Relationship between mean platelet volume and ischemic stroke in patients with patent foramen ovale

Patent foramen ovale olan hastalarda ortalama trombosit hacmi ve iskemik inme arasındaki ilişki

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ABSTRACT

Objective: Patent foramen ovale (PFO) is commonly encountered in patients with cryptogenic stroke. Mean platelet volume (MPV), an indicator of platelet reactivity, has been reported in recent trials to be higher in patients with PFO than in normal population. The aim of this study was to investigate whether there is a difference in MPV between patients with PFO and stroke or transient ischemic attack (TIA) and that of patients with asymptomatic PFO.

Methods: Patients with PFO who were younger than 55 years of age were enrolled in this retrospective study. Hemogram parameters of patients with ischemic stroke or TIA (symptomatic group) were obtained during hospitalization once they had stable clinical status.

Results: Total of 108 patients, 51 of whom were symptomatic, were included in the study. MPV was determined to be higher in symptomatic group compared with asymptomatic group (median 10.0 fl [25th-75th percentile: 9.0–11.0] vs median 8.56 fl [25th-75th percentile: 8.0–9.0], respectively; p<0.001,. Cut-off point of 9.0 fl for MPV had 70% sensitivity and 86% specificity in predicting symptomatic PFO patients.

Conclusion: MPV is higher in symptomatic than in asymptomatic PFO patients. This finding may be a subsidiary risk factor to identify patients with PFO and high risk of cardioembolic stroke.

ÖZET

Amaç: Kriptojenik inme geçiren hastalarda foramen ovale açıklığı (FOA) varlığına daha sık rastlanmaktadır. Trombosit reaktivitesinin göstergesi olarak kabul edilen ortalama trombosit hacminin (OTH), FOA'lılarda normal popülasyondan yüksek olduğu bildirilmiştir. Bu çalışmada, FOA'lılarda nedeni bilinmeyen iskemik inme veya geçici iskemik atak (GİA) geçiren hastalar ile semptomsuz olgular arasında OTH yönünden fark olup olmadığı araştırıldı.

Yöntemler: Bu geriye dönük çalışmaya FOA saptanan 55 yaş altı olgular alındı. Nedeni bilinmeyen iskemik inme veya GİA geçiren hastaların (semptomlu grup) yatış esnasında klinik olarak stabilize olduklarında alınan hemogram parametreleri kaydedildi.

Bulgular: Çalışmaya 51'i semptomlu grupta olan 108 hasta alındı. Semptomlu grupta ortalama trombosit hacmi semptomsuz gruptan yüksek bulundu (sırasıyla, ortanca 10.0 fl [25-75 persentil: 9.0–11.0] ve ortanca 8.56 fl [25-75 persentil: 8.0–9.0], p<0.001). OTH'nin 9.0 fl ve üzerinde olmasının semptomlu oluşu göstermede %70 duyarlılık ve %86 özgüllüğe sahip olduğu bulundu.

Sonuç: FOA'lı semptomlu hastalarda OTH semptomsuz olgulardan yüksektir. Bu bulgu FOA'lılarda iskemik inme veya geçici iskemik atak riski yüksek olanları belirlemede yardımcı ek risk faktörü olabilir.

Presence of patent foramen ovale (PFO) is common in patients with cryptogenic stroke (CS) and transient ischemic attack (TIA).[1,2] Prevalence in those patients has been reported as 50% in autopsy trials. However, prevalence is 25% in normal population; therefore, other risk factors are also thought to have impact on stroke development.[3–5] Projected pathophysiology of CS in patients with PFO is passage of

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thrombus formed in venous system to arterial system via PFO, causing paradoxical embolism. However, deep venous thrombosis was detected in 10% of patients with symptomatic PFO.[6] In recent trials, MPV values have been reported to be higher in patients with PFO than in normal population.[7,8] These findings indicate that in addition to paradoxical embolism, environmental and genetic factors may also play a role in prothrombotic condition in PFO patients.

The present study was designed to find out whether there is a difference in MPV between symptomatic and asymptomatic PFO patients.

METHODS

Total of 108 patients with PFO who were younger than 55 years of age and who had 2-dimensional transesophageal echocardiography (TEE) performed between 2010 and 2016 were enrolled in this retrospective study. The study protocol was approved by the local ethics committee. Clinical and demographic data were obtained from patient records. CS and TIA were diagnosed through physical examination, cranial magnetic resonance imaging (MRI) and cranial computerized tomography (CT) findings. In physical examination, risk factors for stroke, such as high blood pressure, smoking, heart disease, and personal or family history of stroke were evaluated, as well as mental alertness, coordination, and balance. Patients were also assessed for numbness or weakness in face, arms, and legs; confusion; and trouble speaking or seeing clearly. MRI was used to detect a wide variety of brain and blood vessel abnormalities and to determine area of the brain damaged by ischemic stroke. CT was performed right after stroke was suspected to reveal any bleeding in the brain or damage to brain cells as result of stroke. Diagnosis of symptomatic patients was made on the basis of all these results. Hemogram parameters of symptomatic (CS or TIA) patients were obtained during their hospital stay once patients were in stable condition, and also recorded for asymptomatic patients in whom PFO was diagnosed incidentally. MPV of symptomatic and asymptomatic groups was compared.

Patients with additional disease that could influence hemogram parameters (e.g., acute infection, inflammatory disease), or coronary artery disease, acute coronary syndrome, atrial fibrillation, renal or hepatic failure, pulmonary embolism, or organic hematological disease, and those with significant structural cardiac abnormalities other than PFO (e.g., moderate to severe valvular disease, left ventricular dysfunction) were not enrolled in the study.

Abbreviations:

CI	*Confidence interval*
CS	*Cryptogenic stroke*
CT	*Computed tomography*
MPV	*Mean platelet volume*
MRI	*Magnetic resonance imaging*
OR	*Odds ratios*
PFO	*Patent foramen ovale*
ROC	*Receiver operating characteristic*
TIA	*Transient ischemic attack*

Blood samples were drawn with careful venopuncture from the antecubital vein into a 21-G sterile syringe without stasis at between 8:00 and 10:00 a.m. after a fasting period of 12 hours. Glucose level, creatinine level, and lipid profiles were determined by standard methods. MPV was measured in blood sample collected in dipotassium ethylenediaminetetraacetic acid tubes. Automatic blood counter (Beckman Coulter Inc., Indianapolis, IN, USA) was used for whole blood count, including MPV. Reference limits of MPV were accepted as 6-10 fl. MPV was measured within an hour after sampling.

TTE and TEE records of patients were analyzed (EPIQ 7 cardiac ultrasound; Philips Healthcare, Inc., Andover, MA, USA). All echocardiographic findings were carefully evaluated by 2 cardiologists. All measurements were taken according to recommendations of the American Society of Echocardiography. Left atrial diameter and left ventricular end-systolic and end-diastolic diameters were measured in parasternal long axis view with M-mode echocardiography. Ejection fraction was measured using modified Simpson's rule.

Statistical analysis

Data were analyzed with SPSS software, version 22.0 (IBM Corp., Armonk, NY, USA) and MedCalc (MedCalc Software, Ostend, Belgium) statistical software. Categorical variables were presented as frequency and percentage. Chi-squared test was used to compare categorical variables. Kolmogorov-Smirnov test was used to assess distribution of continuous variables. Student's t-test was used for variables with normal distribution, and values were presented as mean±SD. Continuous variables without normal distribution were analyzed using Mann-Whitney U test and values obtained were presented as median [50th] value and interquartile range [25th and 75th]. Significance of effective variables for ischemic stroke was initially assessed

using univariate regression analysis. Among variables that had level of significance of p<0.25, final model was created by identified the most decisive factors to distinguish between groups using a backward logistic regression method. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. Optimum cut-off level of MPV for symptomatic group was determined automatically using MedCalc software receiver operating characteristic (ROC) curve analysis. A 2-tailed p value of <0.05 was considered statistically significant.

RESULTS

Of total 108 patients enrolled in the study, 51 were symptomatic. Mean age of patients in asymptomatic group was 38.9±9.4 years and mean age was 44.2±8.8 years in symptomatic group. Sixteen patients had TIA and 35 patients had stroke in symptomatic group. All symptomatic patients were using acetylsalicylic acid. Baseline characteristics of patients with symptomatic and asymptomatic PFO are provided in Table 1.

Complete blood count parameters are listed in Table 2. No significant difference was found in white blood cell and hemoglobin level between the 2 groups. Platelet count was higher in symptomatic group compared with asymptomatic group (296.0 $10^3/\mu$L [range: 279.0–324.0 $10^3/\mu$L] vs 248.0 $10^3/\mu$L [range: 212.5–282.5 $10^3/\mu$L], respectively; p<0.001). Lymphocyte count was lower in symptomatic group than in asymp-

Table 1. Clinical characteristics of the study population

Variable	Asymptomatic PFO (n=57)			Symptomatic PFO (n=51)			*p*
	n	%	Mean±SD	n	%	Mean±SD	
Age (years)			38.9±9.4			44.2±8.8	0.003
Female	29	50.9		17	33.3		0.066
Hypertension	24	42.1		40	78.1		<0.001
Diabetes mellitus	7	12.3		13	25.5		0.078
Total cholesterol (mg/dL)			186.8±40.5			217.7±42.8	<0.001
Low density lipoprotein (mg/dL)			116.2±34.3			144.1±37.9	<0.001
High density lipoprotein (mg/dL)			43.7±9.1			41.6±12.6	0.056
Triglyceride (mg/dL)			120.0 (93.5–179.0)			160.0 (112.0–210.0)	0.008
C-reactive protein (mg/dL)			4.58±4.02			4.86±2.8	0.675
Glucose (mg/dL)			82.7±11.4			96.1±14.6	0.026

Continuous variables are presented as mean (standard deviation) or median (25th-75th percentile). Categorical variables are presented as number (percentage). PFO: Patent foramen ovale; SD: Standard deviation.

Table 2. Common hemogram parameters of the patients

Variable	Asymptomatic PFO (n=57)	Symptomatic PFO (n=51)	*p*
Hemoglobin (g/dL)	12.9±2.0	13.5±1.6	0.075
White blood cell count (×10^3 per μL)	7.6±1.5	8.0±1.2	0.156
Platelet count (×10^3 per μL)	248.0 (212.5–282.5)	296.0 (279.0–324.0)	<0.001
Lymphocyte count (×10^3 per μL)	1.9±0.8	1.4±0.5	<0.001
Platelet to lymphocyte ratio	86.0 (101.0–133.0)	162.0 (150.0–178.0)	<0.001
Mean platelet volume (fl)	8.56 (8.0–9.0)	10.0 (9.0–11.0)	<0.001

Continuous variables are presented as mean (standard deviation) or median (25th-75th percentile). Categorical variables are presented as number (percentage). PFO: Patent foramen ovale.

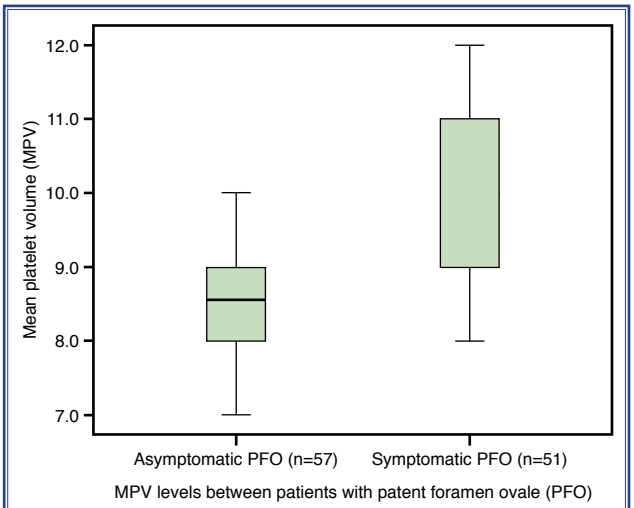

Figure 1. Mean platelet volume in symptomatic and asymptomatic PFO patients. MPV: Mean platelet volume; PFO: Patent foramen ovale.

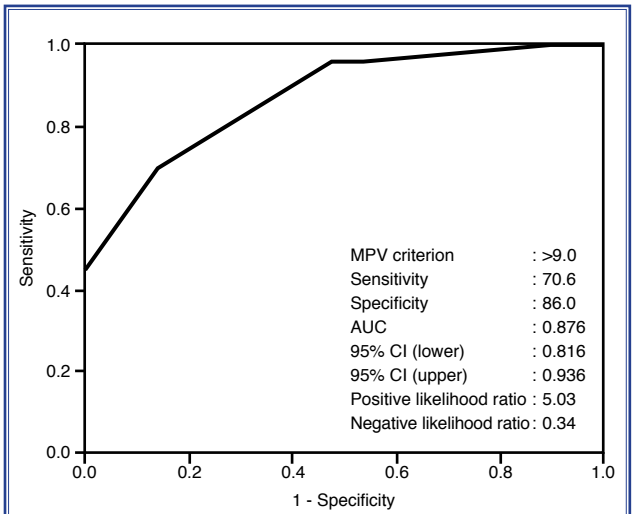

Figure 2. Receiver operating characteristics curve of mean platelet volume for symptomatic patent foramen ovale. MPV: Mean platelet volume.

tomatic group (1.4±0.5 $10^3/\mu$L vs 1.9±0.8 $10^3/\mu$L, respectively; p<0.001). Platelet/lymphocyte ratio value was higher in symptomatic group compared with asymptomatic group (162.0 [range: 150.0–178.0] vs 86.0 [range: 101.0–133.0], respectively; p<0.001). Furthermore, MPV was higher in symptomatic group when compared with asymptomatic group (10.0 fl [range: 9.0–11.0 fl] vs 8.56 [range: 8.0–9.0 fl], respectively; p<0.001). ROC curve analysis revealed MPV >9.0 fl had 70% sensitivity and 86% specificity in predicting symptomatic PFO patients (area under the curve: 0.876; p<0.001) (Figure 1, Figure 2).

Among echocardiographic parameters, left ventricular ejection fraction, left ventricular end-diastolic diameter, left ventricular end-systolic diameter, and left atrial diameter were not significantly different between the 2 groups. However, right atrial diameter was significantly greater in symptomatic group (32.0 mm [range: 30.0–37.0 mm] vs 30.0 mm [range: 28.5–33.0 mm]; p=0.014) (Table 3).

Univariate and multivariate analysis of symptomatic PFO group factors was performed using logistic regression. Univariate logistic regression analysis demonstrated significant differences in age, platelet count, lymphocyte count, and hypertension. MPV >9.0 was found to be an independent predictor of symptomatic PFO in backward logistic regression analysis (OR: 52.176; 95% CI: 6.171–431.248; p<0.001) (Table 4).

DISCUSSION

In the present study, elevated MPV was found to be associated with history of stroke/TIA in patients with

Table 3. Conventional transthoracic echocardiographic parameters of the study population

Variable	Asymptomatic PFO (n=57)	Symptomatic PFO (n=51)	*p*
Left ventricular ejection fraction (%)	62.8±2.6	62.0±3.4	0.405
Left ventricular end diastolic diameter (mm)	42.0 (39.0–46.0)	45.0 (42.0–50.0)	0.162
Left ventricular end systolic diameter (mm)	26.0 (24.0–30.0)	28.0 (25.0–31.0)	0.174
Left atrium diameter (mm)	32.0 (31.0–36.5)	33.0 (30.0–36.0)	0.831
Right atrium diameter (mm)	30.0 (28.5–33.0)	32.0 (30.0–37.0)	0.014

Continuous variables are presented as mean (standard deviation) or median (25th-75th percentile). Categorical variables are presented as number (percentage). PFO: Patent foramen ovale.

Table 4. Evaluation of the factors affecting symptomatic PFO patients using univariate and backward multivariate logistic regression analysis

	Univariate		Multivariate	
Variable	OR (95% CI)	*p*	Adjusted OR (95% CI)	*p*
Age	1.066 (1.019–1.114)	0.005	1.105 (1.007–1.213)	0.035
Left ventricle ejection fraction	0.917 (0.805–1.43)	0.186		
Left atrium diameter	0.993 (0.915–1.077)	0.865		
Mean platelet volume >9.0	14.700 (5.629–38.388)	<0.001	58.926 (7.795–445.424)	<0.001
White blood cell count	1.227 (0.933–1.614)	0.143	2.992 (1.182–7.574)	0.021
Platelet count	1.009 (1.002–1.016)	0.008	1.033 (1.009–1.057)	0.007
Hemoglobin count	1.181 (0.963–1.449)	0.110		
Lymphocyte count	0.280 (0.141–0.555)	<0.001	0.011 (0.001–0.132)	<0.001
C-reactive protein	1.024 (0.918–1.142)	0.673		
Diabetes mellitus	2.443 (0.889–6.716)	0.083		
Hypertension	5.000 (2.138–11.693)	<0.001		
Triglyceride	1.009 (1.002–1.015)	0.007		

PFO. Cut-off value of 9.0 fl for MPV ascertained with ROC curve analysis was found to have sensitivity of 70% and specificity of 86% to predict stroke/TIA. This finding may aid prediction of stroke risk in patients with PFO. Moreover, it may help to identify patients with PFO who require antiaggregant/antithrombotic treatment.

Etiology of 40% of acute ischemic strokes cannot be determined; they are what is referred to as CS.[9] Prevalence of PFO in patients with CS has been demonstrated to be higher than in normal population. However, data regarding PFO as an independent risk factor for CS is contradictory. Since PFO is also found in normal population (25%), studies have been conducted with the intent of identifying which patients with PFO have higher risk of stroke. Certain morphological features (e.g., PFO size, concomitant atrial septal aneurysm, ratio of right to left shunt) have been reported to assist in determination of symptomatic patients.[10–12]

Projected mechanism of stroke in patients with PFO is paradoxical embolism. PFO is a potential route for embolic transit of platelet aggregations, thrombi, gas bubbles, or other particulate matter from systemic venous circulation to the brain. PFO could also be nidus for in situ thrombus formation, which could potentially embolize.[13] Prevalence of deep venous thrombosis has been reported to be higher in patients with PFO and CS than patients without PFO. On the other hand, deep venous thrombosis was detected in only 10% of patients in a study that enrolled ischemic stroke patients without risk factors except PFO.6 Furthermore, pelvic vein thrombosis was found in 20% of CS patients, whereas finding was 4% in ischemic stroke patients in the Paradoxical Emboli from Large Veins in Ischemic Stroke (PELVIS) trial.[14] Certain genetic and environmental factors were thought to lead to prothrombotic state due to the fact that majority of CS patients do not have deep venous thrombosis. Lantz et al. stated that prothrombin gene polymorphism (20210G/A) might play a role in stroke development in patients with PFO.[15] Moreover, in another trial, factor V Leiden and 20210G/A mutations were encountered more frequently in patients with PFO and CS.[16,17]

In addition to above-mentioned data, coagulation defects may accompany patients with PFO. Undas et al. stated that fibrin clot abnormalities were found in patients with cerebral ischemic episodes and PFO, which might explain increased tendency for embolic episodes in some patients with PFO and a concomitant disorder.[18] Demir et al. reported that MPV was higher in asymptomatic patients with PFO than in patients without PFO.[7] This data might be significant in relationship between PFO and CS.

Platelets play a major role in thromboembolic events. MPV, which is an indicator of platelet reactiv-

ity, is a cheap and feasible hemogram parameter.[19] It was determined in recent trials that there is a relationship between increased MPV and cardiovascular mortality.[20] Medications could also alter MPV. De Luca et al. stated that dual antiplatelet therapy with acetylsalicylic acid and clopidogrel may enhance MPV paradoxically in patients with acute coronary syndrome.[21] On the other hand, Shah et al. reported that acetylsalicylic acid administered to healthy volunteers did not have an impact on MPV.[22] In our trial, most of the symptomatic patients were taking acetylsalicylic acid, which may have increased MPV.

Shear stress and deformation of platelets during passage through PFO, which is a tubular structure, may cause platelet activation that results in further increased MPV.[7] Enhanced MPV signifies increased platelet reactivity, and consequently tendency to thrombosis. Huge platelets produce more thromboxane A2 with high enzymatic activity.[23] Aggregation is the clumping of activated platelets. Platelet aggregation is the principal step toward formation of thrombus. Measuring MPV is an easy and inexpensive method to evaluate platelet function and is a physiological variable with hemostatic significance.[19] Giant platelets are more reactive, produce more prothrombotic factors, and clump together more easily. Giant platelets contain denser granules and secrete more serotonin and beta-thromboglobulin.[24–26] Increased MPV is associated with increased in vitro aggregation in response to adenosine diphosphate and collagen.[27]

Treatment protocols are not precise in patients with PFO. According to contemporary guidelines, medication is not recommended for asymptomatic patients with PFO. Optimal medical treatment is controversial in symptomatic patients. Mohr et al. reported that acetylsalicylic acid and warfarin have similar impact in terms of precluding recurrent CS.[28] PFO may be occluded in patients with high recurrent TIA or stroke. However, transcatheter PFO closure was not demonstrated to be superior to medical treatment in prevention of recurrent TIA or stroke in the CLOSURE I trial.[29] Moreover, transcatheter PFO closure was also not found to be superior to medical treatment in the Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment (RESPECT) trial, which enrolled 980 patients.[30] In addition, a meta-analysis of 2303 patients with PFO and CS/TIA found that PFO closure did have better outcomes than medical treatment.[31] These findings indicate that it is not just paradoxical embolism that is responsible for stroke in patients with PFO; genetic, thrombotic, and atherosclerotic factors may also play a role.

Limitations

MPV of prestroke period of symptomatic patients was not available due to the fact that our study was retrospective. However, MPV levels were obtained after clinical stabilization of patients. Therefore, impact of CS/TIA on MPV is thought to be minimal.

Conclusion

MPV evaluation may aid in identification of patients with PFO who may become symptomatic. Furthermore, the results of our study may encourage use of antiaggregant/antithrombotic therapy in patients with PFO and enhanced MPV.

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Keywords: Mean platelet volume; patent foramen ovale; stroke.

Anahtar sözcükler: Ortalama trombosit hacmi; patent foramen ovale; inme.