CLINICAL CARDIOLOGY

Association between mean platelet volume and autonomic nervous system functions: Increased mean platelet volume reflects sympathetic overactivity

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BACKGROUND: Increased mean platelet volume (MPV) may reflect increased platelet activation or increased numbers of large, hyperaggregable platelets, and is accepted as an independent coronary risk factor. The adrenergic system has effects on platelet activation and thrombocytopoiesis.

OBJECTIVE: To assess the effects of autonomic nervous system activity on MPV in patients with acute myocardial infarction (MI).

METHODS AND RESULTS: Forty-seven patients with acute anterior MI were compared with 32 patients with healthy coronary arteries. All patients underwent heart rate (HR) variability analysis using 24 h Holter monitoring. Blood samples were taken for MPV measurements twice a day (day- and nighttime) during Holter monitoring. Mean HR, low frequency band of HR variability power spectrum to high frequency band of HR variability power spectrum (LF:HF) ratio, LF and MPV were higher in patients with anterior MI than in the control group. SD of all NN (RR) intervals, root mean square of successive differences, number of NN intervals that differed by more than 50 ms from the adjacent interval divided by the total number of all NN intervals, HF bands and platelet counts were lower in the patients with anterior MI than in the control group. Daytime LF bands, LF:HF ratio and MPV were significantly higher, and HF bands were significantly lower than the nighttime values for both groups. The differences in daytime and nighttime measurements were more significant in the patients with acute MI than in the control group. Pearson's correlation analysis showed that MPV was positively correlated with ventricle score, degree of left anterior descending artery stenosis, mean HR, LF bands and LF:HF ratio; and negatively correlated with the SD of all NN intervals, HF bands and platelet count. Multivariate analysis revealed that MPV was significantly affected by ventricle score and the LF:HF ratio.

CONCLUSIONS: MPV was significantly higher in the patients with acute MI. In both groups, MPV showed great daytime and nighttime variation, which can be attributed to alterations in the autonomic nervous system. The authors suggest that the prognostic role of increased MPV in patients with acute MI is closely associated with increased sympathetic activity and decreased HR variability.

Key Words: *Heart rate variability; Mean platelet volume; Myocardial infarction; Sympathetic activity*

Platelets and their interaction with the vessel wall are important in the development of atherosclerosis and arterial thrombosis (1,2). Moreover, platelet behaviour is an important determinant of both the first (3) and recurrent myocardial infarction (MI) (4,5). Large platelets have been found immediately after an MI (6) and are more reactive than small ones (7). Increased mean platelet volume (MPV) may reflect increased platelet activation or increased numbers of large, hyperaggregable platelets (8), and is accepted as an independent coronary risk factor (4,5).

Sympathetic activity is increased during acute MI (9). Increased adrenaline activates and aggregates blood platelets (10). Heart rate variability (HRV) analysis has been extensively used to evaluate autonomic modulation of the sinus node and to identify patients at risk for increased cardiac mortality (11). Some HRV parameters, such as decreased SD of all NN (RR) intervals (SDNN) and increased low frequency to high frequency bands of HRV power spectrum (LF:HF) ratio, are associated with increased cardiac mortality in almost all clinical conditions characterized by an autonomic imbalance (eg, after an MI) (12-17). Moreover, HRV analysis reflects sympathovagal balance and has previously been used to define the role of autonomic nervous system activity in certain cardiac disorders (18). In the present study, we aimed to show the effects of increased sympathetic activity on platelet size during acute MI.

PATIENTS AND METHODS

Study population

Forty-seven patients admitted to the Yüksek Ihtisas Hospital clinic (Ankara, Turkey) diagnosed with acute anterior MI and who underwent thrombolytic therapy (streptokinase 1,500,000 U) were compared with 32 age- and sex-matched patients. The control group comprised patients who underwent coronary angiography due to suspicion of coronary artery disease and angiography revealed healthy coronary arteries. Diagnosis of acute MI was established by ST segment elevation, subsequently defined in more than two leads and associated with typical chest pain, and confirmed by the elevation of serum creatine kinase-MB isoenzyme

concentrations to a level greater than two times the normal upper limit during the patients' clinical course. All patients underwent thrombolytic therapy within 6 h of symptom onset and received standard medical therapy in accordance with conventional guidelines. Informed written consent was obtained from all patients, and the Yüksek Ihtisas Hospital ethics committee approved the trial. Patients with abnormal serum electrolytes; historical and/or electrocardiographic findings of a previous MI; chronic treatment with antiarrhythmic drugs and/or digitalis; clinical signs of left ventricular failure, cardiogenic shock or mechanical complications at admission; pre-excitation syndromes; ventricular pacing; bundle branch block; intraventricular conduction disorders; atrial fibrillation; previous bypass surgery; or admission more than 6 h after the onset of symptoms were excluded from the study. Moreover, patients with acute or chronic inflammatory disease; myeloproliferative disorders; malignances; renal, hepatic or thyroid disease; a hematocrit less than 0.30 or greater than 0.52; a platelet count less than 100×10^9/L; or those treated with immunosuppressive or cytotoxic drugs were also excluded.

Coronary angiography

All cineangiograms were reviewed by an experienced cardiologist who was blinded to the patients' symptomatic status and laboratory findings. The degree of coronary narrowing was determined by visual assessment from a review of at least two orthogonal views of each coronary artery. Coronary artery lesions with 50% or more reduction in diameter were considered significant. Regional wall motion was assessed from the left ventricle roentgenogram in the 30° right anterior oblique projection, according to the method described by Gelberg et al (19). The wall motion for segments was assessed visually and graded using the following score system: 0, normal; 1, hypokinesis; 2, akinesis; 3, dyskinesis; and 4, aneurysm. The sum of these scores was divided by the number of myocardial segments to determine the wall motion score index.

Blood sampling and laboratory determinations

Blood samples were drawn from each subject by antecubital venipuncture in the morning between 08:00 and 10:00, and at night between 22:00 and 24:00. The first millilitres of blood were discarded to avoid spontaneous platelet activation. Blood was taken 24 h after cessation of heparin therapy in the patients with acute anterior MI on the sixth day after admission. Citrated blood (0.129 M trisodium citrate; diluted 1:10) was used for MPV analysis using a SEQ500R Sysmex Roche Counter (Sysmex, USA) counting system. Blood was collected into an EDTA tube (4.5 mL) for a platelet count and hematocrit analysis. All analyses were performed 1 h to 2 h after blood collection. Total cholesterol, high density lipoprotein cholesterol and triglyceride levels were measured enzymatically with an autoanalyzer (Hitachi 911, Japan). Leukocyte and platelet counts were performed using a BCD autoanalyzer (Dade Behring, Germany).

HRV analysis

All patients underwent three-channel 24 h Holter ambulatory electrocardiogram monitoring (Biomedical System Century 2000/3000 Holter System, Version 1.32; Biomedical Systems, USA). Recordings were analyzed by Biomedical Systems Century 2000/3000 HRV Package System (Biomedical systems) following manual adjustment of the RR intervals. HRV analysis was performed in the patients with MI on the sixth day after the MI. No patients were restricted to bed during HRV analysis. Analogue

data were digitized at 200 Hz and edited by a cardiologist blinded to the patients' status and laboratory findings. Recordings with less than 18 h of data or less than 85% of qualified sinus beats were excluded. The time and frequency domain analyses of HRV were performed according to published recommendations (11). The mean HR, SDNN, root mean square of successive differences and number of NN intervals that differed by more than 50 ms from the adjacent interval divided by the total number of all NN intervals were measured in the time domain analysis of HRV. A reduced SDNN reflects diminished vagal and increased sympathetic modulation of the sinus node. The power spectrum of HRV was measured using fast-Fourier transformation analysis (11) in four frequency bands: less than 0.0033 Hz (ultra-low frequency), 0.0033 Hz to 0.04 Hz (very low frequency [VLF]), 0.04 Hz to 0.15 Hz (LF) and 0.15 Hz to 0.40 Hz (HF). HF bands were used as a marker of parasympathetic nervous system activity and LF bands were used a marker of sympathetic activity (11). The power of these components was expressed in normalized units (nu). The normalization procedure is crucial for the interpretation of data (20). The LF:HF ratio was also measured, which reflects the sympathovagal balance. High values indicate dominant sympathetic activity (20). For frequency domain parameters, three circadian periods were considered: the complete 24 h, the diurnal (daytime) and the nocturnal (nighttime) periods defined on the basis of patient diaries. Diurnal periods covered lengths of at least 6 h to a maximum of 10 h; nocturnal periods covered a minimum of 4 h to a maximum of 6 h. Normalized LF and HF components were defined by dividing the corresponding raw power by total power (TP) minus the power in the VLF band (LFnu=LF/[TP−VLF]).

RESULTS

Forty-seven patients admitted to Yüksek Ihtisas Hospital clinic diagnosed with acute anterior MI and who underwent thrombolytic therapy were compared with 32 patients with healthy coronary arteries. There were no differences between the two groups with respect to age, sex, coronary risk factors (eg, hypertension, hyperlipidemia, smoking and diabetes mellitus) or medical treatment (eg, beta-blocking agents and angiotensin-converting enzyme inhibitors). Although blood hematocrit levels were similar between the two groups, the white blood cell count and fibrinogen levels were higher in the patients with acute anterior wall MI than in the control group (Table 1). Previous angina history was present in only nine of the patients with MI (19%), and their mean ventricle score index and degree of mean left anterior descending artery stenosis were 1.6±0.3 and 80.4±14.5%, respectively.

Mean HR, LF bands, LF:HF ratio and MPV were higher in patients with anterior MI than in the control group. SDNN, root mean square of successive differences, number of NN intervals that differed by more than 50 ms from the adjacent interval divided by the total number of all NN intervals, HF bands and platelet counts were lower in the patients with anterior MI than in the control group. Daytime LF bands, LF:HF ratio and MPV were significantly higher, and daytime HF bands were significantly lower, compared with the nighttime values for both groups. The difference between daytime and nighttime measurements was more significant in the patients with acute MI than the difference observed in the control group (Table 2). The platelet counts did not significantly change during day- and nighttime in both groups, in contrast with the MPV results.

TABLE 1
Basal characteristics of the patients with acute anterior myocardial infarction (MI) and the control group

Variable	Patients with anterior MI (n=47)	Control group (n=32)	P
Age (years)	56.4±6.6	52.8±8.1	0.2
Male:female	29:18	20:12	0.7
Smoking, n (%)	25 (53)	15 (47)	0.5
Diabetes mellitus, n (%)	18 (38)	12 (38)	0.7
Hypertension, n (%)	17 (36)	10 (31)	0.4
Hyperlipidemia, n (%)	30 (64)	18 (56)	0.2
Body mass index	26.5±3.7	25.8±4.3	0.3
Medical treatment, n (%)			
Beta-blocking agents	40 (85)	25 (78)	0.2
ACE-I	32 (68)	17 (53)	0.1
Statins	32 (68)	18 (56)	0.4
Nitrates	27 (57)	16 (50)	0.5
Others	12 (26)	8 (25)	0.7
White blood cells (×10^9/L)	0.12±0.04	0.9±0.03	0.001
Hematocrit	37.2±2.1	38.1± 3.1	0.3
Fibrinogen (µmol/L)	13.9±7.8	10.0±6.6	0.001

ACE-I Angiotensin-converting enzyme inhibitor

Pearson's correlation analysis showed that MPV was positively correlated with ventricle score (r=0.7, P=0.001), degree of left anterior descending artery stenosis (r=0.5, P=0.001), mean HR (r=0.4, P=0.007), LF bands (r=0.6, P=0.001) and LF:HF ratio (r=0.8, P=0.001). MPV was negatively correlated with SDNN (r=–0.5, P=0.001), HF bands (r=–0.8, P=0.001) and platelet count (r=–0.6, P=0.001). Multivariate analysis revealed that MPV was significantly affected by the ventricle score and LF:HF ratio (Table 3).

DISCUSSION

Platelets are known to be involved in the pathogenesis of coronary artery disease (1) and coronary occlusion (2). Larger platelets are known to be more active than smaller ones, and show increased hemostatic capacity (7). In patients with MI, platelet counts tend to be lower and MPV higher due to an increase in the production of large, hyperaggregable platelets by the bone marrow or increased platelet consumption at the site of infarction (6,21,22). Thus, it is largely accepted that MPV is an independent risk factor for the first (3) and recurrent MI (4,5). Three major parameters have been postulated as determinants of platelet volume: age-dependent processes that can modify platelet size in the circulation; heterogeneity and maturity of the bone marrow megakaryocyte population; and peripheral size-related sequestration of platelets in storage pools (23). However, there is evidence that MPV is largely determined at or before the time of megakaryocyte fragmentation into platelets (24).

MPV is known to be increased in patients at the time of admission for MI (6), and it is likely that alterations in the entire megakaryocyte-platelet-hemostatic axis precede MI (21,25). Martin et al (6) postulated that MPV increases before MI for three reasons: the life span of platelets is approximately eight days, and the increase in MPV is seen within the first 12 h of admission; the increase in MPV persists six weeks after discharge when the infarct would be largely healed; and log normality of platelet volume is preserved. Furthermore,

TABLE 2
Comparison of heart rate variability parameters between patients with anterior myocardial infarction (MI) and the control group

Variable	Patients with anterior MI (n=47)	Control group (n=32)	P
Mean heart rate, beats/min	71.6±9.5	65.8±7.1	0.001
SDNN, ms	83.4±20.5	118.8±26.6	0.001
RMSSD, ms	23.8±7.7	35.9±14.2	0.001
PNN50, %	5.1±2.7	10.1±4.7	0.001
Daytime			
HF band, nu	28.6±4.6**	38.8±12.1*	0.001
HF band, ms²	312.2±187.8**	462.8±168.9**	0.001
LF band, nu	66.3±8.9**	54.8±9.2*	0.001
LF band, ms²	988.8±356.6**	544.4±233.8**	0.001
LF:HF ratio	2.4±0.6**	1.6±0.5*	0.001
Platelet count, ×10^9/L	203.4±35.1	234.4±18.9	0.001
Mean platelet volume, fL	10.1±1.4**	8.0±1.1*	0.001
Nighttime			
HF band, nu	32.4±5.8	44.3±8.8	0.001
HF band, ms²	388.2±187.9	318.8±169.9	0.001
LF band, nu	54.7±9.3	50.6±6.2	0.001
LF band, ms²	583.6±233.9	398.9±198.8	0.001
LF:HF	1.6±0.3	1.2±0.2	0.001
Platelet count, ×10^9/L	205.3±33.4	232.6±14.8	0.001
Mean platelet volume, fL	10.5±1.6	8.2±2.2	0.001

HF High frequency band of power spectrum of heart rate variability; LF Low frequency band of power spectrum of heart rate variability; PNN50 Number of NN intervals that differed by more than 50 ms from adjacent interval divided by the total number of all NN intervals; RMSSD Root mean square of successive differences; SDNN SD of all NN intervals. *P<0.05 compared with nighttime values; **P<0.001 compared with nighttime values

TABLE 3
Independent variables affecting mean platelet volume

Variable	SE	Beta	t	P
Age	0.87	–0.07	–0.3	0.7
Sex	0.3	–0.02	–0.2	0.8
Smoking	0.3	–0.1	–1.3	0.2
Diabetes mellitus	0.3	–0.02	–0.3	0.8
Hypertension	0.3	–0.1	–1.3	0.2
Hyperlipidemia	0.3	0.02	0.3	0.8
Previous angina	0.3	0.01	0.2	0.9
Degree of LAD stenosis	0.009	–0.07	–0.3	0.7
Abnormal wall motion score index	0.02	1.2	2.9	0.006
Multivessel disease	0.16	–0.003	–0.4	0.7
Hematocrit	0.06	0.04	0.8	0.4
Fibrinogen	0.4	0.3	0.2	0.1
Platelet count	0.1	0.8	–2.1	0.07
White blood cells	0.05	0.3	1.1	0.08
Heart rate	0.02	0.07	0.8	0.5
SDNN	0.02	–0.03	–0.1	0.9
RMSSD	0.04	0.3	1.5	0.2
PNN50	0.09	0.2	1.2	0.2
HF band	0.05	–0.4	–1.5	0.1
LF band	0.1	0.2	1.2	0.07
LF:HF ratio	1.4	2.0	3.7	0.001

HF High frequency band of power spectrum of heart rate variability; LAD Left anterior descending artery; LF Low frequency band of power spectrum of heart rate variability; PNN50 Number of NN intervals that differed by more than 50 ms from adjacent interval divided by the total number of NN intervals; RMSSD Root mean square of successive differences; SDNN SD of all NN intervals

although MPV was correlated with the ventricle score index in the present study, some authors (26) have reported that the platelet size changes in acute MI are not correlated to the size or site of the infarction. Therefore, instead of the consumption theory, the response of megakaryocytes in bone marrow hypothesis seems more valid. Although this cannot be confirmed because investigation of the bone marrow during acute MI would not be ethical, there is some evidence that the megakaryocytes in bone marrow change and, as a result, changes in platelet size occur before the insult of acute MI (27). Thus, it seems likely that changes occuring in the megakaryocytes are important for the development of vascular disease and its complications (25).

In the present study, we found that MPV was higher in the patients with acute MI, and that there was a correlation between sympathetic activity and MPV in these patients. This may be explained by the effects of the adrenergic system on peripheral platelet activation and thrombocytopoiesis in bone marrow (10,28-30). The effects of the adrenergic system can occur in two ways in peripheral circulation. First, platelet activation via alpha$_2$-adrenoreceptor activation (31) causes shape change and, thereby, increases MPV (32,33). Second, larger, activated platelets sequestered in the spleen (34,35) can be released into the circulation following exercise (36) or the administration of adrenaline (34), and contribute to the increase in MPV following physical effort. Studies (28-31) have shown that neuroendocrine and neural factors may also regulate hematopoiesis. Plasma thrombocytopoietin has been found to markedly stimulate thrombocytopoiesis in

conjunction with beta-adrenergic stimulation with isoprenaline, and pretreatment with propranolol prevents this stimulation (37).

Coronary platelet sensitivity has been shown to be reduced with beta-blockade in patients with coronary artery disease due to decreased platelet consumption, increased prostacycline synthesis or reduced shear stress (38). Our results contribute to the growing interest in the possibility that cardiovascular drugs, such as beta-blockers, may influence platelet function, and these additional effects may influence treatment outcome. In accordance with our results, in hyperthyroidism, which is characterized by increased adrenergic activity, MPV is also increased and reverts to normal with the achievement of a euthyroid state (39). Thus, we conclude that increased sympathetic activity has an important role in MPV, either by peripheral activation and splenic release or by effects on thrombocytopoiesis.

There were limitations in the present study. MPV has been reported to be dependent on a number of variables, including the time of analysis after venipuncture, method of analysis, anticoagulant used and specimen storage temperature (7). In addition, plasma catecholamine levels and other markers of platelet activation were not measured in our study.

CONCLUSIONS

MPV was significantly higher in the patients with MI, and MPV in both groups showed great diurnal and nocturnal variation that can be attributed to alterations in the autonomic nervous system.

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