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Original Article CARDIOLOGY

The use of monocyte to HDL ratio to predict postoperative atrial fibrillation after aortocoronary bypass graft surgery

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ABSTRACT

OBJECTIVE: Postoperative atrial fibrillation (POAF) is a frequent and serious complication after aortocoronary bypass graft (ACBG) surgery and one that, unfortunately, increases morbidity and mortality. Postoperative stroke, hemodynamic instability, renal failure, infection, need for inotropic agent and coronary unit are complications caused by POAF. Inflammation and oxidative stress are among several mechanisms that contribute to pathogenesis of POAF. Monocyte to HDL (M/H) ratio is a newly defined parameter of both inflammation and oxidative stress. In this study, M/H ratio was investigated as predictor of POAF after ACBG surgery.

METHODS: Total of 311 patients who underwent ACBG surgery were included in the study. Blood samples for analysis of routine biochemistry and lipid panel were obtained from the patients on the morning of ACBG surgery after 12 hours of fasting. Patients were continuously monitored for occurrence of POAF throughout hospitalization.

RESULTS: POAF was observed in 71 patients following ACBG operation. M/H ratio was significantly higher in POAF(+) group compared with POAF(-) group ($p<0.001$). Median age of POAF(+) patients was 62.0±10.1 years, which was significantly higher than mean age of POAF(-) patients. Other atrial fibrillation (AF) risk factors, such as hypertension, diabetes mellitus, smoking, and alcohol consumption, were similar between groups. Potassium level was statistically lower in POAF(+) group compared with POAF(-) group ($p=0.01$).

CONCLUSION: M/H ratio is an indicator of inflammation and oxidative stress, both of which play important role in pathogenesis of AF. M/H ratio was found be statistically significantly higher in POAF(+) patients than in POAF(-) patients.

Keywords: Atrial fibrillation; monocyte to high-density lipoprotein ratio; postoperative atrial fibrillation.

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Postoperative atrial fibrillation (POAF) is one of the most common complications seen after cardiac surgery, and contributes to mortality and morbidity. Incidence of PAOF has been demonstrated to be 15% to 60% in studies [1–3]. POAF can lead to stroke, infection, need for inotropic agent, hemodynamic instability, and renal failure in postoperative patients. In the literature, development of POAF has been proven to increase acute renal failure and stroke incidence 4 to 5 times in postoperative patients [4]. For this reason, there is interest among clinicians in POAF pathophysiology and management, including search for parameters that may predict POAF in order to prevent its complications. Inflammation and oxidative stress are among several mechanisms contributing to pathogenesis of atrial fibrillation (AF). Leukocyte activation and subsequent release of various proinflammatory and pro-oxidant cytokines and chemokines lead to pathological structural and electrical remodeling in the left atria, which is considered to be important prerequisite for development of AF [5].

High-density lipoprotein (HDL) molecule exhibits anti-inflammatory and antioxidant properties via several pathways, including inhibiting transmigration of monocytes in response to oxidized low-density lipoprotein (LDL), expression of endothelial adhesion proteins, and promoting reverse transport of oxidized molecules [6]. Secondary to these protective effects, low HDL level has been associated with occurrence of AF [7].

Despite the fact that there are many studies evaluating M/H ratio, and particularly correlation with inflammation processes, to our knowledge there is no study examining M/H ratio and POAF. Presently described is investigation of relationship between M/H ratio and POAF.

MATERIALS AND METHODS

Total of 311 patients who underwent coronary artery bypass surgery between February 2015 and June 2015 were consecutively enrolled in the study. Patients who underwent additional cardiovascular surgeries (valvular surgery, aorta surgery, peripheral vascular surgery) were excluded. Patients with valvular heart disease, atrial arrhythmia history, renal failure, or on pacemaker rhythm were also excluded from the study. All patients participating in the study provided signed written consent. The study was approved by the Haydarpasa Numune Training and Research Hospital ethical committee.

Baseline demographic parameters and related clinical information of the patients were recorded preoperatively. All patients underwent preoperative electrocardiogram (EKG) and demonstrated normal sinus rhythm. Transthoracic echocardiogram was also administered to all patients preoperatively by an expert in cardiac imaging.

Blood samples were obtained from the patients on the morning of ACBG surgery after 12 hours of fasting for analysis of routine biochemistry and lipid panel. Samples for complete blood count analysis were collected in ethylenediamine tetraacetic acid anticoagulant tubes at the same time. Reference value for monocyte count in our laboratory was 2% to 10% of total white blood cells.

Isolated coronary artery bypass surgery was performed on all patients. Daily EKG was included in monitored follow-up. Patients were divided into 2 groups based on development of AF during hospitalization period: POAF(+) and POAF(-).

All data were evaluated by using IBM SPSS Statistics for Windows, Version 22.0. (IBM Corp., Armonk, NY, USA). Mean and SD were calculated for quantitative variables. Student's t-test was used for normally distributed variables in both groups and Mann-Whitney U test was used for variables that were not normally distributed. Qualitative variables were evaluated with Pearson's chi-square test with Yates's continuity correction. Logistic regression model was applied to multivariate analysis to identify risk factors related to mortality. P value of <0.05 was accepted as statistically significant.

RESULTS

Total of 311 patients (mean age 60.1±8.7 years) who underwent isolated ACBG surgery between February 2015 and June 2015 were included in the present study. Patients (66.7% male) were divided

Table 1. Demographic variables of the study population

Parameters	Total (n=311)			POAF(-) (n=240)			POAF(+) (n=71)			p
	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	
Age (years)			60.1±8.7			59.5±8.2			62.0±10.1	**0.041****
Women	106	33.3		85	35.4		21	29.6		0.362
BMI			26.8±2.8			26.9±3.7			26.5±4.0	0.480
Diabetes mellitus	105	33.8		76	31.7		29	40.8		0.151
Hypertension	116	37.3		83	34.6		33	46.5		0.069
Alcohol consumption	43	13.8		31	12.9		12	16.9		0.393
Smoker	122	39.1		93	38.7		29	40.8		0.751

BMI: Body mass index; SD: Standard deviation.

Table 2. Echocardiographic and laboratory parameters

Parameters	Total (n=311)	POAF(-) (n=240)	POAF(+) (n=71)	p
Left atrial diameter (cm)	3.91±0.38	3.91±0.40	3.93±0.38	0.653
Left ventricular ejection fraction (%)	55.01±8.32	55.04±8.33	54.92±8.34	0.921
Serum creatinine (mg/dL)	1.16±0.42	1.16±0.40	1.18±0.48	0.771
Sodium (mEq/L)	139.24±2.71	139.26±2.55	139.18±3.21	0.838
Potassium (mEq/L)	4.40±2.04	4.34±0.59	4.10±0.33	**0.01****
Hemoglobin (g/dL)	13.62±6.95	13.70±7.88	13.35±1.48	0.714
White blood cell (x109 /L)	7.15±1.11	7.13±1.11	7.20±1.13	0.627
Monocyte (x109/L)	370.12±47.17	359.12±43.13	407.32±41.05	**<0.001****
LDL cholesterol (mg/dL)	111.41±26.55	109.93±25.28	116.40±30.11	0.07
HDL cholesterol (mg/dL)	41.76±4.56	42.40±4,08	39.59±5.37	**<0.001****
Monocyte/HDL ratio	8.95±1.46	8.52±1.17	10.41±1.40	**<0.001****

HDL: High-density lipoprotein; LDL: Low-density lipoprotein.

into 2 groups, POAF(+) and POAF(-), according to development of AF during hospitalization period. In all, 71 patients (22.8%) had AF occurrence after ACBG surgery.

Both groups were similar in terms of baseline characteristics, with exception of age. POAF(+) group proved to be statistically significantly older than POAF(-) group (p=0.041) (Table 1) Transthoracic echocardiography and laboratory data of our study groups are listed in Table 2. Potassium level was lower in POAF(+) group (p=0.01). Left atrial diameter and ejection fraction were similar between groups.

Multivariate Cox proportional hazards regression analysis revealed that M/H ratio (odds ratio [OR], 51.814; 95% confidence interval [CI], 11.479–233.865; p<0.01) and serum HDL level (OR,1.874; %95 CI, 1.402–2.505; p<0.01) were independent predictors of POAF in patients after ACBG surgery (Table 3). In receiver operating characteristic curve analysis of M/H ratio, area under curve was found to be 0.844.

Table 3. Multivariate analysis of POAF risk factors

	p	OR	95% CI
Monocyte/HDL ratio	<0.01	51.814	11.479–233.865
LDL cholesterol	0.117	1.010	0.998–1.022
HDL cholesterol	<0.01	1.874	1.402–2.505
WBC	0.400	0.882	0.657–1.182
Monocyte	<0.01	0.934	0.901–0.969
Potassium	0.045	0.487	0.241–0.984

CI: Confidence interval; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; OR: Odds ratio; POAF: Postoperative atrial fibrillation; WBC: White blood cell.

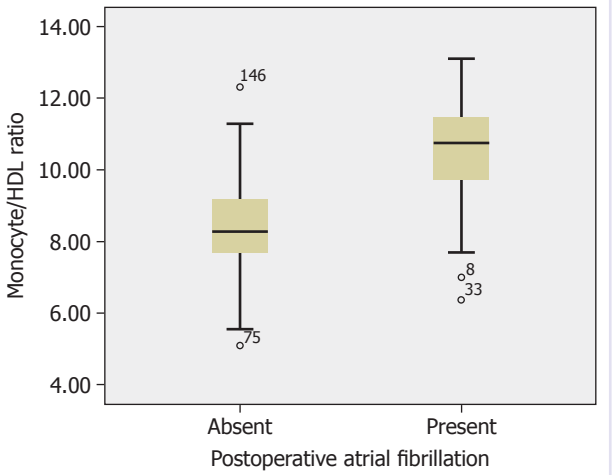

Figure 1. Comparison of preoperative atrial fibrillation and monocyte/HDL ratio. HDL: High-density lipoprotein.

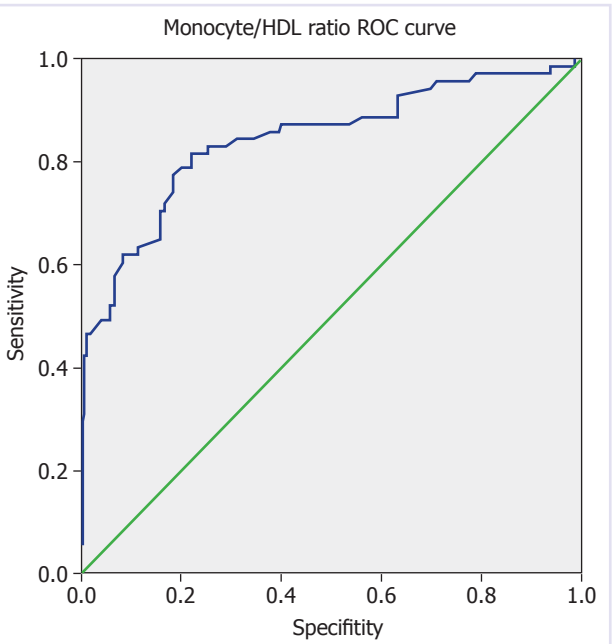

Figure 2. ROC: Receiver operating characteristic. ROC Area under curve: 0.844; cut-off:8.55.

Figure 1 presented the comparison of preoperative atrial fibrillation and monocyte/HDL ratio. Figure 2 presented the ROC analysis showed that the best cut-off value of monocyte/HDL raiot to predict post-operative atrial fibrillation was 8.55.

DISCUSSION

In this prospective study, our aim was to examine and define correlation between M/H ratio and POAF occurrence. After ACBG surgery, patients with higher M/H ratio tended to develop POAF during hospitalization. To our knowledge, present report is the first in the literature illustrating relationship between M/H ratio and POAF in isolated ACBG patients.

Pathogenesis of POAF is multifactorial and involves adrenergic activation, inflammation, atrial ischemia, electrolyte disturbances, and genetic factors [8]. Our study hypothesis originated with inflammation as pathogenesis of AF. Recent reports, including studies of atrial biopsies of patients with AF, have shown structural remodeling caused by inflammation and oxidative damage [9, 10]. Several risk factors for POAF have been identified, such as age older than 70 years, history of prior AF, male gender, left ventricular dysfunction, left atrial enlargement, diabetes, and obesity [8]. In our study, POAF(+) patients were statistically older than those in POAF(-) group. Other risk factors were found to be similar between study groups.

Proinflammatory cytokines have been analyzed many times in connection with POAF correlation. Fontes et al. demonstrated that patients who developed POAF had greater degree of monocyte activation, which is dependent on higher CD11b expression [11]. Other proinflammatory parameters, such as neutrophil/lymphocyte ratio, have been found to be related to increased incidence of POAF [12]. In

addition, C-reactive protein (CRP), an important indicator of inflammation in routine clinical practice, has been studied numerous times to determine correlation with POAF. Unsurprisingly, CRP was found to be statistically higher in POAF patients, which was supportive of inflammatory mechanism for occurrence of AF [13]. Interestingly, peak CRP level occurs on second or third day after operation, which is concurrent with peak incidence of POAF. Other inflammatory parameters involving interleukin (IL)-6, IL-8, IL-10, and vascular endothelial growth factor have also been demonstrated to be higher in AF patients [14]. Based on these studies, we elected to evaluate correlation of inflammatory parameter of M/H ratio to POAF, and found it to be exclusively significant.

Dyslipidemia, which has been repeatedly demonstrated to be risk factor for atherosclerotic vascular disease and AF, as result of oxidative stress and inflammation, is also one of the main sources of POAF pathogenesis. Though there are conflicting studies [15], lower HDL has been considered risk factor for occurrence of AF. Lahoz-Tornos et al. examined HDL value in cardiac surgery patients and found low HDL to be predictor of AF [16]. Mechanism was considered to be secondary to anti-inflammatory and antioxidant functions of HDL. HDL executes its anti-inflammatory effects via several pathways. It inhibits adhesion of immune cells by reducing expression of activated endothelial adhesion molecules, and inhibits monocyte chemoattractant protein-1 molecule, which is chemokine for monocytes in response to LDL oxidation. In a study similar to ours, M/H ratio was used to investigate prediction of AF recurrence after successful cryoballoon-based catheter ablation. M/H was proven to be independent predictor of AF recurrence after cryoablation [17]. Like Canpolat et al., we demonstrated strong correlation between M/H ratio and POAF occurrence in isolated ACBG surgery patients.

The present study had several limitations. First, it was single-center study with small sample size. Secondly, measurement of serum HDL and monocyte count at once may be insufficient to use as parameter. Thirdly, details of surgery, including on-pump, off-pump, and cross-clamp times, were not known and could have been independent factors in development of POAF. Finally, study population included isolated ACBG patients from short period of time.

Conclusion

Despite many investigations, POAF remains a serious factor for morbidity and mortality in ACBG surgery patients. M/H is a novel biomarker and shows strong correlation with POAF occurrence, based on inflammation and oxidative stress mechanisms. Increased M/H ratio will help clinicians predict POAF.

Conflict of Interest: None declared.

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