ORIGINAL ARTICLE

Association between Mean Platelet Volume and Autonomic Nervous System Functions: Increased Mean Platelet Volume Reflects Sympathetic Overactivity

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Aim: Increased mean platelet volume (MPV) may reflect increased platelet activation and accepted as an independent coronary risk factor. Adrenergic system has effects on platelet activation and thrombocytopoiesis. In this study, we assessed the effects of autonomic nervous system activity on MPV in patients with acute myocardial infarction (MI).

Materials and Methods: Forty-seven patients with acute anterior MI were compared with 32 patients having normal coronary arteries. All patients underwent heart rate variability analysis by 24-h holter monitoring and blood samples were taken for MPV measurements during day and night times during holter monitoring.

Results: Mean heart rate (HR), Low frequency (LF), LF/High frequency (HF) ratio, MPV were higher, standard deviation of all NN intervals (SDNN), root mean square of successive differences (RMSSD), the number of NN intervals that differed by more than 50 ms from adjacent interval divided by the total number of all NN intervals (PNN50), HF and platelet counts were lower in the patients with anterior MI compared to the control group. Day time LF, LF/HF, and MPV were significantly higher and HF were significantly lower compared to those measured during night time in both groups. Pearson's correlation analysis showed that MPV was positively correlated with ventricle score, degree of left anterior descending artery stenosis, mean HR, LF, LF/HF, and negatively correlated with SDNN, HF, and platelet count. Multivariate analysis revealed that MPV was affected by ventricle score and LF/HF ratio.

Conclusions: MPV is significantly higher in the patients with MI and MPV in both groups shows great diurnal and nocturnal variation that is attributed to the alterations in the autonomic nervous system. We suggest that prognostic role of increased MPV in patients with MI are closely associated with increased sympathetic activity and decreased heart rate variability in these patients.

Key Words: Mean platelet volume, myocardial ınfarction, sympathetic activity, heart rate variability

Ortalama Trombosit Hacmi ve Otonomik Sinir Sistemi Fonksiyonları Arasındaki İlişki: Artmış Ortalama Trombosit Hacmi Sempatetik Aktivite Artışını Yansıtır

Amaç: Artmış ortalama trombosit hacmi (OTH) trombosit aktivasyonundaki artışı yansıtır ve bağımsız bir koroner risk faktörü olarak kabul edilir. Adrenerjik sistemin trombosit aktivasyonu ve trombosit oluşumunda etkileri vardır. Bu çalışmada, akut miyokard enfarktüslü (ME) hastalarda otonomik sinir sistemi aktivasyonunun OTH üzerine etkileri araştırılmıştır.

Yöntem ve Gereç: Akut ön duvar enfarktüslü 47 hasta koroner arterleri normal olan 32 hasta ile karşılaştırılmıştır. Tüm hastalara 24 saatlik holter monitörizasyonu ile kalp hız değişikliği analizi yapılmış ve OTH ölçümü için kan örnekleri alınmıştır.

Bulgular: Akut ME'lü hastalarda ortalama kalp hızı (KH), Düşük frekans (LF), LF/Yüksek frekans (HF) oranı, OTH kontrol grubundan daha yüksek, Tüm NN aralıklarının standart sapması (SDNN), takip eden farkların kare kökü (RMSSD), bir sonrakinden 50 ms'den fazla farklılık gösteren NN aralıklarının tüm NN aralıklarına oranı (PNN50), HF ve trombosit sayısı daha düşük bulunmuştur. Her iki grupta gündüz LF, LF/HF, ve OTH değerleri geceki değerlerden daha yüksek bulunmuş ancak akut ME'lü hastalarda bu farkın çok daha anlamlı olduğu görülmüştür. Korelasyon analizinde OTH ile ventrikül skoru, sol ön inen arterdeki darlık derecesi, ortalama KH, LF, LF/HF arasında pozitif bir ilişki; SDNN, HF ve trombosit sayısı arasında negatif bir ilişki olduğunu göstermiştir. Multivaryant analiz OTH'nin ventrikül skoru ve LF/HF oranından etkilendiğini göstermiştir.

Sonuç: ME'lü hastalarda OTH anlamlı olarak yüksektir. Her iki çalışma grubunda da gündüz ve gece OTH değerlerinde önemli değişim görülmekte ve bu değişim otonomik sinir sistemindeki değişimden kaynaklanmaktadır. Miyokard enfarktüslü hastalarda artmış OTH'nin prognostik değerinin bu hastalardaki artmış sempatetik aktivite ve azalmış kalp hızı değişikliği ile yakın ilişkili olduğu düşünülebilir.

Anahtar Sözcükler: Ortalama trombosit hacmi, miyokard enfarktüsü, sempatetik aktivite, kalp hızı değişikliği

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Introduction

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

Sympathetic activity is increased during acute MI (9) and increased adrenaline activates and aggregates blood platelets (10). Heart rate variability (HRV) analysis has been extensively used to evaluate autonomic modulation of sinus node and to identify patients at risk for an increased cardiac mortality (11). Some HRV parameters, such as decreased SDNN and increased LF/HF ratio, are associated with an increased cardiac mortality in almost all clinical conditions characterized by an autonomic imbalance, such as after MI (12-14). Moreover, HRV analysis is shown to reflect sympatho-vagal balance and used previously to define the role of autonomic nervous system activity in certain cardiac disorders (15). In this study, we aimed to show the effects of increased sympathetic activity on platelet size during acute MI.

Materials and Methods

Study population

Forty-seven patients admitted to our clinics, diagnosed with acute anterior myocardial infarction, and underwent thrombolytic therapy (streptokinase 1.5 million unit) were compared with age- and gender-matched 32 patients who underwent coronary angiography due to coronary heart disease suspicion, and angiography revealed normal coronary arteries. Diagnoses of acute MI was established by ST segment elevation, defined subsequently, in more than 2 leads associated with typical chest pain and confirmed by elevation of serum creatine kinase MB isoenzyme greater than twice the normal upper limit during the patients' clinical course. All patients underwent thrombolytic therapy within 6 h after symptoms and all patients received standard medical therapy in accordance with conventional guidelines. An informed written consent was obtained from all patients and the local ethics committee

approved the trial. Patients with abnormal serum electrolytes, historical and/or electrocardiographic findings of a previous myocardial infarction, chronic treatment with antiarrhythmic drugs, digitalis, clinical signs of left ventricular failure and cardiogenic shock or mechanic complications at admission, with preexcitation syndromes, ventricular pacing, bundle branch block, intraventricular conduction disorders, atrial fibrillation, previous bypass surgery, admitted after 6 h from 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 or those treated with immunosuppressive or cytotoxic drugs, a hematocrit <0.30 or >0.52 and a platelet count <100.000 /mm^3 were also excluded.

Coronary angiography

All cineangiograms were reviewed by an experienced cardiologist, who was blinded to the symptomatic status of the patients and laboratory findings. The degree of coronary narrowing was determined by visual assessment from a review of at least 2 orthogonal views of each coronary artery. Coronary artery lesions with ≥50% 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 and co-workers (16). 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 graded scores were divided by the number of myocardial segments and expressed as an abnormal wall motion score index for each patient.

Blood sampling and laboratory determinations

Blood samples were drawn from each subject at 08:00 and 10 AM, and 10 PM and 12 AM. Blood was taken 24 h after cessation of heparin therapy in the patients with acute anterior MI on day 6. They were withdrawn by antecubital venipuncture and first few milliliters of blood were discarded to avoid spontaneous platelet activation. Citrated blood (0.129 M trisodium citrate in dilution 1:10) was used with an automated blood counter (Sysmex, Roche) and 4.5 ml blood were collected in ethylene diamine tetra acetic acid (EDTA) tube for platelet count and hematocrits. All analyses were performed within a period of 1-2 h after blood collection. Total cholesterol, HDL cholesterol, and triglyceride levels were measured

enzymatically by an autoanalyzer (Hitachi 911, Japan). LDL cholesterol levels were determined with Friedewald formula. Leukocyte and platelet counts were performed using a BCD auto-analyzer (Dade Behring, Germany).

Heart rate variability analysis

All patients underwent 3-channel 24-h Holter ambulatory ECG monitoring (Biomedical System Century 2000/3000 Holter System, Version 1.32). Recordings were analyzed by a Biomedical Systems Century 2000/3000 HRV Package System, following the manual adjustment of RR intervals. HRV analysis was performed in patients with MI on day 6 after MI. None of the patients was restricted to bed during the HRV analysis. Analog data was digitized at 200 Hz and edited by a cardiologist blinded to the status of the patients and laboratory findings. The validation procedure comprises beat labeling and tagging of noisy regions. The continuous series of RR (NN) intervals (tachogram) was obtained and all 5-min segments with at most 5 isolated ectopic beats were retained for spectral analysis. Recordings with <18 h of data or <85% of qualified sinus beats were excluded. The time and frequency-domain analysis of HRV were performed according to the recommendation of the task force (11). The mean heart rate (HR), SDNN, root mean square of successive differences (RMSSD), and the number of NN intervals that differed by more than 50 ms from adjacent interval divided by the total number of all NN intervals (PNN50) were measured in the time domain analysis of HRV. A reduced SDNN was considered reflecting diminished vagal and increased sympathetic modulation of the sinus node. The power spectrum of HRV was measured using fast-Fourier transform analysis in 4 frequency bands: <0.0033 Hz (ultra low frequency, ULF), 0.0033 to 0.04 (very low frequency, VLF), 0.04 to 0.15 (low frequency, LF), and 0.15 to 0.40 (high frequency, HF). HF was used as a marker of parasympathetic nervous system and LF was used as a marker of sympathetic activity (11). The power of these components was stated as normalized unit (nu). The normalization procedure is crucial for the interpretation of data (17). We also measured the ratio of low to high frequency power (LF/HF) reflecting the sympatho-vagal balance. High values indicated the dominant sympathetic activity (17). For frequency domain parameters 3 circadian periods were considered: complete 24 h and the diurnal and the nocturnal 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 dividing the corresponding raw power by total power (TP) minus the power in the VLF band [LFnu = LF / (TP-VLF)].

Statistical analysis

All statistical analyses were performed with SPSS version 13 (SPSS INC., Chicago, Illinois, USA). Continuous variables were expressed as mean ± SD, and categorical variables were expressed as a percentage. Comparison of continuous variables between groups was performed using the Student's t-test and Mann-Whitney U test. The Chi-square test was used for the analysis of categorical variables. Besides some clinical variables, Pearson's correlation analysis was used to define the correlation between MPV and HRV parameters. Independent factors associated with MPV were investigated using multivariate logistic regression analysis. P values less than 0.05 were considered as statistically significant.

Results

Forty-seven patients admitted to our clinics, diagnosed with acute anterior MI, and underwent thrombolytic therapy were compared with 32 patients having normal coronary arteries. There were no differences between the 2 groups concerning age, gender, coronary risk factors, such as hypertension, hyperlipidemia, smoking, diabetes mellitus, and medical treatment, such as beta blocking agents and ACE inhibitors. Although blood hematocrit levels were similar, white blood cell count and fibrinogen levels were higher in the patients with acute anterior wall myocardial infarction compared to those in the control group (Table 1). Previous angina history was present only in 9 of the patients with MI (19%), mean ventricle score index was 1.6 ± 0.3, and mean LAD stenosis degree was 80.4 ± 14.5% in these patients.

Mean heart rate, LF, LF/HF ratio, and MPV were higher; SDNN, RMSSD, PNN50, HF, and platelet counts were lower in the patients with anterior MI compared to the control group. Day time LF, LF/HF, and MPV were significantly higher and HF were significantly lower compared to those measured during night time in both groups. The differences in diurnal and nocturnal measurements were much more significant in the patients with acute MI (Table 2). However, the platelet counts did

Table 1. Basal characteristics of the patients with acute anterior myocardial infarction and the control group.

Variables	Patients with anterior MI (n = 47)	Control group (n = 32)	P-value
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 (39%)	12 (38%)	0.7
Hypertension, n (%)	17 (36%)	10 (32%)	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			
β-blocking agents	40 (85%)	25 (78%)	0.2
ACE-I	32 (68%)	17 (54%)	0.1
Statins	32 (68%)	18 (60%)	0.4
Nitrates	27 (58%)	16 (50%)	0.5
Others	12 (26%)	8 (25%)	0.7
White blood cells (nl-1)	11.8 ± 3.8	8.8 ± 3.4	0.001
Hematocrit	37.2 ± 2.1	38.1 ± 3.1	0.3
Fibrinogen (mg/dl)	4.9± 2.8	3.4 ± 2.2	0.001

MI: Myocardial infarction, ACE-I: Angiotensin converting enzyme inhibitor

Table 2. Comparison of heart rate variability parameters in both groups.

	Variables	Patients with anterior MI (n = 47)	Control group (n = 32)	P-value
	Mean heart rate	71.69.5	65.87.1	0.001
	SDNN (msec)	83.4 ± 20.5	118.8 ± 26.6	0.001
	RMSSD (msec)	23.8 ± 7.7	35.9 ± 14.2	0.001
	PNN50 (%)	5.1 ± 2.7	10.1 ± 4.7	0.001
	HF (nu)	28.6 ± 4.6*	38.8 ± 12.1†	0.001
D	LF (nu)	66.3 ± 8.9*	54.8 ± 9.2†	0.001
A	LF/HF	2.4 ± 0.6*	1.6 ± 0.5†	0.001
Y	Platelet count (10^3/mm^3)	203.4 ± 35.1	234.4 ± 18.9	0.001
	MPV (fl)	10.1 ± 1.4*	8.0 ± 1.1†	0.001
N	HF (nu)	32.4 ± 5.8	44.3 ± 8.8	0.001
I	LF (nu)	54.7 ± 9.3	50.6 ± 6.2	0.001
G	LF/HF	1.6 ± 0.3	1.2 ± 0.2	0.001
H	Platelet count (10^3/mm^3)	205.3 ± 33.4	232.6 ± 14.8	0.001
T	MPV (fl)	10.5±1.6	8.2±2.2	0.001

SDNN: Standard deviation of all NN intervals, RMSSD: Root mean square of successive differences, PNN50: Number of NN intervals that differed by more than 50 ms from adjacent interval divided by the total number of all NN intervals, HF: High frequency, LF: Low frequency, MPV: Mean platelet volume.* P < 0.001 compared to night, † P < 0.05 compared to night in each group.

not change significantly during day and night time in both groups unlike MPV.

Pearson's correlation analysis showed that MPV was positively correlated with ventricle score ($r = 0.7$, $P = 0.001$), degree of LAD stenosis ($r = 0.5$, $P = 0.01$), mean heart rate ($r = 0.4$, $P = 0.007$), LF ($r = 0.6$, $P = 0.001$), and LF/HF ($r = 0.8$, $P = 0.001$); and, negatively correlated with SDNN ($r = -0.5$, $P = 0.002$), HF ($r = -0.8$, $P = 0.001$), 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 the smaller ones and show increased haemostatic capacity (7). Platelet counts tend to be lower and mean platelet volumes are higher in patients with myocardial infarction (MI) due to an increase in the production of large, hyperaggregable platelets by the bone marrow or increased platelet consumption at the site of infarction (6,18,19). Thus, it is largely accepted that MPV is an independent risk factor for the first (3) and recurrent MI (4,5). Although 3 major parameters have been postulated as determinants of platelet volume including 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 (20), there is evidence that MPV is largely determined at or before the time of megakaryocyte fragmentation into platelets (21).

MPV is known to be increased in patients at the time of admission for MI (6) and its likely that alterations in the entire megakaryocyte-platelet-haemostatic axis precede MI (18,22). Martin JF et al. postulated that MPV increases before MI for 3 reasons: 1) The life span of platelets is about 8 days and the increase in MPV is seen within the first 12 h of admission; 2) The increase in MPV persists 6 weeks after discharge when the infarct would be largely healed; 3) Log normality of platelet volume is preserved (6). Furthermore, although MPV was correlated with ventricle score index in our study, some authors reported that the platelet size changes in acute MI are not correlated to the size or site of the infarction (23). Therefore, instead of consumption theory, response of megakaryocytes in bone marrow hypothesis appears more valid. However, this cannot be confirmed totally since the investigation of the bone marrow during acute MI is not ethical. However, there is some evidence that bone marrow changes in megakaryocytes and, as a result, in platelet size occurs before the insult of acute MI (24). So, it seems likely that changes occurring in the megakaryocytes are important for the development of vascular disease and its complications (22).

Adrenergic system affects both peripheral platelet activation and thrombocytopoiesis in bone marrow (10,25-27). Sympathoadrenal activation may stimulate platelets via $_2$-adrenoreceptor activation (28). Platelet activation causes shape change and thereby increases MPV (29,30). Lande K et al. (31) showed that MPV significantly increased during adrenaline infusion reflecting either swelling and shape change of platelets due to activation of platelets or release of larger, activated platelets from spleen. Approximately 30% of the circulating platelets are sequestered in the spleen and these splenic platelets tend to be larger (32). These splenic platelets can be released into the circulation following exercise (33) or the administration of epinephrine (31) and contribute to the increase in MPV following physical effort. Furthermore, adrenergic 2 receptor stimulation was found to induce a transient lowering of the peripheral platelet count (34) and this

Table 3. The independent variables affecting mean platelet volume.

Variables	S.E.	β	t	p
Ventricle score	0.02	1.2	2.9	0.006
Platelet count	0.1	0.8	-2.1	0.07
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	0.05	-0.4	-1.5	0.1
LF	0.1	0.2	1.2	0.07
LF/HF	1.4	2.0	3.7	0.001

SDNN: Standard deviation of all NN intervals, RMSSD: Root mean square of successive differences, PNN50: Number of NN intervals that differed by more than 50 ms from adjacent interval divided by the total number of all NN intervals, HF: High frequency, LF: Low frequency

may also partly explain the decrease in platelets during acute MI. Recent studies have shown that neuroendocrine and neural factors may also regulate hematopoiesis (25-27). Plasma thrombocytopoietin was found to stimulate markedly thrombocytopoiesis on the background of beta-adrenergic stimulation with isoprenaline and pretreatment with propranolol prevents this stimulation (35).

Coronary platelet sensitivity was shown to be reduced by blockade in patients with coronary heart disease due to the decreased platelet consumption, increased prostacycline synthesis, or reduced shear stress (36). Our results contribute to a growing interest in the possibility that cardiovascular drugs such as blockers might influence platelet function and such additional effects of these drugs might influence the treatment outcome. In accordance with our results, in hyperthyroidism that is characterized with increased adrenergic activity, MPV is also increased and reverts to normal on the achievement of euthyroid state (37). Thus, we concluded that increased sympathetic activity has an important role in mean platelet volume either by peripheral activation and splenic release or effects on thrombocytopoiesis.

As a result, that MPV is significantly higher in the patients with MI and MPV in both groups shows great diurnal and nocturnal variation that is attributed to the alterations in autonomic nervous system. We suggest that this increase in MPV and prognostic role of MPV in patients with MI are closely associated with increased sympathetic activity and decreased heart rate variability in these patients.

Study Limitations

The mean platelet volume is dependent on a number of variables, including time of analysis after venipuncture, method of analysis, anticoagulant used, and specimen storage temperature as reported in previous reports, and plasma catecholamine levels, other markers of platelet activation, were not measured in our study.

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