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ORIGINAL ARTICLE – OPEN ACCESS

Relationship Between Heart Rate Recovery and Mean Platelet Volume in Healthy Individuals

Halil Aktaş[1], Murat Gül[1], Sinan İnci[1], Oğuz Yıldırım[2]

ABSTRACT

Objective: Heart rate recovery index (HRRI) and mean platelet volume (MPV) are two cardiovascular prognostic markers. Low HRRI and high MPV values have been observed in several diseases and conditions. However, the relationship between these two markers is unclear. In this study, the relationship between HRRI and MPV in healthy individuals is examined.

Materials and Methods: The exercise tests performed between January and December 2020 were evaluated, and 120 individuals who met the study criteria were included in the present study. An abnormal HRRI was defined as a decrease in heart rate of 12 beats or more until one minute after the peak of exercise. Those with abnormal HRRI were defined as the study group (n=60), and those with normal HRRI as the control group (n=60).

Results: A total of 120 healthy individuals were included in the study (54% female; mean age 40.14±7.90 years). Higher MPV values were detected in the study group when compared to the control group (10.27±0.10 fl vs. 9.44±0.12 fl; p<0.001). This significance continued in the logistic regression analysis (odds ratio=3.78, p<0.001). In addition, a moderate negative correlation was found between HRRI and MPV (r=-0.404, p<0.001). The MPV value of 10.25 fl was identified as an effective cutoff point for the prediction of abnormal HRRI (area under the curve [AUC]: 0.758; 95% confidence interval [CI]: 0.674–0.843).

Conclusion: Healthy individuals with abnormal HRRI have elevated MPV levels. Additionally, a negative correlation between MPV and HRRI in healthy subjects indicates a causal relation between MPV and autonomic dysfunction.

Keywords: Cardiovascular marker, exercise test, healthy individuals, heart rate recovery, mean platelet volume

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[1]Department of Cardiology, Aksaray University Faculty of Medicine, Aksaray, Türkiye
[2]Department of Cardiology, Aksaray Training and Research Hospital, Aksaray, Türkiye

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Correspondence
Sinan İnci,
Aksaray University Faculty of Medicine, Department of Cardiology, Aksaray, Türkiye
Phone: +90 530 777 66 29
e-mail:
doktorsinaninci@gmail.com

INTRODUCTION

The autonomic nervous system plays an important role in cardiovascular regulation, and autonomic dysfunction is closely related to all-cause mortality (1). The heart rate recovery index (HRRI), a crucial indicator of autonomic dysfunction, is calculated by the arithmetic difference between the maximum heart rate during treadmill stress testing and post-exercise resting heart rate (2). The decrease in the early rest period is related to the parasympathetic system, and the late period is more associated with the reduced effect of the sympathetic nervous system (3, 4). Abnormal HRRI has been defined as a reduction by less than 12 bpm in the first-minute heart rate in the resting period and has been shown as an independent risk factor for cardiovascular mortality in several studies (5, 6). In addition, faster heart rate decreasing during the first minute of resting was associated with lower mortality (7).

Platelets and their interaction with the vessel wall are key factors in the development of atherosclerosis. Larger platelets are more active both enzymatically and metabolically. Mean platelet volume (MPV) is a common measure of platelet size and provides important information on the platelet function and reactivity (8). Elevated MPV is related to increased aggregation, thromboxane synthesis, β-thromboglobulin release, and adhesion molecule expression (9). Higher MPV levels were detected in patients with hypertension, hypercholesterolemia, diabetes mellitus, smoking, and metabolic syndrome (10–14).Furthermore, it has long been recognized as a potent risk factor associated with cardiovascular morbidity and mortality (15).

Appropriate exercise regulates autonomic dysfunction and normalizes HRRI; therefore, it may be a modifiable risk factor for cardiovascular diseases (16). It is unclear whether there is a relationship between HRRI, which is a cardiovascular prognostic factor, and MPV. In the present study, the relations between HRRI and MPV in healthy subjects who underwent exercise testing were analyzed.

MATERIALS and METHODS

Ethics committee approval was obtained for this retrospective study (Aksaray University, Human Research Ethics Committee: 2021/01-59).

Study Population

This study is a retrospective observational study conducted in a single tertiary health-care center between January and December 2020. While planning our study, to calculate the sample size that would find a 10% difference between group means significant in terms of MPV variable, we found the total number of subjects to be 108 according to the two-sided Student's t-test, at a minimum power of 90% and error level of 0.05. One hundred twenty subjects (60 subjects in each group) were planned to be included the study. It was decided to divide the subjects into two groups: abnormal HRRI (study group) and normal HRRI (control group). Exclusion criteria were being older than 60 years, coronary artery disease, heart failure, moderate or severe valvular heart disease, past cerebrovascular event, hypertension, diabetes mellitus, malignancy, overt/active hematological disorders, and patients with renal, hepatobiliary, respiratory, infectious, inflammatory, or thyroid disorders. Patients who could not reach the maximum target heart rate during exercise and continuous medication use were also excluded from the study. All subjects who fulfilled the definition criteria were classified in the determined time interval in the list by file scanning. A total of 868 patients were analyzed, and 168 subjects (65 abnormal HRRI + 103 normal HRRI) fulfilled the inclusion criteria. Thereafter, we used the randomization method to select the number of patients to be calculated for our sample size. For this purpose, we used the double-block randomization method. Afterward, the subjects were divided into two groups: study group (n=60) and control group (n=60). The data of the patients, e.g., demographic characteristics, medical background, and laboratory examination results, were recorded and analyzed.

Laboratory Measurements

All patients underwent laboratory tests using standard procedures following overnight fasting to estimate fasting plasma total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol, and creatinine. Baseline white blood cells, neutrophils, lymphocytes, platelet counts, and hemoglobin levels were also measured using an automated analyzer (Sysmex XN-1000 Hematology Analyzer, Kobe, Japan). MPV values were obtained automatically by the devices in routine hemogram parameters.

Treadmill Exercise Test

The Bruce protocol was used for the exercise test. Continuous ECG was digitally recorded at a speed of 25 mm/s (CARDIOVIT CS-200, Schiller AG, Baar, Switzerland). Heart rate, blood pressure, and ECGs were continuously recorded before and after exercise. The duration of exercise (seconds) and their maximum exercise capacity (metabolic equation [MET]) were recorded. The target heart rate was found using the 220-age formula. Those who reached at least 85% of the target heart rate were included in the study. Those with a positive exercise test were excluded from the study. During the exercise test or recovery period, horizontal or downsloping ST depression of 1 mm or more in at least two leads and a 30 mmHg drop in systolic blood pressure and/or ventricular arrhythmia and/or angina during the exercise test were accepted as a positive exercise test. HRRI values were found by subtracting the heart rate at the first minute of rest from the maximum heart rate during the exercise of the subjects included in the study. An abnormal HRRI was defined as decreased heart rate (12 beats or more) until one minute after exercise peak (17).

Statistical Analysis

The data were analyzed with the SPSS 17 for Windows program (SPSS Inc., Chicago, IL, USA). Results were presented as mean±standard deviation for the variables that were distributed normally, median (minimum-maximum) for the variables that were not distributed normally, and percentage (%) for categorical variables. To identify the distribution pattern of the variables, the Kolmogorov-Smirnov normality test was employed. Student's t-test and Mann–Whitney U test were employed for the comparison of continuous variables, and the chi-square test for the comparison of the categorical variables. Pearson correlation analysis was used to evaluate the relations between HRRI and MPV. Multivariate logistic regression analysis was performed to identify risk factors for the outcome variable (abnormal HRRI). All covariates with missing data in less than 20% of observations and a p value <0.05 in univariate testing (according to the results of group comparisons obtained by Mann–Whitney U test, Student's t-test, and chi-square analysis) were considered for inclusion in the final multivariate regression model and retained if the p value was <0.05 or if they were known as evidence of significant confounding such as gender. Highly collinear covariates (defined as correlation coefficient >0.6) were not included together in the final multivariate model. To evaluate the predictive power of MPV for abnormal HRRI, a receiver operating characteristic (ROC) curve was drawn. The threshold value, sensitivity, and specificity were determined by ROC analysis. A p value was taken as statistically significant when <0.05.

RESULTS

The study cohort was composed of 120 consecutive participants (mean age 40.14±7.90, 54% of whom were female). The study group was older (42.02±7.52 vs. 38.27±7.89, p=0.009) than the control group. Both groups were similar regarding gender (p=0.360), smoking (p=0.637), family history (p=0.143), heart rate (p=0.101), systolic blood pressure (p=0.645), diastolic blood pressure (p=0.084), glucose (p=0.070), LDL (p=0.461), triglyceride (p=0.912), HDL (p=0.815), hemoglobin (p=0.113), white blood cell (p=0.5), and thrombocyte count (p=0.458). The MPV level was higher in the study group at a significant level than in the control group (10.27±0.76 vs. 9.44±0.89, p<0.001). The basal clinical, demographic, laboratory, and exercise values of the study population are given in Table 1.

Exercise parameters such as maximum exercise duration (369.67±87.73 sec. vs. 426.35±72.17 sec., p<0.001), maximum exercise capacity (8.30 METs vs. 9.54 METs, p=0.018), and HRRI (5.90±2.87 vs. 20.57±8.49, p<0.001) were found to be lower in the study group at a significant level (Table 1). Further, a negative and moderate significant correlation was detected between HRRI and MPV (r=-0.404, p<0.001) (Fig. 1).

Multivariate logistic regression analysis was used to determine the independent predictors of HRRI in the study population. MPV (OR=3.78, confidence interval [CI]: 2.06–6.96, p<0.001) was identified as the independent predictor of abnormal HRRI (Table 2). ROC analysis was used to identify the area under the curve (AUC) of MPV to predict abnormal HRRI. The MPV value of 10.25 fl was the best point to discriminate between the control and abnormal HRRI (AUC: 0.758, CI: 0.674–0.843, p<0.001) with 55% sensitivity and 85% specificity (Fig. 2).

Table 1. Comparison of demographic, laboratory, and exercise test data between the groups

	Study group (n=60)	Control group (n=60)	p
Age (years, mean±SD)	42.02±7.52	38.27±7.89	**0.009***
Sex (female) n (%)	35 (58)	30 (50)	0.360
Smoking, n (%)	10 (17)	12 (20)	0.637
Family history, n (%)	6 (10)	2 (3)	0.143
Heart rate (beats/min)	93.20±15.09	88.77±14.25	0.101
Systolic blood pressure (mmHg)	120 (90–150)	120 (90–160)	0.645
Diastolic blood pressure (mmHg)	80 (60–90)	70 (60–90)	0.084
Glucose (mg/dL)	99.73±13.52	95.33±12.84	0.070
LDL cholesterol (mg/dL)	134.30±22.11	138.05±32.47	0.461
HDL cholesterol (mg/dL)	47.58±10.96	47.13±9.72	0.815
Triglyceride (mg/dL)	145.73±62.8	147.03±66.2	0.912
Hemoglobin (g/dL)	13.64±1.11	13.99±1.25	0.113
White blood cell count (10^3/uL)	7.05±1.62	6.87±1.30	0.500
Platelet count (10^3/uL)	266.43±84,41	277.30±75.23	0.458
Mean platelet volume (fl)	10.27±0.76	9,44±0.89	<**0.001***
Maximum exercise time (seconds)	369.67±87.73	426.35±72.17	<**0.001***
Heart rate recovery index (beats)	5.90±2.87	20.57±8.49	<**0.001***
Maximum exercise capacity (METs)	8.30 (6.87–12.14)	9.54 (6.87–12.14)	**0.018***

HDL: High-density lipoprotein; LDL: Low-density lipoprotein; METs: Metabolic equation; *: P value <0.05 statistically significant. *Mean±standard deviation for normally distributed variables and median (minimum–maximum) values for non-normally distributed variables were used

Table 2. Logistic regression analysis for abnormal heart rate recovery index

Variable	B	SE	Wald	df	Sig.	Exp(B)	95% CI for Exp(B)	
							Lower	Upper
Age	0.062	0.034	3.288	1	0.070	1.064	0.995	1.138
Gender (male)	-0.152	0.533	0.081	1	0.775	0.859	0.302	2.440
MPV	1.330	0.311	18.290	1	<**0.001***	3.782	2.056	6.958
Maximum exercise capacity	0.004	0.197	0.000	1	0.983	1.004	0.682	1.478
Maximum exercise time	-0.007	0.004	3.406	1	0.065	0.993	0.986	1.000

SE: Standard error; MPV: Mean platelet volume; CI: Confidence interval; *: P value <0.05 statistically significant. (-2 log likelihood,124.049; Cox and Snell pseudo-R^2, 0.297; Nagelkerke pseudo-R^2, 0.396; p<0.001). Hosmer and Lemeshow test: 0.686

DISCUSSION

In this study, it was found that abnormal HRRI was associated with increased MPV, advanced age, and exercise parameters such as maximum exercise time and maximum exercise capacity in healthy individuals. Heart rate variability represents the balance between sympathetic and parasympathetic system activity (2). Elevated heart rate during exercise is predominantly driven by the activation of the sympathetic nervous system and simultaneous suppression of the parasympathetic nervous system (17). However, heart rate recovery after exercise is interpreted in two stages. The first is a rapid heart rate decrease in the early period of resting caused by vagal activation. Second, the heart rate decreases more slowly in the later period due to sympathetic withdrawal (2). Heart rate recovery focuses mainly on vagal reactivation and provides information about the balance between sympathetic and parasympathetic tones (2). Therefore, impaired HRRI is deemed a reflection of autonomic dysfunction, associated with decreased vagal activity and sympathetic hyperactivity.

Impaired HRRI is closely associated with numerous disorders, e.g., coronary heart disease, heart failure, obstructive sleep apnea syndrome, diabetes mellitus, and Behcet's disease (1). Further, impaired HRRI following exercise is an independent predictor for cardiovascular and all-cause mortality, even in healthy people (17, 18). Our results indicate that healthy individuals with increased MPV values have impaired HRRI compared with healthy controls. In addition, a moderate negative correlation was detected between HRRI and MPV. For this reason, we speculate that MPV might be a simple, noninvasive measure to evaluate autonomic dysfunction.

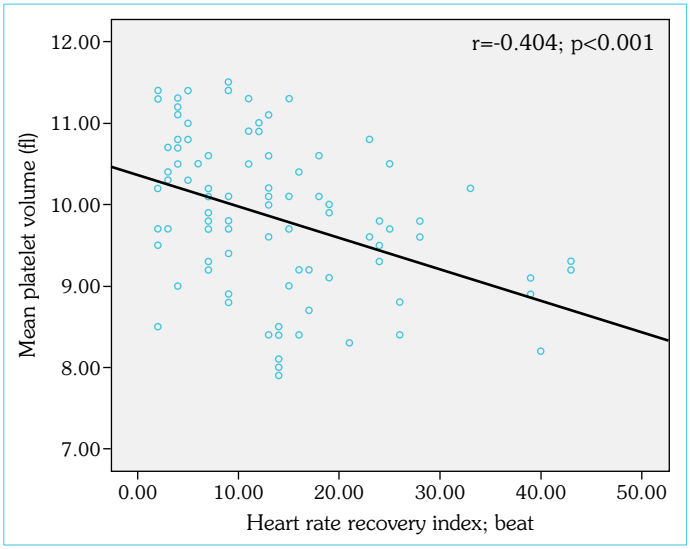

Figure 1. Pearson correlation analysis between heart rate recovery index and mean platelet volume

Platelets produce and express many substances, which are important mediators of coagulation, atherosclerosis, and inflammation (19). As a determinant of platelet function, MPV is a valuable prognostic marker in cardiovascular patients (19). Sympathetic activity plays a critical role in MPV through peripheral activation and spleen release or thrombocytopoiesis (20). Further, increased adrenaline levels also contribute to platelet release and platelet volume (21). According to the findings obtained here, this hypothesis is confirmed by showing autonomic imbalance (i.e., impaired HRRI) in healthy individuals with increased MPV values compared with controls.

As assessed by heart rate variability and heart rate recovery, cardiac autonomic nervous activity is associated with inflammatory markers (22). It has been revealed that the rate of neutrophil-lymphocyte, which is an indicator of the inflammatory process, is higher in those with abnormal HRRI (16). Additionally, both abnormal HRRI and increased MPV are predictors of endothelial dysfunction (23, 24). Based on these data, it is possible to argue that impaired HRRI and increased MPV have similar underlying pathogenic mechanisms. Therefore, it can be considered that both of them have the potential to reflect autonomic dysfunction.

This study is limited in several ways. First, it included a modest sampling size and was carried out in one single center that lacks external validation. In this respect, these findings need further multi-institutional validation with a larger sampling. Second, HRRI and MPV were evaluated on admission to the hospital, but their dynamic changes were not evaluated.

CONCLUSION

Healthy individuals with abnormal HRRI and no substantial cardiovascular risk factors have elevated MPV values. Additionally, a negative correlation between MPV and HRRI in healthy subjects indicates that there is a causal relation between MPV and autonomic dysfunction. For this reason, prospective and randomized studies are needed to confirm such a causal association.

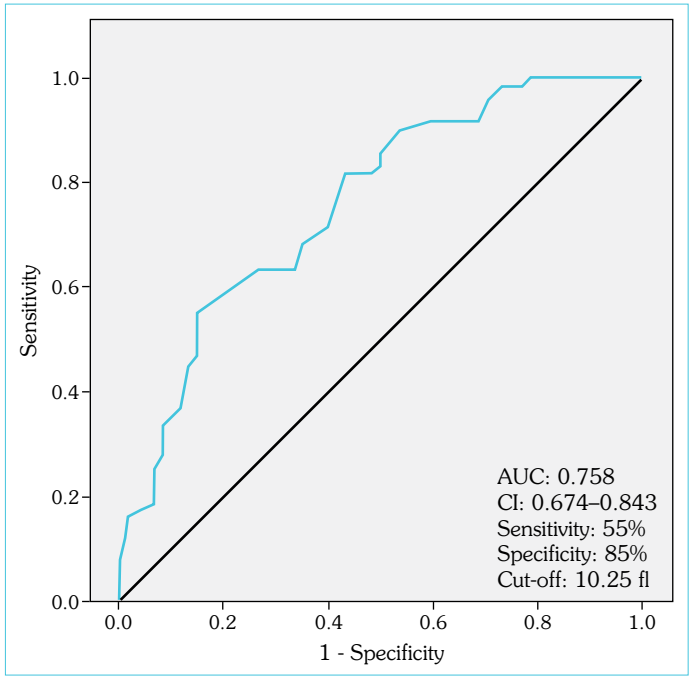

Figure 2. ROC curve analysis to evaluate the predictive power of MPV for abnormal HRRI

AUC: Area under the curve; MPV: Mean platelet volume; HRRI: Heart rate recovery index; ROC: Receiver operating characteristic

Ethics Committee Approval: The Aksaray University, Human Research Ethics Committee granted approval for this study (date: 22.02.2021, number: 2021/01-59).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – HA, Sİ; Design – MG, HA; Supervision – Sİ, OY; Resource – OY, MG, Sİ; Materials – HA, Sİ; Data Collection and/or Processing – MG, OY; Analysis and/or Interpretation – HA, Sİ; Literature Search – MG, OY; Writing – MG, Sİ; Critical Reviews – OY, Sİ.

Conflict of Interest: The authors have no conflict of interest to declare.

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