

# Mean platelet volume is associated with aortic intima-media thickness in patients without clinical manifestation of atherosclerotic cardiovascular disease

Gülhan Yüksel Kalkan, Mustafa Gür<sup>1</sup>, Ahmet Oytun Baykan, Hakan Uçar, Zafer Elbasan, Durmuş Yıldırım Şahin, Mevlüt Koç, Abdülrezzak Börekçi<sup>1</sup>, Murat Çaylı

Clinic of Cardiology, Adana Numune Training and Research Hospital; Adana-Turkey

<sup>1</sup>Department of Cardiology, Faculty of Medicine, Kafkas University; Ağrı-Turkey

## ABSTRACT

**Objective:** Mean platelet volume (MPV) plays a pivotal role in the pathophysiology of atherosclerotic disease. Thoracic aortic intima-media thickness (IMT) was reported as an earlier marker of preclinical atherosclerosis than carotid IMT. However, the relationship between MPV and aortic IMT was not investigated. We aimed to assess the relationship between thoracic aortic IMT and MPV in patients undergoing transesophageal echocardiography (TEE) examination for different indications.

**Methods:** We studied 190 patients (mean age 37.0±12.5 years) who underwent TEE for different indications. The patients who have known atherosclerotic disease were excluded from study. The patients were divided into 2 groups according to the median thoracic aortic IMT values (IMT<sub>low</sub> group ≤13 mm and IMT<sub>high</sub> group >13 mm). Platelet count and MPV were analyzed with an automated hematology analyzer. A multiple stepwise linear regression analysis was performed to identify the independent associations of thoracic aortic IMT.

**Results:** The highest MPV values were observed in the IMT<sub>high</sub> group compared with the IMT<sub>low</sub> group (9.5±10 fL vs. 10.9±1.2 fL, p<0.001). Also, the IMT<sub>high</sub> group had higher age, hs-CRP, and uric acid levels (p<0.05 for all). Multiple linear regression analysis showed that aortic IMT was independently related with age (β=0.340, p<0.001), uric acid (β=0.111, p=0.041), hs-CRP (β=0.200, p<0.001), and MPV (β=0.482, p<0.001).

**Conclusion:** MPV is independently related to the extent of subclinical thoracic aortic atherosclerosis. Increases in MPV may be a crucial biochemical marker for initial atherosclerosis. (*Anatol J Cardiol* 2015; 15: 753-8)

**Keywords:** mean platelet volume, aorta, intima media thickness, and atherosclerosis

## Introduction

It has been demonstrated that mean platelet volume (MPV) is an indicator of platelet activation that plays a crucial role in the pathophysiology of atherosclerotic disease (1, 2). Early stages of atherogenesis are thrombocyte activation and aggregation, which leads to proliferation and migration of smooth muscle cells from the media to endothelium (1, 2). In several studies, it has been demonstrated that platelet size is associated with platelet function and activation, and large platelets behave more actively when compared with smaller ones (3, 4). According to these early results, MPV may be treated as a marker of thrombocyte activation, which may also reverberate atherosclerosis (5, 6). Contrary to these reports, more recent studies revealed that the measurements of platelet indices, including MPV, are not used as platelet function tests (7, 8). Beyan et al. (7) investi-

gated whether platelet indices have a correlation with platelet aggregation responses using an optical method in healthy adults. They did not observe a correlation between any of the platelet indices and platelet aggregation responses using light transmission turbidimetric platelet aggregometry. Also, De Luca et al. (8) investigated whether MPV was associated with platelet reactivity and the extent of coronary artery disease among diabetic patients. They performed a cohort study including 1016 consecutive diabetic patients undergoing coronary angiography and showed that MPV was not related to platelet reactivity.

Although there have been numerous recent studies on the association between MPV and diseases of the cardiovascular system (5, 6, 9-11), there is a lack of research directly examining the relevance between MPV and thoracic aortic intima-media thickness (IMT). However, atherosclerotic lesions of the aorta, determined on transesophageal echocardiography (TEE), are

**Address for Correspondence:** Dr. Gülhan Yüksel Kalkan, Adana Numune Eğitim Araştırma Hastanesi, Çukurova/Adana-Türkiye

Phone: +90 322 291 25 25 Fax: +90 322 338 33 69 E-mail: gulhankalkan@yahoo.com.tr

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markers of diffuse atherosclerotic disease (12, 13), and it has been shown that as an early marker of preclinical atherosclerosis, IMT of the thoracic aorta is better than carotid IMT (14). Therefore, the main purpose of the present study is to assess the relationship between thoracic aortic IMT and MPV in patients undergoing TEE examination for different indications.

## Methods

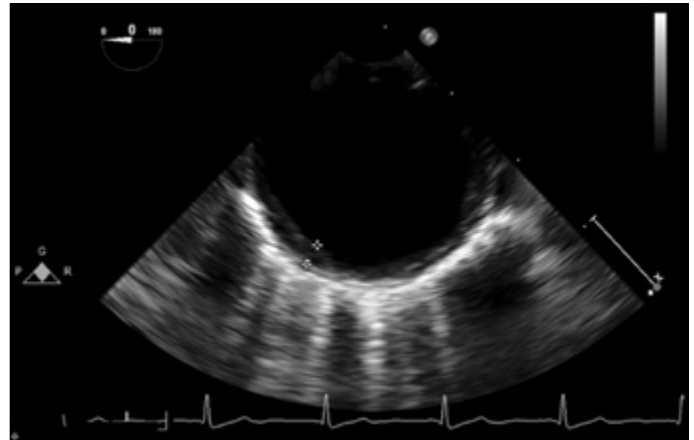
### Study design

Of the 582 TEE procedures performed between January 2013 and July 2013 in Adana Numune Training and Research Hospital Cardiology Clinic. We evaluated 190 patients who had non-atherosclerotic heart disease and who underwent TEE examination for different indications (112 females, 78 males; mean age  $37.0 \pm 12.5$  years), which included evaluation and management of valvular heart disease (26 patients for bicuspid aortic valve, 30 patients for mitral valve disease), suspected atrial septal defect (112 patients), and lone atrial fibrillation (22 patients). Patients with known coronary artery disease or clinical signs of ischemic heart disease, heart failure, peripheral vascular disease, kidney diseases, hepatobiliary disease, alcohol consumption, malignancy, hypertension, or diabetes mellitus; those taking any medical treatment; and patients with a history of carotid artery surgery or stroke were excluded from the study. We also excluded patients with familial hypercholesterolemia, aortic dissection, or aortic aneurysm, as well as patients with poor ultrasonographic recording quality with no clear delineation of the intima-media complex. A positive exercise treadmill test was also an exclusion criterion in our study. The institutional Ethics Committee approved the study, and written informed consent for participation in the study was obtained from all individuals.

Age and gender were recorded. Body mass index (BMI) was computed as weight divided by height squared ( $\text{kg}/\text{m}^2$ ).

### Blood sampling

Fasting blood samples were collected 1 day before TEE for the evaluation of low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride, serum bilirubin level, and uric acid levels. Plasma triglyceride, total cholesterol, LDL-C, and HDL-C concentrations; uric acid; and fasting glucose were measured using an automated chemistry analyzer (Aeroset; Abbott, Holliston, MN, USA) with commercial kits (Abbott). The cut-off value for uric acid was 3.4-7.0 mg/dL. hs-CRP was measured using a commercial spectrophotometric kit (Scil Diagnostics GmbH, Viernheim, Germany). The cut-off value for hs-CRP was  $<3$  mg/dL. We collected the blood samples into tubes containing dipotassium EDTA for the measurements of platelet count and MPV. The samples were analyzed within 20 minutes after collection using a Sysmex XT 1800i automated hematology analyzer (Roche Diagnostic, Shanghai, China) (15, 16). The cut-off value for platelet count was  $136\text{-}380 \times 10^3/\mu\text{L}$  and  $9\text{-}13$  fL for MPV. The analytical coefficient of variation for MPV was 1.72%.



**Figure 1. Measurement of thoracic aortic intima-media thickness**

### Transthoracic and transesophageal echocardiography

Transthoracic echocardiography and TEE were obtained by using an ultrasonograph (Philips IE 33 system, Andover, MA, USA) and a multiplane probe and were performed in all study subjects. Left ventricular ejection fraction (EF) was determined by modified Simpson's method (17). After a 4-h fasting period, all patients underwent TEE by using a 5 Mhz multiplane transesophageal transducer. The oropharynx was anesthetized with topical lidocaine spray, and subjects were placed in left decubitus with the left arm under the head, which was kept in a flexed position. The transducer was put into the esophagus and gastric cavity to scan the cardiac and aortic structures through the mouth. TEE was performed by an experienced cardiologist who was blinded to other laboratory results. All patients tolerated the TEE procedure well, and no complications occurred. All studies were recorded and were evaluated independently by an experienced observer.

After the cardiac examination, the transducer was rotated posteriorly, advanced to the distal esophagus (approximately 40 cm from the incisor teeth), and slowly withdrawn to obtain detailed images from the distal thoracic aorta to the aortic arch. Thoracic aortic IMT was defined as the distance from the leading edge of the lumen-intima interface to the leading edge of the media-adventitia interface of the far wall. The measurement of IMT in the thoracic aorta was made in 6 separate segments (length of 1 segment 5 cm): ascending aorta, arch, from 0 to 5 cm distal to the arch, from 5 to 10 cm distal to the arch, from 10 to 15 cm distal to the arch, and from 15 to 20 cm distal to the arch. The maximum IMT was measured in each segment, and the mean value for the maximum IMT among the 6 segments was taken as the evaluable IMT of the thoracic aorta (18). The patients were divided into 2 groups according to the median IMT value ( $\text{IMT}_{\text{low}}$  group  $\leq 13$  mm and  $\text{IMT}_{\text{high}}$  group  $>13$  mm). A sample measurement of thoracic aortic IMT is shown in Figure 1.

### Statistical analysis

All analyses were conducted using SPSS 17.0 (SPSS for Windows 17.0, Chicago, IL, USA). Comparison of categorical variables between the groups was performed using the chi-

**Table 1. Comparison of baseline, laboratory, echocardiographic, and clinical characteristics**

Variables	IMT <sub>low</sub> Group (n=95) (mean±SD)	IMT <sub>high</sub> Group (n=95) (mean±SD)	P
<b>Baseline characteristics</b>			
Age, years	32.3±10.1	41.8±13.0	<0.001
Gender, male	34 (35.8%)	44 (46.3%)	0.092
BMI, kg/m <sup>2</sup>	26.2±3.4	26.0±3.0	0.716
SBP, mm Hg	117.9±13.5	118.2±11.5	0.812
DBP, mm Hg	72.4±9.2	73.9±9.1	0.282
Heart rate, b/m	82.5±9.3	84.1±8.7	0.217
<b>Laboratory findings</b>			
Glucose, mg/dL	83.0±9.8	83.8±9.5	0.576
Total cholesterol, mg/dL	181.4±37.5	181.9±44.7	0.932
Triglyceride, mg/dL	110.5±56.5	132.6±79.0	0.034
HDL, mg/dL	51.2±13.1	46.5±13.3	0.018
LDL, mg/dL	114.5±33.7	117.6±40.0	0.586
Creatinine, mg/dL	0.71±0.14	0.76±0.19	0.056
Uric acid, mg/dL	4.4±1.0	5.0±1.8	0.010
hs-CRP, mg/dL	0.64±0.13	0.74±0.19	<0.001
Hemoglobin, mg/dL	13.7±2.3	13.5±2.3	0.493
Platelet count	276.3±84.8	249.6±79.4	0.026
MPV, fL	9.5±1.0	10.9±1.2	<0.001
<b>Echocardiography</b>			
EF, %	63.0±3.9	62.4±4.2	0.312
IMT, mm	10.2±1.8	18.4±5.6	<0.001
<b>Previous diagnosis</b>			
ASD, n (%)	58 (61.1%)	54 (56.8%)	0.329
AF, n (%)	9 (9.5%)	13 (13.7%)	0.249
Valvular disease	28 (29.5%)	28 (29.5%)	0.563
AF - atrial fibrillation; ASD - atrial septal defect; BMI - body mass index; DBP - diastolic blood pressure; EF - ejection fraction; HDL-C - high-density lipoprotein cholesterol; hs-CRP - high-sensitivity C reactive protein; IMT - intima-media thickness; LDL-C - low-density lipoprotein cholesterol; MPV - mean platelet volume; SBP - systolic blood pressure; SD - standard deviation			

square ( $\chi^2$ ) test. Analysis of normality was performed with the Kolmogorov-Smirnov test. All variables were distributed normally. Independent samples t-test was used in the analysis of continuous variables. The correlations between thoracic aortic IMT and laboratory, hemodynamic, and echocardiographic parameters were assessed by the Pearson correlation test. All significant ( $p<0.05$ ) parameters in the univariate analysis were selected in the multivariate model. To avoid overfitting and collinearity in assessing the multivariate model, independent variables were tested for intercorrelation. Collinearity between variables was excluded before modeling. Finally, age, uric acid, hs-CRP, and MPV were selected in the multivariate model. A multiple stepwise linear regression analysis was performed to

**Table 2. Bivariate relationships of IMT**

Variables	Pearson correlation coefficient	P
Age, years	0.550	<0.001
Uric acid, mg/dL	0.306	<0.001
Platelet count	-0.192	0.008
Triglyceride	0.153	0.044
MPV	0.665	<0.001
HDL	-0.112	0.140
hs-CRP	0.511	<0.001
HDL-C - high-density lipoprotein cholesterol; hs-CRP - high-sensitivity C reactive protein; IMT - intima-media thickness; MPV - mean platelet volume		

**Table 3. Multivariate relationships of IMT**

Variables	Standardized $\beta$ regression coefficients	P	95% CI Lower-upper
Age, years	0.340	<0.001	0.06-0.16
Uric acid, mg/dL	0.111	0.041	0.00-0.01
Platelet count	-0.049	0.332	-
Triglyceride	0.035	0.529	-
MPV	0.482	<0.001	1.4-2.3
hs-CRP	0.200	<0.001	(-) 0.03-0.03
CI - confidence interval; hs-CRP - high-sensitivity C-reactive protein; MPV - mean platelet volume			

identify the independent associations of thoracic aortic IMT. All significant ( $p<0.05$ ) parameters in the univariate analysis (age, uric acid, hs-CRP, MPV) were selected in the multivariate model. A two-tailed  $p<0.05$  was considered significant.

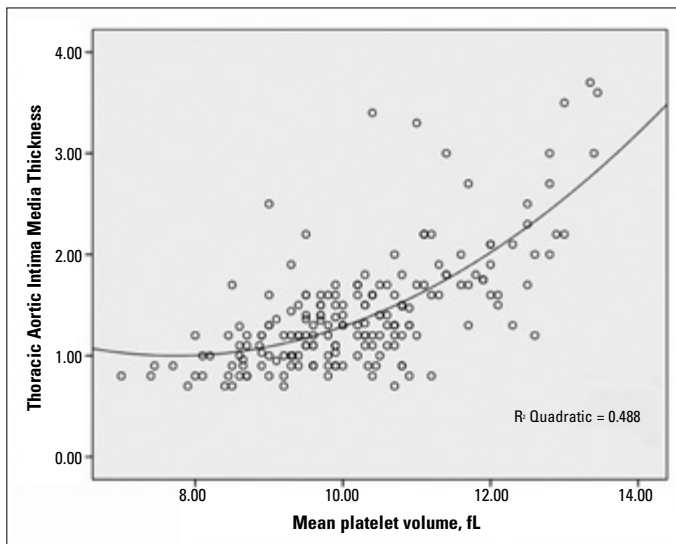
### Reproducibility

Aortic IMT measurements were repeated by the second observer, and inter-observer variability was calculated as the difference in two measurements of the 60 patients by the observer divided by the mean value. The inter-observer variability was 7.4%.

### Results

The baseline, clinical, laboratory, and echocardiographic characteristics of the groups are shown in Table 1. The highest MPV values were observed in the IMT<sub>high</sub> group compared with the IMT<sub>low</sub> group (9.5±1.0 vs. 10.9±1.2 fL,  $p<0.001$ ). Age and triglyceride, hs-CRP, and uric acid levels were significantly higher in the subjects with IMT<sub>high</sub> than in the subjects with IMT<sub>low</sub> ( $p<0.05$  for all). The HDL-C cholesterol levels and platelet count levels were significantly lower in the IMT<sub>high</sub> group than the IMT<sub>low</sub> group ( $p<0.05$  for all).

Bivariate and multivariate relationships of thoracic aortic IMT are demonstrated in Table 2 and Table 3. Thoracic aortic IMT was found to be associated with age ( $r=0.550$ ,  $p<0.001$ ), uric acid ( $r=0.306$ ,  $p<0.001$ ), platelet count ( $r=-0.192$ ,  $p=0.008$ ), triglyceride ( $r=0.153$ ,  $p=0.044$ ), hs-CRP ( $r=0.511$ ,  $p<0.001$ ), and MPV



**Figure 2. Relationship between mean platelet volume and aortic intima-media thickness**

( $r=0.665$ ,  $p<0.001$ ) in the bivariate analysis. The relationships between aortic IMT and MPV are shown in Figure 2.

Multiple linear regression analysis showed that aortic IMT was independently related with age [ $\beta=0.340$ , 95% CI (0.061-0.164),  $p<0.001$ ], uric acid [ $\beta=0.111$ , 95% CI (0.00-0.019),  $p=0.041$ ], hs-CRP [ $\beta=0.200$ , 95% CI (-0.03-0.03),  $p<0.001$ ], and MPV [ $\beta=0.551$ , 95% CI (1.4-2.3),  $p<0.001$ ].

## Discussion

This is the first study that has investigated the relationship between MPV and thoracic aortic IMT in patients without clinical manifestation of CVD. Our results showed that the extent of thoracic aorta IMT is independently associated with MPV, as well as age, hs-CRP, and serum uric acid level.

Atherosclerotic lesions in the aorta detected by TEE are markers of diffuse atherosclerotic disease (12, 13). In a previous study, it was shown that calcification of the thoracic aorta correlated with increasing severity of carotid atherosclerotic burden, as measured by carotid IMT (17). It also has been reported that aortic IMT is better than carotid IMT as an earlier marker of preclinical atherosclerosis (14). In recent years, in light of preventive medicine, several studies on predictors or risk factors of atherosclerosis have been conducted, and numerous factors in this relation have been considered.

In our study, we showed a significant relation between MPV and increased thoracic aortic IMT that strongly suggests an important role of systemic thrombocyte activation in the course of atherosclerosis. Earlier studies demonstrated that platelet reactivity is increased in larger platelets when compared to the smaller ones (6). This effect is also seen when platelet agreeability is referred to platelet volume. A possible explanation might be that large platelets produce more thromboxane A<sub>2</sub> (4). On the other hand, previous studies demonstrated that platelets play a critical role in carotid atherosclerosis, and P-selectin that

is stored in platelet secretory granules is important for the development of atherosclerosis. Also, they directly affected the degree of plaque maturation, including the existence of smooth muscle cells and calcification. Plaque maturation was dependent on endothelial as well as platelet P-selectin as a product of platelet activation (19). According to these findings, it is logical to say that high MPV is related with increased CCA thickness, as platelet agreeability is known to be an important factor in the etiopathogenesis of atherosclerosis. There is evidence that platelet activity, shown as larger MPV, is an important factor of the preclinical development of atherosclerosis. A relationship between MPV and coronary and carotid atherosclerosis has been reported (11, 20-22). On the other hand, the present study showed that MPV is associated with the extent of thoracic aortic IMT, which is a marker of preclinical systemic atherosclerosis. It has been shown that thoracic aortic IMT is an earlier marker of preclinical atherosclerosis than carotid IMT (14).

Controversial results have been reported recently about the relations between atherosclerosis and MPV. It has been demonstrated there is no relationship between MPV, platelet aggregation, carotid IMT, and the extent of coronary artery disease (23). However, a positive correlation between MPV and carotid IMT in obese adolescents was shown recently (24). Also, our study population consisted of patients who had non-atherosclerotic heart disease, and we found a positive correlation between thoracic aorta IMT and MPV.

Recently, De Luca et al. (8) investigated whether MPV was associated with platelet reactivity and the extent of coronary artery disease among diabetic patients. They performed a cohort study including 1016 consecutive diabetic patients undergoing coronary angiography and showed that MPV was not related to platelet reactivity. Different methods, like flow cytometry, optical aggregometry, platelet reactivity tests, and platelet aggregation, can be used to assess platelet activation (25). But, all of these methods have some limitations, such as complex preanalytic factors, reduced specificity, and poor reproducibility. MPV is a marker that does not require any advanced or expensive technology (25). Therefore, we used MPV, a simple hematologic parameter, to assess this relationship. Further studies combining MPV and other platelet functional tests may provide additional data to show the effects of platelets on the pathogenesis of atherosclerosis.

In recent studies, the role of the chronic inflammatory course in the development of atherosclerosis has been demonstrated (26), and hs-CRP, a common marker of inflammation, has been shown to be independently related with cardiovascular diseases in some clinical conditions (27, 28). In the present study, we found an independent association with hs-CRP levels and thoracic aorta IMT. Our results support previous studies that have shown a role of the chronic inflammatory course, reflected by increased hs-CRP levels, in the progress of atherosclerosis (26-28).

It has been reported that uric acid induces intracellular oxidative stress and inflammation (29-31). In several studies, an

inverse relationship between the levels of uric acid and atherosclerosis has been shown (28, 32-34). In a recent study, significant associations between carotid IMT, serum uric acid level, and other major atherosclerotic risk factors have been demonstrated (32). Also, they showed that higher serum uric acid levels are associated with atherogenesis. In another study, Wang et al. (33) reported a significant positive correlation between serum uric acid concentration and subclinical atherosclerosis amongst young to middle-aged adults during a 25-year follow-up. In the present study, we showed an independent relation between thoracic aorta IMT and serum uric acid level, which supports previous reports (28, 32, 33).

Age, male gender, hypertension, hyperlipidemia, and smoking, which were acceptable as coronary artery disease risk factors related with aortic atherosclerosis (35-37). In our study, age, which is one of the coronary risk factors, was independently associated with thoracic IMT. However, the effect of diabetes and hypertension on thoracic atherosclerosis could not be concluded in our study, because patients with hypertension and diabetes were not included the study. In the present study, we showed an association of IMT with age and serum lipid levels, supporting a recent study of Matsuzaki et al. (35), who determined that age seems to become a more important determinant of irrespective of blood pressure and serum cholesterol levels.

### Study limitations

In our study, all participants were chosen among people with several disease states; however, thoracic aorta IMT was not related to the diagnosis of these patients. Another limitation is that coronary artery disease was not excluded by coronary angiography, although it was excluded according to clinical characteristics and patient history, electrocardiography, and treadmill exercise test results.

The MPV does not report a routine part of the complete blood count because of the anticoagulant-induced changes over time. Although the samples were analyzed within 20 minutes after collection in this study, MPV increased up to 30% within 5 minutes of exposure to EDTA and further by 10% to 15% over the next 2 hours (38).

We observed that age and platelet count were statistically different between the two groups. Furthermore, MPV is influenced by platelet count, so this may affect our results.

This is a single-center and relatively small-scale cross-sectional study, and further investigations are needed to confirm our findings.

### Conclusion

Men platelet volume and uric acid levels are independently associated with subclinical thoracic atherosclerosis. Increases in MPV, as well as hs-CRP and uric acid, may be crucial biochemical markers for initial atherosclerosis. Therefore, higher levels of MPV may indicate high risk patients undergoing TEE.

**Conflict of interest:** None declared.

**Peer-review:** Externally peer-reviewed.

**Authorship contributions:** Concept - M.G., Z.E.; Design - M.G., A.B.; Supervision - G.Y.K., M.K., H.U.; Materials - H.U., A.B., D.Y.Ş.; Data collection &/or processing - M.G., M.Ç.; Analysis &/or interpretation - A.O.B., A.B., Z.E., D.Y.Ş.; Literature search - A.B., Z.E., D.Y.Ş.; Writing - G.Y.K., M.G., M.Ç.; Critical review - M.Ç., M.G.

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