European Review for Medical and Pharmacological Sciences 2014; 18: 235-241

Increased sympathetic activation in patients with vasovagal syncope is associated with higher mean platelet volume levels

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Abstract. – OBJECTIVES: Vasovagal syncope (VVS) is supposed to be modulated by increased sympathetic tone following an orthostatic maneuver. Increased sympathetic activity may have an important role in mean platelet volume (MPV), either by peripheral activation or by effects on thrombocytopoiesis. We aimed to show the effects of increased sympathetic activity on platelet size in patients with VVS in the present study.

PATIENTS AND METHODS: Thirty-seven patients with VVS were compared with age- and sex-matched 33 patients without VVS. All patients have undergone 24 hour holter monitoring for heart rate variability (HRV) and time-domain HRV analysis. Blood samples for MPV measurements were taken before 24 hour holter monitoring.

RESULTS: Group 1 was consisted of 37 patients with VVS and group 2 was consisted of 33 patients without VVS. We observed that SDNN, SDNN index, SDSD, RMSDD, PNN50 count were significantly lower and MPV was found significantly higher in patients with VVS ($p < 0.05$ for all). Pearson's correlation analysis showed that MPV was moderately negatively correlated with SDNN (r = –0.421), SDSD (r = –0.396), NN50 count (r = –0.395) and RMSDD (r = –0.393). Multivariate regression analysis showed that SDNN was the only independent variable, which had a significant effect on increased MPV level ($\beta = -0.295$, $p = 0.016$)

CONCLUSIONS: We found that MPV was closely associated with increased sympathetic activity in patients with VVS. Our analysis supports the hypothesis that alterations in autonomic status might play a role in the development of platelet size.

Key Words:
Vasovagal syncope, Heart rate variability, Mean platelet volume.

Introduction

Vasovagal syncope (VVS) is the most frequent reason of unexplained syncope, which is responsible for approximately 66% of patients admitted to the Emergency Department with syncope[1]. It generally begins at a young age and the clinical course is quite variable. Apart from syncope episodes, subjects with VVS usually have normal blood pressure regulation, and why certain subjects are more susceptible to VVS than others remains largely unknown. Impaired autonomic nervous system (ANS) control of the heart rate and blood pressure is a commonly suggested mechanism for increased susceptibility to VVS.

Heart rate variability (HRV) analysis reflects sympathovagal balance and has been previously used to define the role of ANS activity in certain cardiac disorders. HRV analysis is a simple and intriguing test in the assessment of complex etiology of syncope. In their study, Balaji et al[2] and Perry et al[3] concluded that patients with positive head-upright tilt-table (HUTT) test response tend to have higher resting sympathetic tone and decreased parasympathetic tone compared to those with a negative response.

Increased mean platelet volume (MPV) indicates large-sized hyperaggregable platelets, which are metabolically and enzymatically more active than normal-sized platelets, and accepted as an independent cardiovascular risk factor[4]. Sympathetic activity may have a significant impact on MPV, either by peripheral activation and splenic release of platelets or depending on the increased thrombocytopoiesis in bone marrow[5-7]. Since sympathovagal balance is affected in favor of the sympathetic activation in patients with VVS, MPV levels may also show alterations consistent with sympathetic hyperactivity in patients with VVS. In this study, we evaluated the effect of changes in the baseline ANS function assessed by 24-hour HRV analysis on platelet size in patients with VVS.

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Patients and Methods

Patients

Patients referred to our Cardiology Clinic for evaluation and treatment of unexplained syncope during the period of October 2012 and May 2013 and meeting the following criteria were enrolled in the study: history of two or more episodes of syncope; normal neurological evaluation; absence of structural heart disease; absence of supraventricular or ventricular arrhythmias; and no history of any chronic disease. All patients had an initial evaluation consisting of history, physical examination, 12-lead ECG, transthoracic echocardiography, complete blood count analysis and then HUTT test and 24-hour holter monitoring for HRV analysis. Patients were divided into 2 groups according to their HUTT test results. Group 1 was consisted of patients with positive HUTT test response, whereas group 2 was consisted of age- and sex-matched patients with negative HUTT test response.

All patients included in this study signed written informed consent. The regional Ethics Committee of our Institute approved the study protocol, and the study was conducted in accordance with the regulations of Declaration of Helsinki.

Head-Upright Tilt-Table (HUTT) Test

After an overnight fasting period, HUTT test was conducted in the morning hours (between 9 a.m. and 11 a.m) in a silent, softly lighted room. A peripheral intravenous access was obtained for emergency intervention before starting the test. Patients laid down on an electrically driven table and strapped. The ECG was monitored continuously and blood pressure was recorded noninvasively, at 3 minute intervals and promptly in case of any clinical symptoms. The HUTT test protocol started with baseline recordings acquired at the end of a 10-minute resting period in a supine position. Afterwards, patients were tilted to 60° for 20 minutes. In case of negative response a puff of sublingual nitrate spray (Nitrolingual Pump Spray, G.Pohl-Boskamp GmbH, Germany; 400 mcg/puff) was administered and the test was extended for another 15 minutes at 60° tilt angle. The test was ended after 45 min, if no loss of consciousness or no symptoms such as dizziness, chest discomfort or nausea were observed. The test results were interpreted in accordance with the recommendation of the Task Force on Syncope of the European Society of Cardiology[8]. The test result was accepted as positive if sudden development of syncope occurred or if there was presyncope associated with hypotension (systolic blood pressure < 70 mm Hg or diastolic blood pressure < 40 mm Hg), bradycardia (< 75% of resting heart rate during), or both. Vasodepressor response was defined as marked fall in systolic blood pressure without bradycardia.

HRV Analysis

Two to four days after the HUTT test, all patients had three-channel 24 hour Holter ambulatory ECG monitoring (Rozinn RZ 152 digital holter recorder, Rozinn Electronics, Inc., Glendale, NY, USA) with a sampling rate of 1024 Hz. The software of the same device automatically analyzed HRV. The time domain variables of HRV analysis consisted of standard deviation of all R-R intervals (SDNN), standard deviation of the successive NN differences (SDSD), standard deviation of the averages of the R-R intervals in all 5 min segments of R-R intervals (SDANN), the mean of all the 5 minute standard deviations of NN (normal RR) intervals during the 24-hour period (SDNN index), the root of the mean square of the difference of successive R-R intervals (RMSSD), successive NN intervals differing more than 50 ms (NN50 count), and the proportion of adjacent normal R-R intervals < 50 ms (pNN50). Among those indices, SDNN, SDANN and SDNN reflect the heart rate and their decrease is related with diminished vagal and increased sympathetic modulation of the sinus node[9]. HRV analyses of the subjects with VVS were compared with those of without VVS.

Blood Sampling and Complete Blood Count (CBC) Analysis

Blood samples for CBC analysis were obtained following the venipuncture on the morning of the day before 24-hour holter monitoring. The blood samples collected in tripotassium EDTA tubes and were analyzed using an automatic blood counter. The CBC parameters related to red blood cells and platelets were compared between the two groups.

Statistical Analysis

The categorical variables were defined as percentages whereas the continuous variables were reported as the mean ± standard deviation (SD). Chi-Square and Independent-Samples *t* tests were used to compare categorical and quantitative data between two groups, respectively. The correlation between time domain HRV variables and MPV val-

ues was assessed with Pearson's correlation analysis. Multivariate regression analysis was performed to establish the independent association between MPV levels and other variables. Statistical significance was defined as $p < 0.05$. All statistical analyses and calculations were conducted using the SPSS 20.0 Statistical Package Program for Windows (SPSS, Chicago, IL, USA).

Results

A total of 126 patients were evaluated in this study. Seventy patients who met the inclusion criteria were enrolled in the study. The HUTT test was positive with vasodepressive response in 37 patients (22 male and mean age 35.27 ± 20.09 years) and group 1 was consisted of these patients. The group 2 was consisted of 33 patients (25 male and mean age 29.27 ± 11.68 years) with negative HUTT test. There was no statistically significant difference between group 1 and 2 regarding to basal demographic characteristics (Table I).

All subjects were in sinus rhythm without atrial or ventricular arrhythmias. Mean heart rate was similar between the two groups. However, statistical analysis of the time-domain HRV analyses showed a significant decrease in SDNN, SDNN index, SDSD, RMSDD and PNN50 values in group 1 compared to group 2 ($p < 0.05$ for all). The comparison of time domain HRV indices between the two groups is presented in Table II.

MPV was found significantly higher in patients with VVS compared without VVS (9.21 ± 0.70 fL vs. 8.46 ± 0.73 fL, $p < 0.001$). Additionally, platelet distribution width (PDW) was significantly higher in group 1 compared with group 2 (16.39 ± 2.09% vs. 15.21 ± 1.87%, $p = 0.016$). We did not observe any statistically significant difference for other CBC parameters regarding with the red blood cell between two groups ($p > 0.05$ for all). All CBC parameters of study patients are shown in Table III.

When all patients participating in the study were taken together, we observed a statistically significant negative correlation between time domain HRV indices and MPV level. This correlation was continued statistically significant in group 1, whereas it was not significant in group 2. Pearson's correlation analysis showed that MPV was negatively correlated with SDNN (r = –0.421, $p = 0.009$), SDSD (r = –-0.396, $p = 0.015$), NN50 count (r = –0.395, $p = 0.016$), RMSDD (r = –0.393, $p = 0.016$) in group 1. To demonstrate the independent effect of time domain HRV indices on increased MPV level, we performed a standard multivariate regression analysis using the backward method based on independent variables likely to affect the level of MPV. In multivariate analysis, SDNN was the only independent variable, which had a significant effect on increased MPV level ($\beta = –0.295$, $p = 0.016$) (Table IV).

Discussion

This study revealed that MPV was significantly higher in patients with a positive HUTT test

Table I. Basal demographic, clinical characteristics and HUTT results and comparison of two groups.

	Group 1 (n=37) HUTT positive	Group 2 (n=33) HUTT negative	*p* value
Age, (years)	35.27 ± 20.09	29.27 ± 11.68	0.138
Male, n (%)	22 (66.7%)	25 (67.6%)	0.936
Hypertension, n (%)	6 (18.2%)	8 (21.6%)	0.719
Hyperlipidemia, n (%)	4 (12.1%)	5 (13.5%)	0.862
Diabetes mellitus, n (%)	5 (15.2%)	4 (10.8%)	0.588
Smoking, n (%)	8 (24.2%)	8 (21.6%)	0.592
Alcohol, n (%)	7 (21.2%)	6 (16.2%)	0.794
HUTT results			
Pre-test Heart rate, (bpm)	79.24 ± 15.31	80.54 ± 11.57	0.692
Pre-test SBP, (mmHg)	124.13 ± 18.54	122.75 ± 12.653	0.721
Pre-test DBP, (mmHg)	78.67 ± 12.36	77.36 ± 9.14	0.619
Post-test Heart rate, (bpm)	94.78 ± 15.43	94.24 ± 15.43	0.896
Post-test SBP, (mmHg)	85.654 ± 24.34	106.33 ± 20.16	< 0.001
Post-test DBP, (mmHg)	58.05 ± 17.05	70.42 ± 12.20	0.001

HUTT: head-upright tilt-table; SBP: systolic blood pressure; DBP: diastolic blood pressure.

Table II. Comparison of time domain HRV indices between patients with positive HUTT and the control group.

	HUTT positive (n=37)	HUTT negative (n=33)	*p* value
Mean Heart rate (bmp)	75.06 ± 10.65	78.91 ± 13.43	0.191
SDNN, (msec)	149.56 ± 51.55	181.98 ± 59.31	0.017
SDSD, (msec)	44.94 ± 23.40	63.29 ± 39.57	0.020
NN50 count, (%)	12495.81 ± 11010.67	19434.75 ± 13573.27	0.021
RMSDD, (msec)	44.98 ± 23.44	63.35 ± 39.59	0.020
SDANN, (msec)	59.99 ± 54.46	62.00 ± 57.84	0.884
SDNN index	56.97 ± 29.27	75.42 ± 39.94	0.030
PNN50	12.49 ± 12.02	22.71 ± 16.95	0.005

HUTT: head-upright tilt-table; SDNN: standard deviation of all R-R intervals; SDSD: standard deviation of the successive NN differences; NN50 count: successive NN intervals differing more than 50 ms; RMSSD: the root of the mean square of the difference of successive R-R intervals; SDANN: standard deviation of the averages of the R-R intervals in all 5 min segments of R-R intervals; SDNN index: the mean of all the 5 minute standard deviations of NN (normal RR) intervals during the 24 hour period; pNN50: the proportion of adjacent normal R-R intervals < 50 ms.

and higher MPV level is closely associated with increased sympathetic activity in patients with VVS indicating the alterations of autonomic status might play a role in the determination of the platelet size in subjects with VVS.

The pathophysiology of VVS is quite sophisticated. Numerous mechanisms are supposed to be involved in the pathogenesis of VVS. Ventricular mechanoreceptor stimulation by orthostatic stress and venous pooling is a key contributor in the pathogenesis[10]. It is believed that the vasodepressor response is modulated by increased sympathetic tone following an orthostatic maneuver. Decreased venous return and venous pooling cause orthostatic hypotension and subsequent increased sympathetic tone augments the force of left ventricular contractions[11]. However, the vigorous contraction of the myocardium in a relatively unfilled left ventricle activates left ventricular mechanoreceptors (C-fibers) and precipitates the Bezold-Jarisch reflex, which results in withdrawal of sympathetic stimulation, thereby remaining predominant parasympathetic stimulation, which elicits paradoxical hypotension and bradycardia[12].

Patients with VVS do not have the autonomic stability found in healthy subjects, even during asymptomatic periods. These periodic fluctuations in ANS could make them more susceptible for the development of syncope. HRV analysis is a noninvasive, easy and reliable method of cardiac autonomic function assesment. HRV analysis reflects the balance between the sympathetic and parasympathetic innervation of the heart and has been used to describe the role of ANS activity in some cardiovascular disease and condition. Some HRV indices such as decreased SDNN (time domain HRV index) and increased LF/HF ratio (frequency domain HRV index) demonstrate impaired sympathovagal balance and associated with increased cardiac mortality in certain cardiovascular disease.

To determine the role of ANS in the pathogenesis of VVS, a number of studies have utilized

Table III. Statistical comparison of laboratory findings of study and control groups.

	HUTT positive (n=37)	HUTT negative (n=33)	*p* value
White blood cell, (10^3 µL)	6786.48 ± 1787.01	6266.66 ± 1552.35	0.201
Hemoglobin, (g/dL)	13.84 ± 1.51	14.49 ± 1.35	0.064
Hematocrit, (%)	41.74 ± 4.06	43.28 ± 3.65	0.102
Platelet count, (10^3 µL)	254.18 ± 66.28	260.54 ± 52.94	0.662
Mean platelet volume, (fL)	9.21 ± 0.70	8.46 ± 0.73	< 0.001
Platelet distribution width, (%)	16.39 ± 2.09	15.21 ± 1.87	0.016
Mean corpuscular volume, (fL)	85.56 ± 8.10	87.47 ± 4.36	0.232
Red cell distributed width, (%)	14.64 ± 1.65	14.04 ± 1.55	0.084
Neutrophil, (10^3 µL)	3984.05 ± 1569.48	3439.09 ± 1054.88	0.097
Lmphocyte, (10^3 µL)	2063.51 ± 513.21	2137.36 ± 680.63	0.608
Neutrophil/ Lmphocyte ratio	2.03 ± 0.87	1.73 ± 0.78	0.150

Table IV. Multivariate regression analysis based on independent variables likely to affect the level of MPV.

Independent variables	β	95.0% confidence interval for B	p*
Age	-0.071	(-0.016) – (0.009)	0.583
Male gender	-0.182	(-0.758) – (0.119)	0.150
Hypertension	0.109	(-0.953) – (1.402)	0.704
Hyperlipidemia	0.044	(-0.767) – (0.990)	0.800
Diabetes mellitus	-0.072	(-1.198) – (0.818)	0.707
Smoking	0.015	(-0.510) – (0.568)	0.914
Alcohol	-0.034	(-0.617) – (0.477)	0.799
Pre-test SBP	0.118	(-0.013) – (0.026)	0.531
Pre-test DBP	0.150	(-0.014) – (0.036)	0.371
Pre-test HR	-0.088	(-0.020) – (0.010)	0.483
SDNN	-0.295	(-0.008) – (-0.001)	0.016
SDANN	0.056	(-0.003) – (0.005)	0.700
RMSDD	-0.171	(-0.015) – (0.006)	0.424

*p value at the last step, which the independent variables remained in model. MPV: Mean Platelet Volume; Pre-test SBP: systolic blood pressure before head-up tilt testing; Pre-test DBP: diastolic blood pressure before head-up tilt testing; Pre-test HR: heart rate before head-up tilt testing; SDNN: standard deviation of all R-R intervals; SDANN: standard deviation of the averages of the R-R intervals in all 5 min segments of R-R intervals; RMSDD: the root of the mean square of the difference of successive R-R intervals.

the HRV analysis in different age groups; however, the results are conflicting probably due to methodological differences. It is clear that patients with VVS demonstrate abnormal autonomic responses during tilt testing, and HRV analysis, which is performed during or immediately prior to HUTT test, provides more insight about the mechanism of syncope. However, the studies investigated the HRV indices during HUTT test yielded inconsistent results. Some papers reported no differences in 24 hour HRV analysis during asymptomatic periods of patients with VVS compared to age-matched controls[13]. Kochiadakis et al[14] and Hosaka et al[15] reported a parasympathetic predominance in the basal HRV indices of adult patients with VVS; whereas Khalil et al[16] demonstrated an increased sympathetic or decreased parasympathetic tone in patients with VVS during asymptomatic time periods. Despite those disputes in the literature, the most commonly suggested theory is the presence of a significant increase in sympathetic tone caused by preload reduction. Our study results also demonstrated an autonomic imbalance suggesting sympathetic predominance during asymptomatic time periods (over a 24 hour period) in patients with VVS compared to controls.

Platelet size is largely determined at the level of the progenitor cell just before the time of megakaryocyte fragmentation into platelets[17]. Regulation of platelet size is multifactorial. Increased sympathetic activity has a distinct role in platelet production process, either by increased thrombocytopoiesis in bone marrow or by peripheral activation and splenic release of platelets[6]. This process is largely carried out by plasma catecholamines. In their previously published study, Mills et al[5] stated that platelet aggregation is activated by increased adrenaline level with first phase aggregation, second phase aggregation and potentiation of ADP aggregation. Increased plasma adrenaline level can cause changes in the shape and size of platelets via alpha 2-adrenoreceptor activation and, thereby, cause the development of larger platelets[18]. Platelets sequestered in the spleen, which constituted nearly 30% of platelets tend to be larger than normal circulating platelets, and activation of sympathetic system either after exercise[19] or adrenaline infusion[20] was shown to increase the release of these larger and activated platelets from spleen into the circulation. Additionally, Negrev et al[21] demonstrated the presence of the beta-adrenoreceptors in the megakaryocyte series and possibly in its precursors, and observed that thrombocytopoiesis was stimulated after beta-adrenergic stimulation with isoprenaline, suggesting the role of sympathetic system on thrombocytopoiesis in bone marrow.

Increased MPV has been proposed as an indicator of larger, more reactive platelets resulting from an increased platelet turnover. Increased MPV have been found in association with numerous pathological conditions and have been proposed as a predictor of adverse cardiovascular events in patients with these conditions[22-24]. With

regard to the increased sympathetic activity in patients with VVS, some authors demonstrated that the alteration in the level of plasma catecholamine immediately prior to or during spontaneous and tilt-induced syncope might play a pivotal role in the pathogenesis of VVS[25-28]. However, to our knowledge, there is no study in literature investigating the effect of increased sympathetic activity on platelet turnover in patients with VVS. In this regard, our study is the first to evaluate the relationship between MPV and VVS. We found that MPV level was higher and that there was a correlation between increased sympathetic activity demonstrated by time domain HRV indices and MPV levels in patients with VVS compared to control. However, the exact mechanism of the relation between the platelet size and ANS activity still remains obscure and requires further studies.

Although we observed a relationship between increased sympathetic activation and elevated MPV level, we did not measure the level plasma catecholamine in the present study. We evaluated only time-domain HRV indices. However, it is obvious that the results of the study will be more elucidative after including of frequency-domain HRV indices.

Conclusions

We demonstrated that baseline alterations in ANS, increases the susceptibility to VVS. Additionally, we observed that patients with autonomic imbalance tend to have higher MPV levels.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

References

1) Driscoll DJ, Jacobsen SJ, Porter CJ, Wollan PC. Syncope in children and adolescents. J Am Coll Cardiol 1997; 29: 1039-1045.
2) Balaji S, Oslizlok PC, Allen MC, McKay CA, Gillette PC. Neurocardiogenic syncope in children with a normal heart. J Am Coll Cardiol 1994; 23: 779-785.
3) Perry JC, Garson A, Jr. The child with recurrent syncope: autonomic function testing and beta-adrenergic hypersensitivity. J Am Coll Cardiol 1991; 17: 1168-1171.
4) Martin JF, Bath PM, Burr ML. Influence of platelet size on outcome after myocardial infarction. Lancet 1991; 338: 1409-1411.
5) Mills DC, Roberts GC. Effects of adrenaline on human blood platelets. J Physiol 1967; 193: 443-453.
6) Gol'dberg cED, Dygai AM, Khlusov IA, Shakhov VP. [The role of the autonomic nervous system in the mechanisms regulating hemopoiesis in stress]. Patol Fiziol Eksp Ter 1991; (3): 14-17.
7) Maestroni GJ. Neurohormones and catecholamines as functional components of the bone marrow microenvironment. Ann N Y Acad Sci 2000; 917: 29-37.
8) Brignole M, Alboni P, Benditt D, Bergfeldt L, Blanc JJ, Bloch Thomsen PE, Fitzpatrick A, Hohnloser S, Kapoor W, Kenny RA, Theodorakis G, Kulakowski P, Moya A, Raviele A, Sutton R, Wieling W, Janousek J, van Dijk G. Task force on syncope, European Society of Cardiology. Part 2. Diagnostic tests and treatment: summary of recommendations. Europace 2001; 3: 261-268.
9) Zaza A, Lombardi F. Autonomic indexes based on the analysis of heart rate variability: a view from the sinus node. Cardiovasc Res 2001; 50: 434-442.
10) Benditt DG, van Dijk JG, Sutton R, Wieling W, Lin JC, Sakaguchi S, Lu F. Syncope. Curr Probl Cardiol 2004; 29: 152-229.
11) Abi-Samra F, Maloney JD, Fouad-Tarazi FM, Castle LW. The usefulness of head-up tilt testing and hemodynamic investigations in the workup of syncope of unknown origin. Pacing Clin Electrophysiol 1988; 11: 1202-1214.
12) Lippman N, Stein KM, Lerman BB. Failure to decrease parasympathetic tone during upright tilt predicts a positive tilt-table test. Am J Cardiol 1995; 75: 591-595.
13) Akcaboy M, Atalay S, Ucar T, Tutar E. Heart rate variability during asymptomatic periods in children with recurrent neurocardiogenic syncope. Turk J Pediatr 2011; 53: 59-66.
14) Kochiadakis GE, Kanoupakis EM, Rombola AT, Igoumenidis NE, Chlouverakis GI, Vardas PE. Reproducibility of tilt table testing in patients with vasovagal syncope and its relation to variations in autonomic nervous system activity. Pacing Clin Electrophysiol 1998; 21: 1069-1076.
15) Hosaka H, Takase B, Katsushika S, Ohsuzu F, Kurita A. Altered fractal behavior and heart rate variability in daily life in neurally mediated syncope. Biomed Pharmacother 2003; 57(Suppl 1): 77s-82s.
16) Khalil M, Hessling G, Bauch M, Maier C, Dickhaus H, Ulmer HE. Sympathovagal imbalance in pediatric patients with neurocardiogenic syncope during asymptomatic time periods. J Electrocardiol 2004; 37(Suppl): 166-170.
17) Thompson CB, Love DG, Quinn PG, Valeri CR. Platelet size does not correlate with platelet age. Blood 1983; 62: 487-494.

18) Ozdemir O, Soylu M, Alyan O, Geyik B, Demir AD, Aras D, Cihan G, Cagirci G, Kacmaz F, Balbay Y, Sasmaz H, Korkmaz S. Association between mean platelet volume and autonomic nervous system functions: Increased mean platelet volume reflects sympathetic overactivity. Exp Clin Cardiol 2004; 9: 243-247.

19) Peatfield RC, Gawel MJ, Clifford-Rose F, Guthrie DL, Pearson TC. The effects of exercise on platelet numbers and size. Med Lab Sci 1985; 42: 40-43.

20) Lande K, Gjesdal K, Fonstelien E, Kjeldsen SE, Eide I. Effects of adrenaline infusion on platelet number, volume and release reaction. Thromb Haemost 1985; 54: 450-453.

21) Negrev N, Ganchev T. Influence of nonselective beta-adrenergic impacts on the effects of thrombocytopoietin in mice. Acta Physiol Pharmacol Bulg 1987; 13: 35-40.

22) Lance MD, Sloep M, Henskens YM, Marcus MA. Mean platelet volume as a diagnostic marker for cardiovascular disease: drawbacks of preanalytical conditions and measuring techniques. Clin Appl Thromb Hemost 2012; 18: 561-568.

23) Ulusoy R, Yokusoglu M, Kirilmaz A, Nevruz O, Baysan O, Kilicaslan F, Cebeci B. Mean platelet volume in ST elevation and non-ST elevation myocardial infarction. Gulhane Med J 2011; 53: 114-118.

24) Papanas N, Symeonidis G, Maltezos E, Mavridis G, Karavageli E, Vosnakidis T, Lakasas G. Mean platelet volume in patients with type 2 diabetes mellitus. Platelets 2004; 15: 475-478.

25) Cox MM, Perlman BA, Mayor MR, Silberstein TA, Levin E, Pringle L, Castellanos A, Myerburg RJ. Acute and long-term beta-adrenergic blockade for patients with neurocardiogenic syncope. J Am Coll Cardiol 1995; 26: 1293-1298.

26) Gielerak G, Makowski K, Cholewa M. Prognostic value of head-up tilt test with intravenous beta-blocker administration in assessing the efficacy of therapy in patients with vasovagal syncope. Ann Noninvasive Electrocardiol 2005; 10: 65-72.

27) Gielerak G, Makowski K, Dluzniewska E, Stec A, Cholewa M. The usefulness of tilt testing with an intravenous beta-blocker in assessing the efficacy of long-term therapy in patients with vasovagal syncope. Kardiol Pol 2003; 59: 93-104; commentary 103-104.

28) Chosy JJ, Graham DT. Catecholamines in vasovagal fainting. J Psychosom Res 1965; 9: 189-194.