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Role of red blood cell distribution width and epicardial fat in atrial fibrillation after cardiopulmonary bypass

Kerem Özbek[1], Hüseyin Katlandur[2], Bilal Arık[3], Ahmet Kuzgun[4], Murat Yıldız[5], Ahmet Keser[2], Hüseyin Özdil[2]

ABSTRACT

Objective: Postoperative atrial fibrillation (POAF) is a common complication after cardiac surgery, and it remains a challenge for cardiac surgeons despite advances in medicine. A number of studies have been performed to examine various parameters to predict which patients will develop POAF. The present study was performed to investigate the roles of epicardial adipose tissue (EAT) volume and red blood cell distribution width (RDW) as predictors of POAF.

Methods: The medical records of 350 patients undergoing coronary artery bypass grafting in one or more vessels at the Tertiary Cardiac Center, Cardiovascular Surgery Department, Mevlana (Rumi) University Private Hospital (Konya, Turkey), were screened between December 2011 and May 2015. The study population consisted of 149 patients fulfilling the inclusion criteria and undergoing a preoperative evaluation by computed chest tomography. All patient demographics and laboratory parameters were obtained from medical records.

Results: Age, postoperative RDW, and tomography variables, including the left atrial (LA) volume, LA diameters, and EAT volume, were significantly higher while the hemoglobin level and hematocrit were significantly lower in patients developing atrial fibrillation after cardiopulmonary bypass. A logistic multivariate regression analysis was performed on age, postoperative RDW, and tomography variables, including LA volume, LA diameters and EAT volume. Only age (OR 1.0731, 95% CI 1.012–1.138; p = **0.018**) was an independent predictor of the development of POAF.

Conclusions: Although the EAT volume was high in patients developing atrial fibrillation after surgery, age was the only significant predictor of POAF on multivariate analysis. Additional studies regarding the predictive roles of epicardial fat and RDW in POAF are needed.

Keywords: epicardial fat volume, red blood cell distribution width, age, atrial fibrillation, cardiopulmonary bypass

INTRODUCTION

Atrial fibrillation (AF) is common complication after cardiac surgery; the reported incidence of postoperative AF (POAF) after cardiopulmonary bypass is between 17 and 33% (1). The development of POAF after cardiac surgery is associated with a longer hospital stay, increased costs, and increased morbidity, including cerebrovascular events, heart failure, and mortality (2, 3). The cause of POAF is unclear. Atrial trauma after cannulation, acute atrial enlargement with pressure and volume, postoperative electrolyte disturbances, pericarditis, right coronary artery (RCA) grafting, having valvular heart disease, increased sympathetic activity, and beta-blocker discontinuation have been suggested to play etiological roles in the development of POAF (4). Age, hypertension, male sex, RCA stenosis, depressed left ventricular function, and a history of previous AF are important clinical variables related to the development of POAF (4). Bypass with valve replacement, prolonged aortic clamp time, and prolonged bypass time are major risk factors for the development of POAF (5). In addition, recent studies showed that inflammation plays an important role in the pathogenesis of POAF (6, 7).

Pericardial and epicardial adipose tissue lie in the region between the myocardium and the visceral pericardium. Epicardial adipose tissue (EAT) and the myocardium are not separated by fascia, and therefore share the same microcirculation. EAT is an active tissue with inflammatory and endocrine features, and it plays a crucial role in the pathogenesis of cardiac arrhythmias (8, 9). Red blood cell distribution width (RDW), or anisocytosis, is an indicator of

[1] *Mehmet Akif Inan Training and Research Hospital, Department of Cardiology, Sanliurfa, Turkey*
[2] *Department of Cardiology, Medova Hospital, Konya, Turkey*
[3] *Department of Radiology, Magnet Hospital, Ankara, Turkey*
[4] *Department of Cardiovascular Surgery, Rumi Hospital, Konya, Turkey*
[5] *Department of Internal Medicine, Anıt Hospital, Konya, Turkey*

Correspondence: *Assoc. Prof. Kerem Özbek*
Mehmet Akif Inan Training and Research Hospital, Department of Cardiology, Karakopru, Sanliurfa, Turkey
Phone: +90 507 8423831

E-mail: keremozbek@dr.com

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Figure 1: *Tomographic measurement of epicardial adipose tissue volume. Pericardial fat was highlighted in orange after three-dimensional reconstruction*

variability in the size of erythrocytes. Recent studies showed that RDW is also an inflammation marker and may predict POAF (10, 11).

In the present study, we examined whether preoperative inflammation parameters (EAT and RDW) are related to the development of POAF and attempted to determine other predictors of POAF.

MATERIALS AND METHODS

Patients and Procedures

The medical records of 350 patients undergoing coronary artery bypass grafting in one or more vessels at the Tertiary Cardiac Center, Cardiovascular Surgery Department, Mevlana (Rumi) University Private Hospital (Konya, Turkey), were screened between December 2011 and May 2015. Patients with a history of persistent or paroxysmal AF, valvular heart disease, renal replacement therapy, systemic inflammatory disease, terminal illnesses, thyroid disorders, a pacemaker, or who were taking corticosteroids were excluded. The 149 patients that fulfilled the inclusion criteria and underwent a preoperative evaluation by computed tomography (CT) were enrolled in this study. All patient demographics (age, sex, body mass index, comorbidities, and medication history) were obtained from medical records. Perioperative factors such as aortic cross-clamp time, pump time, number of bypass grafts, length of stay in the intensive care unit (ICU), and cardiovascular surgery data were obtained from the surgical records and hospital database. Preoperative transthoracic echocardiography reports were used to assess left ventricular ejection fraction (LVEF). This retrospective cross-sectional study protocol was approved by our university ethics committee.

CT Imaging Protocol

All patients underwent preoperative non-contrast chest CT using a Somatom Sensation 64 (Siemens Medical Solutions, Forchheim, Germany). Continuous 2-mm slices of the heart with 1-mm overlap were acquired from the level of the bifurcation of the pulmonary artery to the diaphragm. The images were analyzed at a dedicated workstation using dedicated software (Siemens Syngo; Siemens Medical Solutions). The operator manually traced the pericardium in each of the slices to create a three-dimensional volume of interest. Pericardial fat was defined as adipose tissue contained in

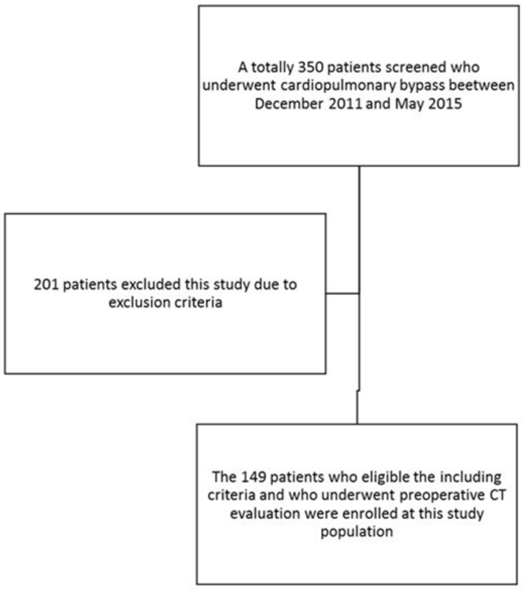

Figure 2: *Study flow diagram*

this volume within the pericardial sac (**Figure 1**). In the examination area, the thresholds were set to –200 and –30 Hounsfield units to distinguish adipose tissue within the volume of interest. All measurements were made by two experienced radiologists blinded to the subject's clinical status. If measurements by the two investigators differed by > 5% for any of the variables, the patient was not included; if the difference was < 5%, the measurements were averaged.

Surgical Protocol

All patients were anesthetized with midazolam, fentanyl, and isoflurane following a standard protocol. Standard sternotomy was performed for all patients to access the aortic fat pad. When the aortopulmonary window was explored, a cross-clamp was placed on the aorta. After starting cardiopulmonary bypass, the body temperature was maintained at 32–34°C using ice slush and cold cardioplegia. The internal mammary artery was usually used to treat left anterior descending artery stenosis, and other grafts were used to treat stenosis of the right coronary artery, circumflex artery, and all branches. All proximal anastomoses were performed with aortic cross-clamping.

Postoperative Follow-Up

At the end of the operation, all patients underwent hemodynamic and rhythm monitoring in the cardiac surgery ICU. A control complete blood count (CBC) was performed after the operation as needed. We evaluated the CBC results 24 hours after cardiopulmonary bypass. Renal function parameters and electrolyte levels (potassium and calcium) were monitored daily. Any hypocalcemia or hypopotassemia was treated immediately with supplementation therapy. Patients were monitored continuously during this period, and monitoring was continued with telemetric electrocardiography (ECG). Twelve-channel ECG was performed when arrhythmia was suspected. Cardiovascular surgery nurses monitored the patients' blood pressure and pulse every 4 hours. Paroxysmal AF was defined as new-onset AF lasting at least 20 minutes and that ended spontaneously or following medical or electrical cardioversion. Patients with established AF were treated with oral or intravenous amiodarone after administering the appropriate loading dose.

Statistical Analysis

Data were analyzed using SPSS software, ver. 22 for Windows (IBM Corp., Armonk, NY). The data are shown as the means ± standard deviation for continuous variables, median (range) for ordinal variables, and frequency and percentage for categorical variables. In all analyses, $p < 0.05$ was taken to indicate statistical significance. Continuous variables were analyzed using the unpaired *t*-test and Mann-Whitney *U* test, and dichotomous data were analyzed using the Pearson's chi-square test or Fisher's exact test. Categorical variables were compared between groups by the chi-square test. A multivariate logistic regression analysis was used to identify independent predictors of POAF. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for independent parameters associated with AF.

Table 1: *Baseline characteristics and procedural differences between patients that developed POAF and those with maintenance of sinus rhythm*

Variables	POAF (n:35)	Sinus Rhythm (n:114)	*p*
Baseline Characteristics			
Age (years)	69.2 ± 8.3	62,1 ± 9.1	**<0.01**
Sex; Female n (%)	12 (34.3)	23 (20.2)	0.465
Diabetes mellitus n (%)	12 (34.3)	49 (43)	0.362
Hypertension n (%)	21 (60)	62 (54.4)	0.492
BMI (kg/m^2)	29,3 ± 5.8	28,1 ± 3,9	0.460
LVEF (%)	54±13	56±11	0.498
Beta blocker therapy n (%)	27 (77)	74 (64)	0.965
Operative and post-operative variables			
Off-pump Bypass n (%)	3 (8.6)	23 (20.2)	0.115
RCA Bypass n (%)	19 (54.3)	61 (53.5)	0.753
Cross Clamp Time (minutes)	69.7 ± 37.3	59.3 ± 24.3	0,355
Pump Time (minutes)	94.7 ± 47.4	84.5 ± 32	0.697
Number of grafts	2.73±1.12	2.90±1.06	0.413
1 n (%)	7 (20)	10 (8.8)	-
2 n (%)	9 (25.7)	34 (29.8)	-
3 n (%)	11 (31.4)	41 (36.6)	-
4 n (%)	6 (17.1)	19 (16.7)	-
5 n (%)	2 (5.4)	10 (8.8)	-
Stay in hospital (Days)	11 ± 3.9	9.4 ± 3	**0.03**
ICU period (Days)	1.9 ± 0.8	3.3 ± 2.9	**<0.01**
Transfusion (Erythrocytes, U)	1.09±0.78	0.77±0.93	0.072

LVEF; Left ventricle ejection fraction, BMI: Body Mass Index, RCA; Right coronary artery, ICU: Intensive care unit
Bolded data indicate significance

Table 2: *Preoperative hematological and biochemical parameters, and the radiological parameters of the two groups*

	POAF (n:35)	Sinus Rhythm (n:114)	*p*
Hematological and biochemical parameters			
Glucose (mg/dl)	129.33±63.03	155.48±85.58	0.060
Urea (mg/dl)	20.05±10.70	18.19±7.90	0.348
Creatinine (mg/dl)	0.88±0.39	0.98±0.56	0.251
WBC (x10^3)	8.04±2.71	7.93±1.72	0.825
Hemoglobin (g/dl)	13.62±1.38	14.14±1.73	0.076
Hematocrit (%)	40.68±3.90	41.49±4.46	0.299
Platelet (x10^3)	251.49±68.38	239.21±57.48	0.341
Neutrophil (x10^3)	5.27±2.54	4.94±1.76	0.474
MPV (fL)	10.38±0.85	10.25±0.93	0.454
RDW (%)	13.73±1.14	13.40±0.93	0.160
CRP	7.74±11.64	7.36±11.55	0.880
Radiologic Parameters			
EAT vol (cm3)	135.71±46.78	118.71±42.85	**0.046**
LA Horizontal (d) mm	47± 8.3	41 ± 6.2	**<0.001**
LA Vertical (d) mm	60.51±8.06	54.42±7.65	**<0.001**
LA (vol) mm^3	72.9±27.2	56.8 ± 15.2	**0.030**

WBC: White blood cell, MPV: Mean platelet volume, RDW: Red cell distribution width, CRP: C-reactive protein, EAT; Epicardial adipose tissue; LA: Left atrium, (d): diameter mm (vol): volume
Bolded data indicate significance

RESULTS

A total of 350 patients who underwent cardiopulmonary bypass surgery between December 2011 and May 2015 at the Tertiary Cardiac Center, Cardiovascular Surgery Department, ------------ Private Hospital, were screened. After excluding 201 patients according to the criteria outlined above, 149 patients were enrolled in this retrospective cross-sectional study (**Figure 2**). POAF occurred in 35 (23%) patients; the remaining 114 (77%) patients remained in sinus rhythm.

The baseline characteristics and procedural differences between patients that developed POAF and those that maintained sinus rhythm are shown in **Table 1**. The mean age of patients in the POAF group (69.2 ± 8.3 years) was

Table 3: *Hematological parameters 24 hours after cardiopulmonary bypass*

	POAF (n:35)	Sinus Rhythm (n:114)	p
	Hematologic Parameters		
WBC	14.65±6.40	14.58±4.82	0.947
Hemoglobin	9.14±1.35	9.95±1.42	**0.003**
Hematocrit	26.85±3.65	29.16±4.13	**0.004**
Platelet	177.66±63.11	192.72±52.33	0.220
Neutrophil	12.31±5.42	12.52±4.63	0.823
MPV	10.67±0.89	10.39±0.92	0.115
RDW	14.46±1.79	13.60±1.37	**0.004**

WBC: White blood cell, MPV: Mean platelet volume, RDW: Red cell distribution width
Bolded data indicate significance

Table 4: *Independent predictors of postoperative atrial fibrillation in a multivariate logistic regression analysis*

Variables	Multivariate Analysis		
	OR	%95 CI	P value
Age	1.073	1.012-1.138	**0.018**
EAT volume	1.008	0.997-1.019	0.139
LA volume	0.994	0.952-1.038	0.789
LA vertical (d)	1.052	0.958-1.155	0.288
LA horizontal (d)	1.065	0.969-1.170	0.190
RDW (post-op)	1.215	0.873-1.691	0.248

RDW: Red cell distribution width, EAT; Epicardial adipose tissue; LA: Left atrium, (d): diameter mm, (vol): volume
Bolded data indicate significance, OR; odds ratio; CI; confidence interval

significantly greater than that in the sinus rhythm group (62.1 ± 9.1 years, p < 0.01). The study population included 35 (23.5%) women, consisting of 12 (34.3%) women in the POAF group and 23 (20.2%) women in the sinus rhythm group (p = 0.465). The mean duration of ICU follow-up was significantly higher (3.3 ± 2.9 days) in the POAF group than the sinus rhythm group (1.9 ± 0.8 days, p < 0.01). The mean total hospitalization period was higher in the POAF group (11 ± 3.9 days) than in the sinus rhythm group (9.4 ± 3 days, p = 0.030). The red blood cell transfusion amount was higher in the POAF group than the sinus rhythm group (1.09 ± 0.78 U vs. 0.77 ± 0.93 U, respectively), but the difference was not statistically significant (p = 0.07). Demographic variables, including diabetes, hypertension, body mass index, LVEF, and beta-blocker therapy, and procedural factors, including cross-clamp time, pump time, and number of bypass grafts, were similar between the groups.

The preoperative hematological and biochemical parameters, as well as the radiological parameters, of the groups are summarized in **Table 2**. The preoperative hematological and biochemical parameters were similar between the groups. The patients that developed POAF had a significantly greater left atrium (LA) diameter than those in the sinus rhythm group (47 ± 8.3 mm vs. 41 ± 6.2 mm, respectively, p < 0.01), and the LA volume was greater in the POAF group than the sinus rhythm group (72.9 ± 27.2 mm^3 vs. 56.8 ± 15.2 mm^3, respectively, p = 0.030). The EAT volume was 135.71 ± 46.78 cm^3 in the POAF group and 118.71 ± 42.85 cm^3 in the sinus rhythm group (p = 0.046).

Postoperative hematological parameters 24 hours after cardiopulmonary bypass are summarized in **Table 3**. The white blood cell, neutrophil, platelet, and mean platelet volume counts were similar between the groups. The hemoglobin level was significantly lower in the POAF group than in the sinus rhythm group (9.14 ± 1.35 vs. 9.95 ± 1.42, respectively, p = 0.003). The hematocrit reading was also significantly lower in the POAF group than in the sinus rhythm group (26.85 ± 3.65 vs. 29.16 ± 4.13, respectively, p = 0.004). The postoperative RDW ratio was significantly higher in the POAF group than the sinus rhythm group (14.46 ± 1.79 vs. 13.60 ± 1.37, respectively, p = 0.004).

A logistic multivariate regression analysis was performed on age, postoperative RDW, and tomography variables, including left atrial volume, left atrial horizontal diameter, and EAT volume. Only age (OR 1.0731, 95% CI 1.012–1.138, p = 0.018) was an independent predictor of the development of POAF (**Table 4**).

DISCUSSION

AF after cardiopulmonary bypass continues to be a significant problem for cardiac surgeons. In recent studies, the rate of AF was reported to be 17–33% after cardiopulmonary bypass (1). In the present study, POAF developed in 23% of all patients, consistent with the current literature. Previous studies indicated that the development of POAF is associated with a longer hospital stay, increased costs, and increased morbidity, including cerebrovascular events, heart failure, and mortality (2, 3). In the present study, the lengths of hospital stay and ICU stay were significantly higher in patients with POAF. Age was an important predictor of developing POAF after cardiac surgery (12). The mean age of the patients in the present study was 63.8 ± 9.4 years, and the patients in the POAF group were significantly older than those in the sinus rhythm group (69.2 ± 8.3 years vs. 62.1 ± 9.1 years, respectively, $p < 0.01$).

Preoperative hematological and biochemical parameters, including inflammation markers such as RDW and C-reactive protein, were similar between the POAF and sinus rhythm groups. LA vertical diameter, LA horizontal diameter, and LA volume were significantly higher in the POAF group. Similar to our results, Nakai *et al.* (13) reported that LA dimensions were independent predictors of POAF after cardiac surgery.

There is accumulating evidence regarding the relationship between AF and inflammation (7). EAT is metabolically active tissue and is thought to be a source of inflammatory cytokines. Several tomographic studies have shown that EAT volume is associated with cardiac arrhythmias, especially the development of AF in surgical and non-surgical patients (8, 9). Al Chekakie *et al.* (14) suggested that EAT volume is a strong independent factor aside from traditional risk factors in the development of paroxysmal and persistent AF. In another study, Wong *et al.* (15) reported that EAT volume was also associated with the severity of AF and ablation outcome. In the present study, EAT volume was significantly higher in patients that developed POAF than in those that maintained sinus rhythm after surgery. Ultrasonography, CT, and magnetic resonance imaging (MRI) have been used to quantify EAT; however, CT may provide a more accurate evaluation of fat tissue due to its higher spatial resolution compared with ultrasonography and MRI. In the present study, we used 64-slice multidetector CT images to quantify EAT.

An increased RDW indicates variation in the size of red blood cells. RDW is also an important inflammatory marker that it is associated with coronary artery disease and both acute and chronic heart failure (16-18). Two previous studies indicated that preoperative RDW levels were associated with POAF (10, 11). In the present study, the preoperative RDW levels were similar between the groups, but the postoperative RDW levels were significantly higher in the POAF group. Postoperative RDW is not important because the RDW level is known to be affected by anemia, transfusion, and acute hemodynamic changes (16-19). In the present study, the hemoglobin level and hematocrit were significantly lower in the POAF group than in the sinus rhythm group. The transfusion rate was higher in the POAF group, but the difference was not statistically significant.

This study has several limitations. First, this was a retrospective study performed at a single center. Important basal characteristics, including patient age, were different between the groups. The study population was also relatively small. Heart rate was not controlled during CT, which may affect image evaluation. There was no information about current medical therapy such as the use of statins and angiotensin-converting enzyme inhibitors.

On multivariate analysis, only age was shown to be a statistically significant independent predictor of developing POAF in the present study. Similar to our results, Tran *et al.* (20) reported that age was the only predictor of the development of POAF after cardiac surgery. They also reported that being > 65 years old is an important predictor of developing POAF (20).

In conclusion, in our present study although the EAT volume was high in patients developing atrial fibrillation after surgery, age was the only significant predictor of POAF on multivariate analysis. There is a great deal of research interest in EAT and RDW; thus, additional studies regarding the predictive roles of epicardial fat and RDW in POAF are needed.

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