files and electronic data system. Surgical information, laboratory data, and ECGs in sinus rhythm were recorded. Patients with at least one 12-lead ECG showing AF within three days after the surgery were included in the POAF group. All patients underwent preoperative 2-dimensional and Doppler echocardiographic evaluation. Logistic regression analysis was used to determine the predictors of POAF. A p-value of less than 0.05 was considered statistically significant.

Results: The incidence of POAF was 19.5%. The incidence of POAF was significantly higher in patients with moderate-severe MR compared to mild MR (p=0.0001). Logistic regression analysis identified moderate-severe MR and erythrocyte suspension (ES) transfusion as independent predictors of POAF.

Conclusion: Preoperative moderate-severe degree of MR may predict POAF, independent of left atrial size in patients undergoing isolated CABG. In addition, the administration of ES also increases the risk of POAF development.

Keywords: Coronary artery bypass grafting; Mitral regurgitation; Postoperative atrial fibrillation.

ÖZET

Amaç: Postoperatif atriyal fibrilasyon (POAF), koroner arter bypass greftlemesini (KABG) takiben sık görülen bir komplikasyondur. Mitral yetersizliği (MR), AF gelişiminde rol oynayabilecek sol atriyal (LA) yapısal değişikliklerle ilişkilidir. Ancak anlamlı LA genişlemesi olmayan MR ile POAF arasındaki ilişki yeterince araştırılmamıştır. Bu çalışmada izole KABG uygulanan hastalarda belirgin LA dilatasyonu olmayan hastalarda MR'nin derecesi ile POAF gelişimi arasındaki ilişkiyi araştırmayı amaçladık.

Yöntem: Ocak 2016 ile Mart 2017 tarihleri arasında hastanemizde KABG operasyonu geçirmiş toplam 262 hasta (51 postoperatif AF olan ve 211 postoperatif AF olmayan) geriye dönük olarak çalışmaya dahil edildi. Hastalar ile ilgili bütün veriler hastane dosyaları ve elektronik data sistemi üzerinden elde edildi. Cerrahi bilgileri, laboratuvar verileri ve sinüs ritmindeki EKG'ler kaydedildi. Operasyon sonrası ilk üç gün içinde atriyal fibrilasyonlu en az 1 adet 12-lead EKG'si olan hastalar postoperatif atriyal fibrilasyonu olan gruba dahil edildi. Bütün hastalara operasyon öncesi 2-Boyutlu ve Doppler ekokardiyografik değerlendirme yapıldı. POAF'ın yordayıcılarını belirlemek için lojistik regresyon analizi kullanıldı. $p < 0.05$ istatistiksel olarak anlamlı kabul edildi.

Bulgular: POAF'ın insidansı %19,5 idi. POAF, orta-şiddetli MR'li hastalarda hafif MR'li hastalara göre anlamlı derecede yüksekti ($p < 0.001$). Lojistik regresyon analizinde, orta-şiddetli MR ve eritrosit süspansiyon (ES) transfüzyonunun POAF'un bağımsız belirleyicileri olduğu tanımlandı.

Sonuç: İzole KABG yapılan hastalarda sol atriyum büyüklüğünden bağımsız olarak preoperatif orta-ileri MR derecesi POAF'ı öngörebilir. Ayrıca ES uygulanması da POAF gelişme riskini arttırmaktadır.

Anahtar sözcükler: Koroner arter bypass greftlemesi; Mitral yetersizliği; Postoperatif atriyal fibrilasyon.

Postoperative atrial fibrillation (POAF) is the most common postoperative arrhythmia, affecting 10-40% of patients who underwent CABG surgery.^[1] POAF is associated with short- and long-term mortality rates and a higher prevalence of postoperative complications (such as stroke, pneumonia, respiratory failure, and longer hospital stay).^[2-5] In addition, POAF after isolated CABG was found to increase the risk of permanent AF and stroke fourfold in long-term follow-up.^[6] Therefore, identifying patients at high risk for POAF is very important for taking preventive measures.

The exact pathophysiology of POAF is not fully understood.^[7] However, atrial ischemia, inflammation, and increased catecholamines are among the potential mechanisms.^[7] It has been shown that increased atrial pressure results in increased atrial stretch, which causes the shortening of the atrial refractory period that may play an essential role in the development of AF.^[8]

Increasing age, male gender, heart failure, coronary artery disease, hypertension, diabetes, heart valve disease, and surgery have been reported as important risk factors for POAF.^[7] Mitral regurgitation (MR) causes an increase in left atrial filling pressure and electrical and structural remodeling. Recent publications have demonstrated MR to be associated with AF recurrence after successful catheter ablation.^[7,9] In addition, MR severity has been shown to be independently associated with new-onset AF in patients with acute coronary syndrome.^[10] Furthermore, MR has been recently reported to be an independent risk factor for POAF in critically ill non-cardiac surgery patients.^[7]

To the best of our knowledge, MR has not been studied in the context of POAF in patients undergoing cardiac surgery. In this study, we investigate the predictive value of MR degree, without significant left atrial dilation, for the development of POAF in patients who underwent isolated CABG.

Methods

A total of 262 patients (51 with POAF and 211 without POAF), aged 26-85 years, who underwent CABG operation in our hospital between January 2016 and March 2017, were included in the study retrospectively. Patients over 18 years of age and preoperatively in sinus rhythm were included in the study. All data were obtained from patients' files and the hospital's electronic data system. Patients with a previous history of atrial arrhythmia, active infection, significant anemia, renal failure, chronic inflammatory disease, and valve repair or replacement in addition to CABG were excluded from the study.

Preoperative complete blood count, biochemical examination, and additional laboratory data, including inflammatory markers such as white blood cell count (WBC) and C-reactive protein (CRP), were recorded. All patients' 12-lead ECGs were recorded 24 hours before the operation and in the first 72 hours after the CABG operation and were analyzed by a cardiologist. In the postoperative first three days, patients with at least one 12-lead ECG showing AF or those treated with medical or electrical cardioversion for AF were included in the POAF group.

2-Dimensional and Doppler echocardiographic evaluation of all patients was performed with a 1-5 MHz S5-1 transducer (iE33, Philips Healthcare, Inc., Andover, MA). The patients were evaluated in the left lateral position, and an average of three consecutive cardiac cycles was recorded. All standard 2-D echocardiographic parasternal long axis, short axis, apical four, three, and two-chamber images, as well as color Doppler images, were recorded in a QRS complex-triggered cine-loop format.

Left ventricular diastolic and systolic diameters were measured using M-mode or 2D echocardiography. Left ventricular ejection fraction (LVEF) was calculated from the four-chamber and two-chamber apical images in systole and diastole according to Simpson's formula. Anteroposterior diameter was measured to evaluate the width of the left atrium. Mitral regurgitation grades were classified ac-

ording to quantitative methods in patients with sufficient data, and according to semi-quantitative and qualitative Doppler methods in patients without sufficient data. In this study, MR was considered as two groups; mild and moderate-severe.

The present study was performed in accordance with the Helsinki Declaration and was approved by a local ethics committee (approval no: 2017/4/3-38, date: 23.05.2017). Due to the retrospective nature of the study, informed consent was not obtained. We did not use artificial intelligence-supported technologies in the production of this study.

Statistical Analysis

Statistical analysis of the present study was performed using Statistical Package for the Social Sciences (SPSS Inc. SPSS Statistics for Windows, Version 17.0. Chicago, Illinois, United states). The Kolmogorov-Smirnov test was used to an-

alyze whether the data was normally distributed. Normally distributed continuous data were presented as mean±standard deviation, and non-normally distributed continuous data were presented as median and first and third quartiles. Categorical data was presented as numbers and percentages. Differences in categorical variables between groups were evaluated with the chi-square test. The relationship between the parameters was evaluated using Pearson's or Spearman's correlation according to the distribution pattern of the data. Differences between groups were tested using the Mann-Whitney U or Student's T-test. Logistic regression analysis was used to determine the independent predictors of POAF. P value of < 0.05 was considered statistically significant.

Results

The demographic findings of the patients are shown in Table 1. In the present study, the incidence of POAF was

Table 1. Clinical, demographic and laboratory characteristics of patients with and without POAF

Variables	Patients with POAF n=51	Patients without POAF n=211	p
Age (Year)	64.4±7.9	61.2±7.9	0.27
Gender M/F (n), %	38/13 (75/25)	170/41 (81/19)	0.33
BMI	28.7±3.7	27.7±3.5	0.09
DM n/N, (%)	20/51 (39)	91/211 (43)	0.61
HT n/N, (%)	30/51 (59)	118/211 (56)	0.70
Cigarette n/N, (%)	23/51 (45)	76/211 (36)	0.23
Hospital admission			
SAP n, (%)	1 (2)	1 (0.5)	0.37
USAP n, (%)	18 (35)	98 (46.5)	
Non-STEMI n, (%)	23 (45)	83 (39)	
STEMI n, (%)	9 (18)	29 (14)	
ES received n, (%)	37 (73)	107 (51)	0.005
ES not received n, (%)	14 (27)	104 (49)	
Fasting glucose (mg/dl)	141 (50-346)	146 (59-544)	0.91
Urea (mg/dl)	41 (24-70)	41 (11-155)	0.63
Creatinine (mg/dl)	1.0 (0.6-4.5)	0.98 (0.4-6.5)	0.27
Hemoglobin (g/dL)	12.7 ±1.8	13.2±1.7	0.07
Platelete (10 ⁹ /L)	244±73	235±70	0.42
White blood cells (10 ⁹ /L)	7.8 (4.4-13.1)	8.2 (4.1-17.5)	0.14
C-reactive protein (mg/L)	1.7 (0.3-14.2)	2.0 (0.3-18)	0.84
RDW (%)	14.6 (12.8-25.8)	14 (12.1-21.7)	0.002
NLR	3.0 (1.26-11.1)	2.9 (0.9-14.8)	0.65
TC (mg/dl)	197±51	193±49	0.65
LDL-C (mg/dl)	120±42	120±41	0.98
HDL-C (mg/dl)	41 (24-70)	39.3 (16-78)	0.19
Triglycerides (mg/dl)	176 (77-383)	176 (39-2337)	0.30

BMI: body mass index; DM: diabetes mellitus; ES: erythrocyte suspension; F: female; HDL-C: high-density lipoprotein cholesterol; HT: hypertension; H: male; LDL-C: low-density lipoprotein cholesterol; NLR: neutrophil to lymphocyte ratio; Non-STEMI: Non-ST-elevation myocardial infarction; POAF: postoperative atrial fibrillation; RDW: red cell distribution width; SAP: stable angina pectoris; STEMI: ST-elevation myocardial infarction; TC: total cholesterol; USAP: unstable angina pectoris.

19.5%. There was no statistically significant difference between the patient groups with and without POAF in terms of age ($p=0.27$), gender ($p=0.33$), diabetes mellitus (DM) ($p=0.61$), hypertension ($p=0.70$), cigarette smoking ($p=0.23$), and body mass index (BMI) ($p=0.09$). Similarly, there was no difference in diagnosis between the two groups at the time of admission to the hospital ($p=0.37$). However, it was observed that the number of patients who received erythrocytes was statistically higher in the group with POAF than in the group without POAF ($p=0.005$).

The laboratory findings of the participants are also shown in Table 1. Only red cell distribution width (RDW) was found to be significantly higher in the POAF group compared to the group without POAF ($p=0.002$).

There was no significant difference between the two groups in terms of left ventricular ejection fraction (LVEF) ($p=0.92$), left ventricular end-diastolic diameter (LVEDD) ($p=0.61$), left

ventricular end-systolic diameter (LVESD) ($p=0.17$), and left atrial anteroposterior diameter ($p=0.09$). However, there was a statistically significant difference between the two groups in terms of the degree of mitral regurgitation ($p<0.001$), as shown in Table 2.

Binary logistic regression was used to evaluate the effect of independent variables on the development of POAF. According to the binary logistic regression model, it was determined that moderate-severe mitral regurgitation and erythrocyte suspension transfusion were independent predictors of POAF (Table 3).

Discussion

The present study showed that preoperative moderate to severe degree of mitral regurgitation is an independent predictor for the development of POAF in patients who underwent isolated CABG operation. Interestingly, the left atrial diam-

Table 2. Echocardiographic features of patients with and without POAF

Variables	Patients with POAF n=51	Patients without POAF n=211	p
Preop EF (%)	54.9 (30-65)	54.5 (30-65)	0.92
LAD (cm)	3.9 (3.0-5.2)	3.7 (2.8-5.0)	0.09
LVEDD (cm)	4.95 (4.1-6.4)	4.9 (4.0-6.8)	0.61
LVESD (cm)	3.3 (2.1-5.0)	3.2 (2.1-5.8)	0.17
MR n, (%)			
Mild	30 (59)	182 (86)	<0.001
Moderate-severe	21 (41)	29 (14)	

POAF: postoperative atrial fibrillation; EF: ejection fraction; LAD: left atrial diameter; LVEDD: left ventricle end-diastolic diameter; LVESD: left ventricle end-systolic diameter.

Table 3. Binary logistic regression analysis demonstrates independent predictors of POAF.

Variables	B	S.E.	Wald	df	p	Exp(B)	95% C.I. for EXP(B)	
							Lower	Upper
Age	0.021	0.019	1.227	1	0.268	1.021	0.984	1.060
Hg*	-0.146	0.130	1.260	1	0.262	0.864	0.670	1.115
LAD	0.484	0.438	1.221	1	0.269	1.622	0.688	3.828
RDW	0.006	0.134	0.002	1	0.962	1.006	0.774	1.308
Monocyte	-0.065	0.535	0.015	1	0.903	0.937	0.328	2.674
Sodium	0.089	0.057	2.441	1	0.118	1.093	0.978	1.221
RDW*	0.146	0.122	1.441	1	0.230	1.158	0.911	1.470
ES (1)	0.818	0.366	4.991	1	0.025	2.265	1.106	4.642
MR (1)	0.943	0.409	5.329	1	0.021	2.568	1.153	5.719
Constant	-17.226	8.396	4.209	1	0.040	<0.001		

ES: erythrocyte suspension; HT: hypertension; LAD: left atrial diameter; MR: mitral regurgitation; NLR: neutrophil-lymphocyte ratio; POAF: postoperative atrial fibrillation; RDW: red cell distribution width. *indicates postoperative measurements.

eter of patients who developed POAF was not significantly enlarged compared to those who did not develop POAF. In addition, the infusion of erythrocyte suspension in the intensive care unit was also independently associated with the development of POAF.

The incidence (19.5%) of POAF in the present study was consistent with previous studies.^[3,11] Atrial fibrillation (AF) is the most common cardiac arrhythmia and is often associated with structural heart diseases.^[12] Numerous risk factors, including acute atrial tension, structural and electrophysiological changes, systemic inflammation, oxidative stress, autonomic imbalance, atrial fibrosis or local atrial myocarditis, genetic predisposition, obesity, sleep apnea, metabolic syndrome, alcohol consumption, and endurance sports, are involved in the pathogenesis of AF.^[13,14]

Inflammation plays a crucial role in the development of POAF.^[13-15] However, in the present study, with the exception of red cell distribution width (RDW), inflammatory markers were not statistically different between the two groups. In addition, RDW was not detected as an independent predictor of POAF. This inconsistency can be explained by the fact that comorbid conditions such as diabetes mellitus (DM), hypertension (HT), and coronary artery disease (CAD), in which inflammation plays an important role, were similar in both groups in the present study.

In several studies, advanced age, arterial hypertension, male gender, and previous history of AF were found to be predictors of POAF.^[16,17] In a study by Folla et al.,^[3] left atrial diameter and age were reported as predictors of POAF. In contrast, Zhang et al.^[7] recently reported similar left atrial volumes in patients with and without POAF. In the present study, the development of POAF was independent of both age and left atrial diameter.

MR leads to volume overload in the left ventricle (LV) and left atrium (LA), which may cause left atrial hypertension, enlargement, and remodeling, predisposing to AF development.^[18,19] Interestingly, in the present study, the development of AF was predicted independently of left atrial enlargement. This finding may suggest the development of AF as a result of only pressure increase before the development of structural changes in the left atrium. Thus, this is the first study to show the relationship between MR and POAF in isolated CABG surgery without left atrial diameter enlargement.

Patients with mitral valve disease have more atrial fibrosis.^[18,19] Moreover, mitral regurgitation (MR) due to degenerative or organic valve abnormalities is associated with the development of chronic AF (5% per year).^[19] In a study by Sharma et al.,^[13] moderate MR was observed more commonly in patients with "Lone AF." According to this study, in patients with MR, annular dilation precedes atrial dilation and may not be apparent early in the development of Lone AF.

In another study by Avdic et al.,^[20] the left atrial volume index was found to be an independent predictor of the development of postoperative AF. As the degree of MR increases, the left atrial volume index also increases. Along with left atrial remodeling and atrial dilation, mechanical stress creates a suitable environment for the development of atrial fibrillation by causing cellular hypertrophy and interstitial fibrosis.^[21] Interstitial fibrosis and cellular dissociation slow down conduction and facilitate the development of atrial fibrillation by providing a reentry mechanism.^[7]

Animal studies have also shown that atrial enlargement due to chronic MR increases the development of AF by inducing changes in atrial electrophysiology and tissue structure.^[22] Evaluation of atrial strain helps in detecting changes in left atrial function before left atrial dilation.^[23] It has been shown that global left atrial peak longitudinal strain (PALS) is significantly affected by the degree of MR in patients with chronic MR.^[23] While patients with mild MR had supernormal PALS due to increased atrial compliance, significant depression was observed in PALS values in patients with severe MR, and this depression was found to be more pronounced in patients with paroxysmal AF episodes.^[23]

Erythrocyte suspension (ES) has been reported to trigger inflammation by producing reactive oxygen species that diffuse to endothelial cells.^[24] Moreover, it has been suggested that the inflammatory response induced by direct infusion of inflammatory mediators increases the risk of AF development by causing atrial tissue damage.^[25] Thus, ES transfusion is likely to predispose to AF. In this context, in this study, similar to the study of Koch et al.,^[25] POAF development was found to be significantly higher in patients who received erythrocyte transfusion compared to patients who did not.

Limitations

The present study has several limitations. This is a retrospective study with a small sample size. Only three postoperative days were considered in the context of POAF development. Therefore, POAF that developed in the following days was not taken into account. Long-term follow-up of patients is not available. Thus, randomized controlled prospective studies are required. In addition, in the context of left atrial size, only the anteroposterior diameter was recorded, and left atrial volume and strain were not assessed.

Conclusion

In conclusion, preoperative moderate-severe degree of mitral regurgitation, independent of left atrial size, may be a risk factor for the development of POAF in patients who underwent CABG operation. In addition, the administration of erythrocyte suspension in the intensive care unit increases the risk of developing POAF.

Disclosures

Ethics Committee Approval: The study was approved by Health Sciences University Kartal Kosuyolu High Specialization Training and Research Hospital Non-Interventional Clinical Research Ethics Committee (No: 2017.4/3-38, Date: 23.05.2017).

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