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Increased Mean Platelet Volume in Hypertrophic Cardiomyopathy

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Abstract

Thromboembolic events may be seen in patients with hypertrophic cardiomyopathy (HCM). We investigated the mean platelet volume (MPV), an indicator of platelet activation in patients with HCM. This study included 112 patients with HCM, in which 40 were patients with hypertrophic obstructive cardiomyopathy (HOCM), and 106 were control participants. The MPV was significantly higher in patients with HCM than in controls (9.1 $\pm$ 0.3 vs 7.9 $\pm$ 0.3 fL, $P = .01$). In the subgroup analyses, MPV was also higher in patients with HOCM compared to those with hypertrophic nonobstructive cardiomyopathy (HNCM; 9.3 $\pm$ 0.3 vs 9.0 $\pm$ 0.2 fL, $P = .01$). Similarly, patients with HNCM had higher MPV values than controls (9.0 $\pm$ 0.2 vs 7.9 $\pm$ 0.3 fL, $P = .01$). The MPV was significantly and positively correlated with left ventricular outflow tract (LVOT) obstruction ($r = .42$, $P = .001$) and septal thickness ($r = .62$, $P = .001$). In linear regression analysis, MPV was independently associated only with septal thickness ($\beta = .07$, 95% confidence interval: 0.04-0.09, $P = .001$). The MPV can be elevated in patients with HCM regardless of the obstruction of LVOT and may be associated with the severity of septal thickness.

Keywords

mean platelet volume, platelet activation, hypertrophic cardiomyopathy

Introduction

Hypertrophic cardiomyopathy (HCM) is a genetic disease with a broad clinical spectrum and different consequences.[1,2] Stroke and systemic embolic events can occur as complications of HCM.[3,4] Evidence from several studies has shown that the coagulation system and platelets can be activated in patients with HCM.[5,6] The obstruction of the left ventricular outflow tract (LVOT) has been reported to be independently associated with enhanced thrombin generation and platelet activity in such patients with sinus rhythm.[6] A previous study has shown that platelet aggregation may be induced spontaneously in patients with HCM, and that it may be positively correlated with left ventricular hypertrophy (LVH).[7] Another study has also shown that morphometric and chemical differences, such as increased cell size, decreased phosphorus concentration, and increased permeability to cations, may occur in platelets of such patients.[8] Mean platelet volume (MPV) is considered to be a simple marker reflecting platelet activation[9,10] and an increased risk of cardiovascular disease.[9,11] There is evidence that larger platelets have higher thrombotic potential.[12] To our knowledge, there is no study evaluating MPV in patients with HCM. Therefore, we aimed to investigate platelet activation in patients with both hypertrophic obstructive cardiomyopathy (HOCM) and hypertrophic obstructive cardiomyopathy (HNCM) using MPV measurement.

Patients and Methods

Study Population

The patient group consisted of 112 consecutive patients (43 females and 69 males, mean age 44.9 $\pm$ 11.8 years) with idiopathic HCM admitted to our university hospital between 2005 and 2012. A total of 106 patients who were matched for age, gender, and body mass index were selected as control group (42 females, 64 males, mean age 45.5 $\pm$ 8.6 years) from those who were admitted to our outpatient clinic for suspicion of heart disease. All the patients underwent echocardiographic examination. Echocardiographic evaluation in the control

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group revealed no abnormalities of cardiac structure and function. The HCM was defined as the presence of a hypertrophied, nondilated ventricle in the absence of underlying cardiac or systemic secondary causes and was based on the World Health Organization/International Society and Federation of Cardiology definition of cardiomyopathies.[13]

Patients with HCM were subdivided into 2 groups: HOCM (n = 40) and HNCM (n = 72). The HOCM was diagnosed when a patient had a left ventricular (LV) pressure gradient >30 mm Hg without provocation in the LVOT and/or midventricle.[14]

Exclusion criteria were acute illness, arterial hypertension, cancer, paroxysmal or persistent atrial fibrillation, autoimmune disorders, history of bleeding or venous thromboembolism, endocarditis, previous cerebrovascular event, myocardial infarction, stroke, renal or hepatic dysfunction, and treatment with oral anticoagulants. Based on echocardiographic data, patients with LV cavity dilatation and depressed contractility were also excluded from the study. The study was approved by the local ethics committee, and all patients gave their informed consent.

Echocardiography

Transthoracic echocardiographic examinations were performed using a VingMed System FiVe machine (GE, Norway). In each patient, M-mode and 2-dimensional echocardiograms were obtained, followed by pulsed- and continuous-wave Doppler recordings. Left atrial and ventricular dimensions and LV ejection fraction were measured by M-mode echocardiography in the parasternal long-axis view using the American Echocardiography Society M-mode technique.[15] The LVOT gradient was measured using Doppler recordings, and a value of $\geq$30 mm Hg was considered significant for HOCM. As in the study of Maron et al, care was taken to report only those gradients derived from Doppler velocity profiles typical of subaortic obstruction, which allows contamination by the mitral regurgitation jet to be avoided.[16] Morphological assessment of the narrowed LVOT was performed by the measurement of the minimal distance between the mitral valve and the ventricular septum during systole in the parasternal long-axis view with M-mode echocardiography.[17]

Biochemical Measurements

Blood samples were drawn from the antecubital vein by careful vein puncture in a 21G sterile syringe without stasis at 08.00 to 10.00 AM, after a fasting period of 12 hours. Glucose, creatinine, and lipid profiles were determined by standard methods. The MPV was measured in a blood sample collected in dipotassium EDTA tubes. An automatic blood counter (Beckman-Coulter Co, Miami, Florida) was used for whole blood counts. The MPV was measured within 30 minutes after sampling to prevent EDTA-induced platelet swelling.

Statistical Analysis

Data were analyzed using the SPSS software version 15.0 for Windows. Continuous variables were reported as mean $\pm$ standard deviation, and categorical variables as percentage. To compare continuous variables, the Student t test or Mann-Whitney U test were used where appropriate. One-way analysis of variance was used to evaluate the difference among the groups, with Scheffe correction for multiple comparisons. Categorical variables were compared with the chi-square test. The correlation of MPV with other variables was evaluated with Pearson correlation analysis. Variables with a $P < .05$ in the correlation analysis were included in the multivariable linear regression analysis to identify the independent variables for MPV. β-value and its 95% confidence interval (CI) were calculated for the variables that were independently associated with MPV. Statistical significance was defined as $P < .05$.

Results

Table 1 summarizes clinical features, laboratory, and echocardiographic findings of patients with HCM and control group. There was no significant difference in dyslipidemia, smoking, diabetes mellitus, systolic and diastolic blood pressures, hemoglobin level, and white blood cell count in the 2 groups. The MPV was significantly higher in patients with HCM than in controls (9.1 $\pm$ 0.3 vs 7.9 $\pm$ 0.3 fL, $P = .01$). In contrast, platelet count was lower in patients with HCM compared to the controls ($P = .01$, Table 1). As expected, left atrial size was larger in patients with HCM than in controls, but diastolic diameter of the left ventricle was smaller. Similarly, interventricular septum was much thicker in patients with HCM than in controls (Table 1).

Table 2 presents clinical features and laboratory findings of patients with obstructive or nonobstructive form of HCM and control group. The MPV was also significantly higher in patients with HOCM compared to those with HNCM and controls (9.3 $\pm$ 0.3 vs 9.0 $\pm$ 0.2 fL, $P = .01$ and 9.3 $\pm$ 0.3 vs 7.9 $\pm$ 0.3 fL, $P = .001$, respectively). The MPV was also significantly higher in patients with HNCM compared with controls ($P = .01$, Table 2). However, platelet count was lower in patients with both HOCM and HNCM compared with controls ($P = .01$).

In the correlation analysis, MPV was significantly and positively correlated with LVOT obstruction ($r = 0.42$, $P = .001$) and septal thickness ($r = 0.62$, $P = .001$). Of the 2 variables, septal thickness (β = .07, 95% CI: 0.04-0.09, $P = .001$) was independently associated with MPV in linear regression analysis.

Discussion

We found that MPV was significantly higher in patients with both HOCM and HNCM compared with controls. Moreover, it was correlated with LVOT obstruction and septal thickness in patients with HCM.

Table 1. Demographic, Clinical, Echocardiography, and Laboratory Characteristics of Patients With Hypertrophic Cardiomyopathy (HCM) and Controls.[a]

Variables	HCM, n = 112	Controls, n = 106	*P*
Age, years	44.9 ± 11.8	45.5 ± 8.6	.71
Sex (M/F)	69/43	64/42	.85
BMI, kg/m^2	27.3 ± 4.0	27.2 ± 3.8	.82
SBP, mm Hg	126 ± 7	124 ± 12	.14
DBP, mm Hg	79 ± 5	79 ± 6	.88
Heart rate, beats/min	67 ± 5	69 ± 5	.03
Diabetes mellitus, n (%)	7 (6.3)	6 (5.7)	.85
Dyslipidemia, n (%)	20 (17.9)	18 (17)	.86
Smoking, n (%)	10 (9.2)	9 (8.5)	.86
Aspirin, n (%)	26 (23.2)	19 (17.9)	.33
Septal thickness, mm	20.9 ± 3.1	10.3 ± 0.9	.01
Left atrium diameter, mm	42.7 ± 4.1	32.2 ± 4.5	.01
LVDD, mm	43.3 ± 4.6	46 ± 2.8	.01
Left ventricle ejection fraction, %	65.5 ± 4.5	65.0 ± 0.9	.35
LVOT gradient >30 mm Hg, n (%)	40 (35.7)		
WBC, $\times 10^3$ cells/μL	7.92 ± 2.17	7.52 ± 1.56	.12
Hemoglobin, g/dL	14.1 ± 1.2	14.3 ± 1.2	.36
Platelet count, $\times$ 10^3 cells/μL	259 ± 67	292 ± 55	.01
MPV, fL	9.1 ± 0.3	7.9 ± 0.3	.01

Abbreviations: M/F, male to female; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVDD, left ventricular diastolic diameter; LVOT, left ventricular outflow tract; WBC, white blood cell; MPV, mean platelet volume; HCM, hypertrophic cardiomyopathy.
[a] *P* value is for comparison between control and study population.

To our knowledge, there is no study investigating MPV in patients with HCM. Thromboembolic events can occur in patients with HCM, and they can lead to an increase in morbidity and mortality.[2,4-6] Platelets may be activated in patients with HCM, and this activation may be associated with systemic thromboembolism.[5]

Dimitrow et al have found that there was an increase in 3 platelet activation markers including soluble CD40 ligand, β-thromboglobulin, and P-selectin in patients with HOCM. However, only P-selectin was higher in patients with HNCM compared with controls. They suggested that the accelerated flow due to LVOT obstruction may stimulate platelets through an increase in shear stress.[6] On the other hand, Lip and Blann have reported that platelet activation can play an important role in the development of LVH.[18]

It has been reported that alterations in the plasma levels of molecular markers of the prothrombotic and fibrinolytic status may be seen in patients with HCM.[5] Among prothrombotic markers, fibrinopeptide A, thrombin–antithrombin III (TAT) complex, and F1 + 2 levels have been reported to be increased in patients with HCM compared with normal patientts.[6,19] Plasma fibrinopeptide A and TAT levels were positively correlated with left atrial diameter but not with LV diastolic volume.[19] Dimitrow et al have showed that TAT and F1 + 2 levels were elevated in patients with HOCM, and that they were positively correlated with the LVOT gradient.[6] Indeed, the turbulent flow in LVOT may contribute to prothrombotic state through an increase in shear stress.[6] Similarly, some studies have shown that shear stress in turbulent flow resulting from the stenotic valves induce platelet activation.[20,21] Two new studies reported elevated MPV in patients with mitral and aortic stenosis.[22,23] These findings imply that turbulent flow in LVOT may trigger platelet activation in patients with HOCM.

The patients with HCM have endothelial dysfunction, which can be detected by means of elevation in endothelial-related biomarkers such as thrombomodulin, tissue factor pathway inhibitor, asymmetric dimethylarginine, and endothelin 1 in peripheral blood.[24,25] Endothelial dysfunction can be associated with multiple proatherogenic conditions including inflammation, smooth muscle cell proliferation, oxidative stress, platelet activation, leukocyte infiltration, and thrombosis.[26,27] According to this important background, we speculate that endothelial dysfunction may lead to an increase in MPV in patients with HCM.

Platelet size is regulated at the level of the megakaryocyte. The presence of inflammation and especially some inflammatory cytokines such as interleukin 3 (IL-3) or IL-6 influences megakaryocyte ploidy and can lead to the production of more reactive and larger platelets.[28-30] The MPV levels have been reported to be significantly correlated with high-sensitivity C-reactive protein (CRP) levels in hypertensive patients.[31] On the other hand, serum IL-6 and CRP levels can be elevated in patients with HCM compared with normal controls.[24,32] Accordingly, it can be suggested that increased IL-6 and CRP levels may contribute to elevation of MPV in patients with HCM by stimulating the megakaryocyte ploidy.

It is well known that increased platelet activation and aggregation are closely related to cardiovascular complications.[11] The MPV is a simple marker reflecting platelet size and activation.[9,11] Larger platelets are enzymatically more active than smaller platelets, and they have higher thrombotic potential.[12] In other words, they have more granules and higher thromboxane

Table 2. Comparison of Clinical and Laboratory Characteristics in Patients With the Obstructive or Nonobstructive Form of Hypertrophic Cardiomyopathy (HCM) and Controls.[a]

Variables	HOCM, n = 40	HNCM, n = 72	Controls, n = 106	*P*
Age, years	46.0 ± 13.5	44.3 ± 10.8	45.5 ± 8.6	.68
Male/female	24/16	45/27	64/42	.95
Diabetes mellitus, n (%)	3 (7.5)	4 (5.6)	6 (5.7)	.90
Dyslipidemia, n (%)	8 (20)	12 (16.7)	18 (17)	.89
Smoking, n (%)	4 (10)	6 (8.7)	9 (8.5)	.96
Aspirin, n (%)	11 (27.5)	15 (20.8)	19 (17.9)	.45
WBC, $\times 10^3$ cells/μL	7.84 ± 1.67	7.97 ± 2.42	7.52 ± 1.56	.29
Hemoglobin, g/dL	14 ± 1.2	14.2 ± 1.3	14.3 ± 1.2	.34
Platelet count, $\times 10^3$ cells/μL	245 ± 67[b]	266 ± 66[b]	292 ± 55	.01
MPV, fL	9.3 ± 0.3[c,d]	9.0 ± 0.2[d]	7.9 ± 0.3	.01

Abbreviations: HOCM, hypertrophic obstructive cardiomyopathy; HNCM, hypertrophic nonobstructive cardiomyopathy; WBC, white blood cell; MPV, mean platelet volume.
[a] *P* value is for comparison among groups.
[b] $P = .01$ HOCM versus controls and HNCM versus controls.
[c] $P = .001$ HOCM versus controls.
[d] $P = .01$ HOCM versus HNCM and HNCM versus controls.

A2 level. They also express more glycoprotein Ib and IIb/IIIa receptors and aggregate more rapidly with collagen.[33,34]

We can extrapolate that increased MPV values may indicate the altered platelet reactivity and aggregation in patients with HCM, and that its increase may facilitate thrombus formation. Therefore, patients with HCM with elevated MPV may have a higher risk of thromboembolic events, and they may need more effective antiplatelet treatment.

Study Limitations

Our control group included diabetic and dyslipidemic patients. The MPV can be elevated in diabetic patients.[35] However, the frequency of diabetes mellitus was comparable among the groups. Similarly, dyslipidemic patient rates were comparable among the groups, although there is an association between MPV and hypercholesterolemia.[36]

In conclusion, our findings show that MPV, an indicator of platelet activation, was significantly higher in patients with HOCM and HNCM than in controls. The LVOT obstruction was independently associated with MPV values. Thus, patients with HCM may need more aggressive antiplatelet therapy, especially for those with HOCM.

Declaration of Conflicting Interests

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