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Lower than Normal Mean Platelet Volume is Associated with Reduced Extent of Coronary Artery Disease

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Abstract

Background: Extent of atherosclerotic coronary artery disease in patients with stable angina has important prognostic and therapeutic implications. In current models of plaque evolution, thrombocytes play an important role in plaque growth. Mean platelet volume is a readily obtainable marker that was shown to correlate with platelet aggregability in vitro and increased values were demonstrated after acute vascular events.

Objective: In this study, we investigated the relationship of mean platelet volume and angiographic extent of coronary artery disease in patients with stable angina.

Methods: Past medical records, complete blood count and angiographic data of 267 eligible stable angina patients were reviewed. Angiographic extent of coronary artery disease was evaluated form angiographic data using Gensini score by an expert in invasive cardiology. Mean platelet volume values were obtained from complete blood counts that obtained one day before angiography. Patients were grouped as those within (n = 176) and lower than (n = 62) population-based range for mean platelet volume. Comparisons between groups and correlation analyses were performed.

Results: There was no linear correlation between total Gensini score and mean platelet volume (p = 0.29), while total thrombocyte count was inversely correlated with mean platelet volume (p < 0.001; r = 0.41). Patients with lower than normal mean platelet volume had significantly lower Gensini score (36.73 ± 32.5 vs. 45.63 ± 32.63; p = 0.023) and three-vessel disease (18% vs. 36%; p = 0.007) compared with those mean platelet volume values within population-based ranges.

Conclusion: Our findings show no linear relationship exists between mean platelet volume and extent of coronary artery disease, while patients with lower than normal mean platelet volume had reduced extent of coronary artery disease (Arq Bras Cardiol. 2013;100(3):255-260).

Keywords: Coronary Artery Disease; Coronary Angiography; Thrombocytopenia

Introduction

Coronary artery disease (CAD) is the leading cause of morbidity and mortality worldwide. Platelets play an important role not only in acute coronary events but also in the genesis and evolution of atherosclerotic lesions[1]. Mean platelet volume (MPV) is considered as an indicator of platelet activity, and was shown to be increased in a variety of acute vascular events, including unstable angina, acute myocardial infarction, and stroke[2,3]. So far, its relationship with stable coronary artery disease could not be demonstrated, and a few studies aimed to show its relationship with extent of CAD failed to do so[4,5]. However, no direct scoring system for CAD was used in these studies that may show a direct relationship between MPV values

and extent of CAD. Moreover, these studies did not specially analyzed patients with MPV values out of population based range. Our aim in this study was to investigate a possible relationship between MPV values and Gensini score in patients with established coronary artery disease, and analyze whether higher than normal or lower than normal MPV values were associated with extent of CAD.

Materials and Methods

Coronary angiography database for the first half of year 2010 was retrospectively reviewed for this study. Patients, who were older than 18 years, had stable angina pectoris and an indication for coronary angiography, and at least one angiographically perceivable coronary lesion were included. Patients with unstable coronary syndromes at the time of cardiac catheterization were excluded from analysis. Patients who experienced any coronary revascularization procedure before index coronary angiography were also excluded, as previous revascularization procedures may cause an underestimation or overestimation of overall coronary atherosclerotic burden. Patients who had disorders which may alter thrombocyte parameters such as blood

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dyscrasias, chronic liver failure or renal disorders were not included, as well as those used drugs that may have an effect on thrombocytes. After evolution, 267 patients were included in analysis.

Demographic data including age, gender, and history of diabetes, hypertension, hyperlipidemia and smoking were collected according to information given by patients. Patients were grouped according to population-based range of MPV[6]. The data between groups were compared to analyze for significant differences. The study was approved by institutional scientific committee.

Mean platelet volume and total thrombocyte count values of patients were obtained from complete blood count (in EDTA) that was performed by a Coulter counter (Gen-S, Coulter Corporation, Malvern, USA) one day before coronary angiography.

Review of coronary angiography records

Only angiograms performed in study institution with institutional angiography devices (Siemens AXIOM-Artis, Siemens Medical Solutions USA Inc, Malvern, PA, USA) was analyzed in study. All recorded coronary angiography views of patients were reviewed by an expert in invasive cardiology (HH). For each perceivable lesion, minimal lumen diameter for lesion and reference vessel diameter was obtained. Views in which lesion diameter was found least regarding to reference diameter was used for analysis. Quantitative analysis was performed using a commercial angiography package (AXIOM Sensis, Siemens Medical Solutions USA Inc., Malvern, PA, USA). Before calculation of Gensini score, each patient was categorized as one, two or three vessel disease if significant stenoses (>50%) were present in main (RCA, LAD or Circumflex arteries) coronary arteries. After that, an appropriate Gensini score was given according to Gensini chart to each lesion[7]. Total Gensini score was calculated by adding each individual lesion score.

Statistical analysis

Statistical analyzes were performed with SPSS 16.0 software (International Business Machines, New Orchard Road, Armonk, New York, USA). Data were given as mean ± SD for continuous variables and percentage for categorical variables. Normal distribution and homogeneity of variance were controlled with one-way Kolmogorov-Smirnov and Levene's tests, respectively. Correlation analysis was performed using Spearman's rho test to determine correlation between MPV values and total Gensini score and Pearson correlation to determine correlation between MPV values and total thrombocyte count. Chi square test was used for categorical variables, while Mann - Whitney U test was used for continuous variables, as marked skewness was present in population distribution. A p value less than 0.05 was considered as statistically significant, while correlation was said to be present when r value is higher than 0.25.

Results

Demographic, clinic, biochemical and angiographic data regarding to patients were given in Table 1. 243 out of 267 patients were grouped according to MPV, as complete data regarding to demographic variables were available in these patients. Only five patients had higher than normal (MPV > 11 fl) MPV values, so comparisons were performed between lower than normal MPV and normal MPV groups, omitting those with higher than normal MPV. However, these patients were included in correlation analyzes. Age, gender, history of diabetes, hypertension, hyperlipidemia and cigarette smoking were indifferent between groups. Total thrombocyte count differed significantly between groups ($p < 0.001$), as patients in lower than normal MPV group (280.34 ± 87.65 / mm[3]) had higher total thrombocyte count compared with those in normal MPV group (233.59 ± 66.71 / mm[3]). Patients with lower than normal MPV values had lower incidence of three vessel disease compared with those having normal MPV values (18% vs. 36%; p = 0,007). Concordant with this finding, patients with lower than normal MPV values had significantly lower total Gensini score than those with normal Gensini score (36,73 ± 32,5 vs. 45.63 ± 32.63; p = 0.023) (Figure 1). No statistically significant correlation was found between MPV and total Gensini score (p = 0.084, r = 0.01), although MPV values correlated with total thrombocyte count (p < 0.001; r = 0.41) (Figure 2).

Discussion

In this study, we used an angiographic scoring system to evaluate a possible correlation between extent of coronary atherosclerosis and mean platelet volume in patients with stable angina. There were no overall correlation between MPV and Gensini score in whole study group. However, patients in whom MPV values were lower than population range had lower total Gensini scores and lesser incidence of three vessel disease compared with those who had normal MPV values.

Plaque thrombosis is thought to play an important role, not only in acute coronary syndromes, but also in the progression of chronic atherosclerotic coronary disease (1). As shown in pathologic examinations made in hearts of individuals died due to noncardiac causes; phases of plaque disruption with superimposed thrombosis happen during the evolution of atherosclerotic plaques[8]. Many of these superficial thromboses does not cause acute coronary syndrome; instead undergo healing periods. However, these "crises" themselves causes a rapid growth of plaques; platelet-driven substances such as TGF-β and PDGF, as well as thrombin that appears during coagulation cascade stimulate collagen synthesis by smooth muscle cells, while in situ produced thrombin promote smooth muscle cell proliferation[8,9]. Both superficial thromboses caused by dysfunctional endothelium[10] and intraplaque hemorrhages also cause an increase in physical size of atheroma plaque and further promote lesion growth[11].

All these findings put a special stress on the importance of platelets, which are essential counterparts of coagulation cascade. From a pathophysiological standpoint, it is expectable that an increase in platelet size and activity may result from increased growth factor content and enhanced production of thrombin during coagulation; which would, in turn, increase the rate of plaque growth via increased smooth muscle cell activity and collagen production when superficial thrombosis or intraplaque hemorrhage happen during atheroma evolution. Albeit there are many precise methods to measure platelet activity to identify individuals with increased risk for

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Table 1 - Demographic, clinical and angiographic data regarding to patients with lower than normal mean platelet volume and normal mean platelet volume. Patients with higher than normal mean platelet volume (n = 5) were not included

Parameter	Patients with lower than normal MPV (MPV<7.8 fl; n=62)	Patients with normal MPV (MPV 7.8-11 fl; n=176)	p value
Demographic			
Age	61.74 ± 11.17	60.20 ± 10.51	0.26
Gender (%Female)	19%	28%	0.19
Clinical			
Diabetes	32%	28%	0.57
Smoking	44%	42%	0.84
Hypertension	50%	53%	0.70
Hyperlipidemia	79%	71%	0.22
Blood Count			
MPV (fl)	7.41 ± 0.41	8.75 ± 0.73	<0.001
TTC (x10^3/mm^3)	280.34 ± 87.66	233.59 ± 66.71	<0.001
Angiographic			
One-vessel	39%	28%	0.11
Two-vessel	39%	30%	0.18
Three-vessel	18%	36%	0.007
Gensini score	36.73 ± 32.50	45.63 ± 32.63	0.007

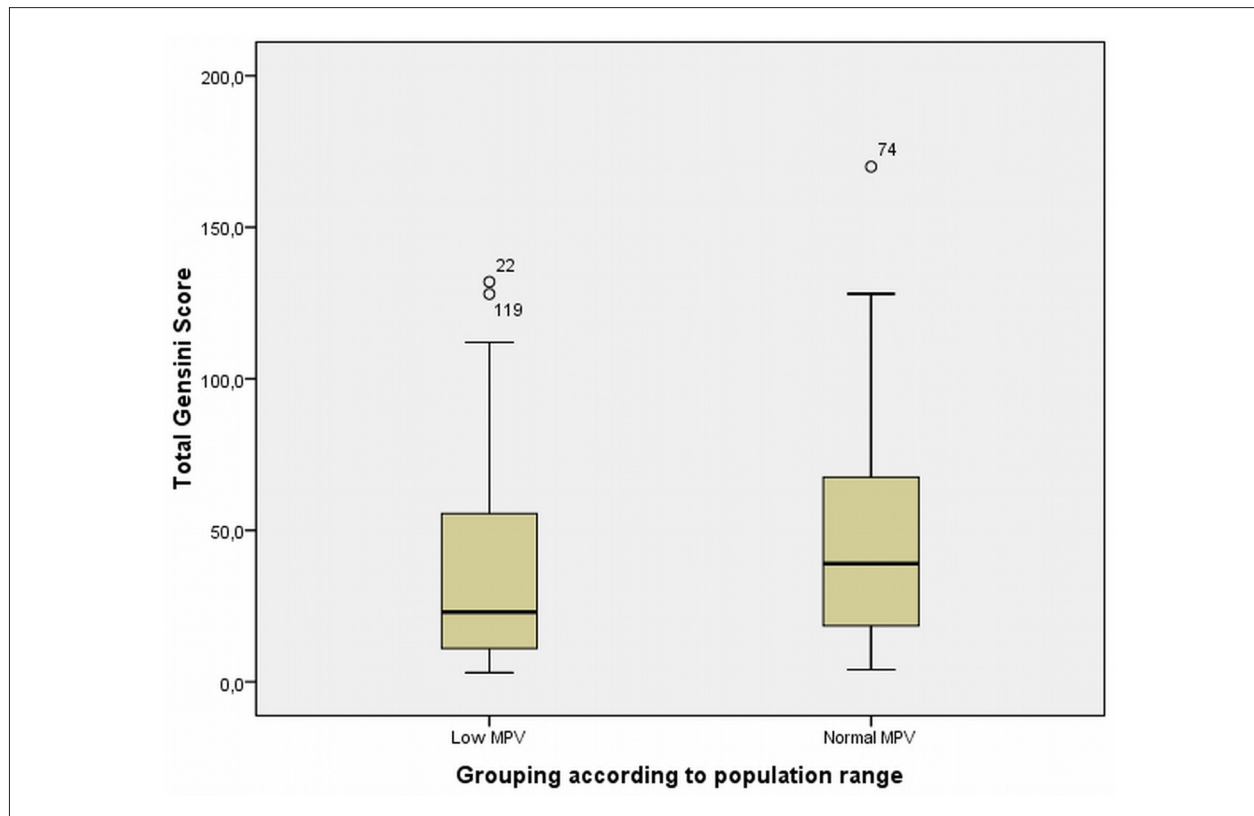MPV: Mean platelet volume; TTC: Total thrombocyte count.

Figure 1 - Total Gensini score in patients with lower than normal mean platelet volume and normal mean platelet volume. Patients with lower than normal (< 7,8 fl) mean platelet volume exhibited significantly lesser Gensini scores.
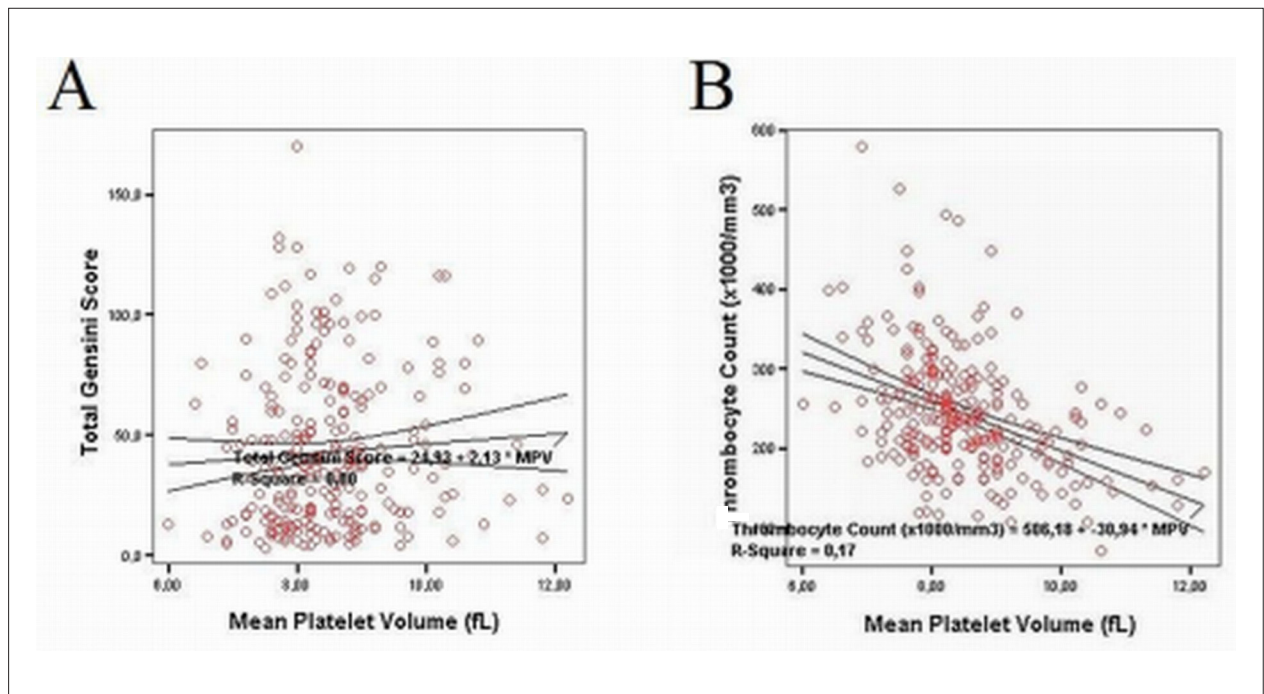
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Figure 2 - *Scatter plot graphics and linear regression analysis showing relationship between (A) Mean platelet volume and total Gensini score and (B) Mean platelet volume and total thrombocyte count.*

cardiovascular diseases, these remain primarily as research tools due to lack of standardization of measurements and uncertainty about cut-off values and interpretation of results. Also, relative cost of these measurements makes these tests rather impractical[12].

A relatively easy and practical way to measure platelet activity is measuring the mean size of platelets. Larger thrombocytes are metabolically and enzymatically more active and have an enhanced prothrombotic potential[13,14]. They tend to show an increased tendency to aggregate, increased synthesis of thromboxane and β-thromboglobulin, and express more adhesion molecules[15]. MPV was shown to be increased in clinical situations where the risk of atherosclerotic disease is increased, namely diabetes mellitus[16], hypertension[17], hypercholesterolemia[18], smoking[19], obesity[20] and metabolic syndrome[21]. Direct evidence from clinical studies had shown that MPV increase in acute thrombotic events such as acute myocardial infarction, unstable angina and stroke[2,3]. Moreover, new studies confirm that this marker is also increased in chronic coronary conditions such as saphenous vein graft disease[22] and coronary ectasia[23]. However, up to date, no studies had been able to show increased MPV values in stable coronary artery disease. In a study conducted by Ihara et al., MPV values did not differ between angiographically proven coronary artery disease patients and aged controls[4]. Similarly, in a large prospective study conducted by De Luca et al. in 1411 patients, MPV failed to correlate with the extent of coronary artery disease, which was evaluated with the number of diseased vessels[5]. All these data implied that increased MPV levels were not a risk factor for the

presence and the extent of atherosclerotic CAD. However, as mentioned above, extent of CAD was measured semi quantitatively by the number of affected vessels rather than using an angiographic scoring system to fully evaluate total atherosclerotic burden. Also, the effect of lower than normal MPV was not analyzed in these studies.

We studied the effect of MPV on the extent of coronary artery disease in a series of 267 patients. Incorporation of an angiographic scoring method allowed us to directly compare MPV levels and extent of CAD. Our results indicate that a linear correlation does not exist between severity and extent of CAD and MPV, which agrees with studies performed so far. However, patients with MPV values lower than previously described threshold in population-based studies had significantly lower total Gensini score and decreased incidence for three vessel disease. Previous studies did not relate higher MPV values with occurrence and extent of coronary artery disease[4,5]. Our analysis, in respect to MPV quartiles and correlation analyzes, are in concordance with those works. However, we have demonstrated that patients with lower-than-normal MPV values may have reduced extent of coronary atherosclerotic disease. Moreover, this finding is independent from coronary risk factors such as age, history of hypertension, diabetes, hyperlipidemia and cigarette smoking. As too few patients with a MPV value of more than 11 fL were present in our study, we were unable to analyze whether if more than normal MPV is associated with increased extent of coronary artery disease. In previous studies, de Luca and associates had shown that MPV values more than 11,5 fL is not associated with higher incidence of three vessel disease[5].

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As much attention has focused on large platelets, information regarding to smaller thrombocytes is rather scarce. These thrombocytes are considered as "mature" counterparts of large platelets, while a study defines them as platelets with lesser life span compared to large ones[24]. Albeit large platelets contain more procoagulant factors, increased coagulability of large platelets is a matter of debate[5]. However, their growth-promoting activity may be more prominent, as they show enhanced release of growth factors[15,25]. In terms of plaque growth, growth-promoting properties of larger platelets may be more important than their procoagulant activity. Moreover, these platelet constituents may be an important factor determining platelet size[26]. Therefore, it would be reasonable to consider smaller platelets as less growth promoting for atherosclerotic plaques compared with large ones, which partly explains our findings.

Conclusion

Our results show that MPV has no linear correlation with extent of CAD, while MPV values lower than reference limits are accompanied by reduced extent of coronary artery disease. Patients with MPV values less than 7,8 fl could be expected to have less Gensini scores and three vessel disease at angiography.

Study limitations

As this study was retrospective in nature, obtained MPV values are subject to measurement errors, as it was previously shown that MPV tend to increase when withdrawn blood waited more than two hours in EDTA. However, institutional procedures dictate bloods should be collected in EDTA and should be analyzed within two hours after collection. While we consider procedural errors are minimal, no certain guarantees could be provided.

Another limitation of this study was the usage of coronary angiography for determining total atherosclerotic burden. It is well known that coronary angiography tend to underestimate plaques that show positive remodeling. So, a definitive result can be obtained by using intravascular ultrasound instead of coronary luminography.

Author contributions

Conception and design of the research: Güvenç TS, Hasdemir H, Erer HB, Çetin R; Acquisition of data: Güvenç TS, Erer HB, İlhan E, Özcan KS, Çalık AN, Çetin R; Analysis and interpretation of the data: Güvenç TS, Hasdemir H, İlhan E, Özcan KS, Çalık NA; Statistical analysis: Güvenç TS, Eren M; Writing of the manuscript: Güvenç TS, Hasdemir H, Erer HB, İlhan E, Özcan KS; Critical revision of the manuscript for intellectual content: Hasdemir H, Eren M.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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