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ORIGINAL ARTICLE

Erectile Dysfunction

Mean platelet volume might be an effective indicator of arterial erectile dysfunction

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The aim of our study was to investigate the role of platelet parameters including mean platelet volume (MPV) and platelet count (PC) in the pathogenesis of penile arteriogenic erectile dysfunction (ED) and to evaluate the association between the platelet parameters and arteriogenic ED. There were 244 patients with ED (based on the International Index of Erectile Function [IIEF]-5 ≤21) and 60 healthy controls (IIEF-5 >21) enrolled. All participants were asked to undergo a laboratory examination, and penile vascular function was evaluated using penile color Doppler ultrasonography (pDUS). Among these ED patients, 24 patients with no abnormality on nocturnal penile tumescence (NPT) and 84 with normal vasculature or mixed vascular abnormalities were excluded. The other patients were classified into three groups as follows: control (n = 60), arteriogenic ED (n = 99), and venous leakage (n = 37) groups. MPV and PC were significantly higher in the arteriogenic ED group compared with the venous and control groups (P < 0.05). Receiver operating characteristic curve analysis revealed that the area under the curve for MPV to predict arteriogenic ED was 0.707. MPV ≥9.65 fl was recognized as a cut-off value for potential arteriogenic ED (sensitivity: 47.5%; specificity: 91.7%). A significant inverse correlation was detected between MPV and 10-min peak systolic velocity (PSV) (r = –0.34; P < 0.001) in the arteriogenic ED group. These findings suggest that the MPV might be a powerful indicator to predict and diagnose arteriogenic ED, and MPV may be a marker for ED when using pDUS.

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Keywords: arterial erectile dysfunction; color Doppler ultrasonography; mean platelet volume; peak systolic velocity; predictive indicator

INTRODUCTION

Erectile dysfunction (ED), defined as the recurrent or consistent inability to attain or maintain the penile erection required for sufficient sexual performance for at least 6 months,[1] is one of the most common diseases in males. It usually affects physical and psychosocial health in affected males and may have a significant impact on their and their partner's quality of life. A Meta-Analysis Consortium study reported that ED was present in nearly 17% of all European males in 2004 and that it will affect 322 million by 2025.[2,3] ED is a complicated interaction between the etiology of vascular, neurogenic, hormonal, psychogenic, iatrogenic, and anatomic causes, which plays an important role in the occurrence of ED.[4] Among these factors, vascular factors have received more attention than before because the penis has a special vascular webbing. It is estimated that vascular factors account for about 25%–70% of ED patients. Based on the vascular involvement, there are three types of vasculogenic ED: arterial insufficiency, venous leakage, or a combination of the two.[5]

Vascular lesions play a crucial role in the atherosclerosis formation phase.[6] Recent studies have shown that symptoms of ED appear approximately 2–5 years before the onset of cardiovascular symptoms.[7] Vasculogenic ED was suggested to be an early manifestation of cardiovascular diseases.[8] A previous study speculated that vascular penile endothelial dysfunction contributed to the occurrence of vasculogenic ED.[9] Moreover, substantial research has shown that endothelial function was significantly different between men with ED and controls,[10,11] especially in those with arteriogenic ED. Vascular disease of the penis is common and is caused by many and various factors including age, smoking, drinking, hypertension, and diabetes. These factors can lead to vasculogenic ED, and thereby to penile hemodynamic dysfunction.[12,13]

A change in platelet activity is common in thrombosis and vascular inflammatory reactions.[14,15] In addition, recent studies have evaluated platelet parameters in patients with ED and found that mean platelet volume (MPV) and platelet distribution width (PDW) are potential indicators to predict ED.[5,16]

Although many researchers investigated the relationship between vasculogenic ED and platelet parameters, there has been no differentiation between arteriogenic, venous leakage, and mixed vascular insufficiency. The current study investigated the relationship between arteriogenic ED and platelet parameters, and we analyzed platelet parameters in patients with arteriogenic ED or venous leakage to determine the potential platelet parameters that may predict arteriogenic ED.

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PARTICIPANTS AND METHODS

Eligibility criteria for participants

Patients who were admitted to the Urology Department at the Second Hospital of Shandong University (Jinan, China) for ED from January 2014 to September 2017 were considered for this study. All participants were asked to complete the International Index of Erectile Function-5 (IIEF-5) questionnaire.[17] After completing the questionnaire, only 244 people scored less than or equal to 21, and these people were identified as having ED. Sixty healthy male volunteers from the Center of Health Management (Jinan, China) during the same period who were sexually active, married, and age-matched men with an ED domain score ≥26 based on the IIEF short form comprised the control group. We controlled the participants with age ranging from 20 to 50 years old to avoid the effect of subclinical cardiovascular disease (CVD) on platelet activity as much as possible.

Exclusion criteria were as follows: stroke, depression, diabetes mellitus, metabolic syndrome, tumor, alcoholism, inflammatory conditions, past pelvic surgery or trauma, cardiovascular and/or hematologic (such as leukocytosis and thrombocytopenia) diseases, psychogenic reasons, hormonal disorders (hyperprolactinemia, hypogonadism), neurological disorders (multiple sclerosis and seizure), failure to obtain their hemograms, or the use of medications that may affect the blood cell count.

The study protocol was approved by the Institutional Ethics Committee of the Second Hospital of Shandong University, and all participants provided written informed consent before participating in the study.

Study design

Two hundred and forty-four patients underwent a detailed clinical investigation including medical history and physical examination, laboratory investigation, nocturnal penile tumescence (NPT), penile color Doppler ultrasonography (pDUS),[18] and neurophysiological test (NT) (**Figure 1**). NPT and pDUS were not performed for healthy controls. Each participant underwent blood tests including blood analysis, hormone profile values, fasting blood glucose, and lipids. Laboratory examinations were conducted at the laboratory of the Second Hospital of Shandong University, using a biochemical analyzer (Modular Analytics, Roche, Mannheim, Germany). In the morning after an 8-h fast, blood samples from each participant were collected from the antecubital vein and drawn into an anticoagulant tube containing dipotassium ethylenediaminetetraacetic acid (EDTA). Complete blood count analysis and other measurements were performed immediately after venipuncture to prevent *in vitro* platelet activation within 1 h after collection of blood samples, which may have affected the experimental results.

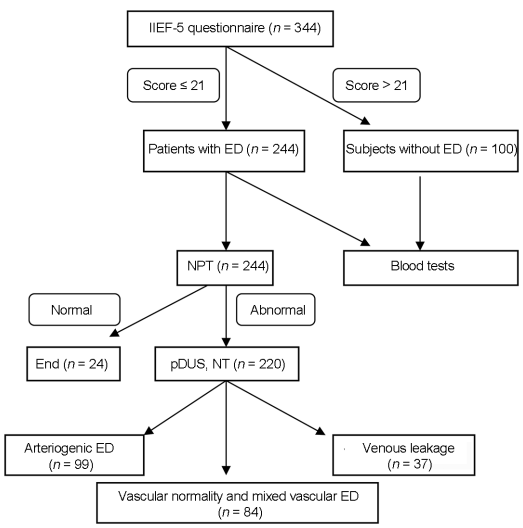

Figure 1: Flow diagram for examination of ED patients. All participants completed IIEF-5 questionnaire and underwent blood tests. Only ED patients underwent NPT, pDUS and NT. ED: erectile dysfunction; IIEF: International Index of Erectile Function; NPT: nocturnal penile tumescence; PDUS: penile color Doppler ultrasonography; NT: neurophysiological test.

NPT tests were performed in all the patients using the Rigiscan® device (Timm Medical Technologies, Inc., Eden Prairie, MN, USA).[19] To ensure the accuracy of the experiment, all patients were asked to avoid insomnia, caffeine, or alcohol intake and to evacuate the bladder before going to sleep. NPT was conducted three times consecutively to avoid the "casus fortuitus", and the data were collected and analyzed the next morning. Normal nocturnal erection was defined as at least three tumescence periods lasting more than 10 min with 70% tip rigidity[20,21] or penile circumference extended to more than 3 cm at the base or 2 cm at the tip.[22]

pDUS (Sonicaid 9900, Medison, Seoul, Korea) was performed in patients with abnormal NPT outcomes by the same well-trained, color Doppler flow imaging (CDFI) certified urologist, in accordance with the criteria proposed by Vignera *et al*.[23] The initial blood flow velocity of the right and left cavernous arteries was recorded, and then 0.1 ml phentolamine (0.5 mg l^{-1}; Novartis, Beijing, China) and 0.7 ml papaverine (30 mg l^{-1}; Henrui Medicine, Lianyungang, China) were given intracavernosally close to the penis base. The peak systolic velocity (PSV) and end diastolic velocity (EDV) at the bottom of bilateral cavernous arteries were measured 5 min and 10 min later. Diagnostic criteria were as follows:[24,25] (1) arterial insufficiency: PSV <25 cm s^{-1} and EDV <5 cm s^{-1}; (2) venous incompetence: PSV >30 cm s^{-1}, and EDV >5 cm s^{-1}, or above with resistance index (RI) persistently <0.6; (3) nonvascular ED: PSV >30 cm s^{-1}, EDVE <5 cm s^{-1}, and RI >0.8; and (4) mixed ED (mixed vascular insufficiency): PSV <25 cm s^{-1}, EDV >5 cm s^{-1}, and RI < 0.6.

Statistical analyses

SPSS statistical software for Windows version 23 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The Kolmogorov–Smirnov test was used to assess whether sample data were normally distributed. All continuous variables were expressed as the mean ± standard deviation (s.d.). One-way analysis of variance (ANOVA) was used for multiple comparisons between groups if the data were consistent with ecological distribution and homogeneity; otherwise, the Kruskal–Wallis *H* test was used. The relationship between platelet parameters and PSV or EDV was analyzed using the Spearman correlation analysis. Receiver operating characteristic (ROC) analysis was performed to evaluate the sensitivity of MPV in arteriogenic ED. $P < 0.05$ was considered statistically significant.

RESULTS

A total of 244 consecutive ED patients and 60 healthy volunteers (control group) were enrolled in the present study. Among these ED patients, 24 patients who had no obvious abnormality in the NPT examination and 84 with pDUS results demonstrating vascular normality or mixed vascular abnormalities were excluded. There were 99 patients diagnosed with arteriogenic ED and 37 patients had venous leakage. The demographic and clinical characteristics are shown in **Table 1**. Hormonal parameters including testosterone, estradiol, progesterone, prolactin hormone (PRL), luteinizing hormone (LH),

follicle-stimulating hormone (FSH), blood lipids, blood glucose, and blood pressure levels were comparable in all participants. According to **Table 1**, all parameters in these three groups showed no significant difference except for high-density lipoprotein (HDL). The mean HDL was 1.11 ± 0.33 mmol l^{-1}, 1.10 ± 0.35 mmol l^{-1}, and 1.44 ± 0.22 mmol l^{-1} for arteriogenic ED, venous leakage, and control groups, respectively ($P < 0.05$).

Table 2 shows the platelet parameters in ED patients and controls. Total platelet counts were higher in the arteriogenic ED group compared with the venous leakage and control groups ([240.50 ± 42.28] × 10^9 l^{-1} *vs* [231.62 ± 40.67] × 10^9 l^{-1} and [223.80 ± 32.48] × 10^9 l^{-1}, respectively, $P < 0.01$). As demonstrated by the Scheffe post hoc multiple comparison test, platelet count (PC) in the arteriogenic ED group was higher than that of the control group ($P < 0.05$), but there was no significant difference in the PC between the arteriogenic ED and venous leakage groups ($P = 0.50$) or between the venous leakage and control groups ($P = 0.63$). MPV was 9.59 ± 0.98 fl compared with 8.90 ± 0.55 fl and 8.91 ± 0.57 fl in penile arteriogenic ED, venous leakage, and control groups, respectively ($P < 0.01$). Multiple comparison of the MPV was performed using the Games–Howell test and MPV was significantly higher in the arteriogenic ED group compared with the ED ($P < 0.01$) and control groups ($P < 0.01$). No statistically significant difference was observed between the venous leakage and control groups ($P = 1.0$).

The correlation between penile vascular velocity and platelet parameters in arteriogenic ED groups was demonstrated in **Figure 2**. MPV had a negative effect on 10-min PSV ($r = -0.34$, $P < 0.001$), but there was no significant correlation with 5-min PSV, 5-min EDV, or 10-min EDV ($r = -0.12$, $P = 0.22$; $r = 0.005$, $P = 0.96$; $r = -0.038$, $P = 0.7$, respectively).

Table 1: Laboratory evaluations among the 3 groups

Characteristic	*Control group (n=60)*	*Arteriogenic ED group (n=99)*	*Venous leakage group (n=37)*	*P*
Age[a] (year)	29.51±6.13	29.41±8.06	28.78±7.17	0.28
Estradiol[a] (pg ml^{-1})	61.33±17.76	62.59±19.13	61.91±17.72	0.91
FSH[a] (mIU ml^{-1})	4.64±1.99	4.61±1.72	4.03±1.83	0.21
LH[b] (mIU ml^{-1})	3.99±1.22	4.06±1.63	4.64±1.99	0.12
PRL[b] (ng ml^{-1})	15.85±4.89	15.41±4.43	14.68±3.58	0.39
Progesterone[b] (ng ml^{-1})	1.01±0.65	0.93±0.70	0.79±0.27	0.41
Testosterone[b] (ng ml^{-1})	4.15±1.28	4.25±1.37	4.11±1.08	0.82
TG[b] (mmol l^{-1})	1.17±0.90	1.08±0.50	1.23±0.56	0.23
TC[b] (mmol l^{-1})	4.56±0.95	4.39±1.05	4.20±0.87	0.82
HDL[b] (mmol l^{-1})	1.44±0.22	1.11±0.33	1.10±0.35	<0.05
LDL[b] (mmol l^{-1})	2.70±0.78	2.73±1.73	2.27±0.68	0.12
FPG[b] (mmol l^{-1})	4.75±0.33	4.72±0.55	4.67±0.51	0.77

[a]Value: pertain to statistically significant difference by one-way ANOVA; [b]Value: pertain to statistically significant difference by Kruskal–Wallis *H* test. ED: erectile dysfunction; FSH: follicle-stimulating hormone; LH: luteinizing hormone; PRL: prolactin hormone; TG: triglycerides; TC: total cholesterol; LDL: low-density lipoprotein; HDL: high-density lipoprotein; FPG: fasting plasma glucose; ANOVA: analysis of variance

Table 2: Platelet indices among the 3 groups

Indices	*Control group*	*Arteriogenic ED group*	*Venous leakage group*	*P*
PC[a] (10^9 l^{-1})	223.80±32.48	240.50±42.28	231.62±40.67	<0.01
MPV[b] (fl)	8.91±0.57	9.59±0.98	8.90±0.55	<0.01
PDW[b] (%)	16.04±0.25	16.04±0.37	15.93±0.42	0.28

[a]Value: compared with one-way ANOVA; [b]Value: denoted statistically significant difference by Kruskal–Wallis *H* test. ED: erectile dysfunction; PC: platelet count; MPV: mean platelet volume; PDW: platelet distribution width; ANOVA: analysis of variance

ROC regression analysis identified MPV ≥9.65 fl as a cut-off value for potential arteriogenic ED (area under the curve [AUC]: 0.707, 95% CI: 0.628–0.786) with a sensitivity of 47.5% and specificity of 91.7% (**Figure 3**). There was no statistically significant diagnostic value for PC (AUC = 0.414), even though a statistical difference was observed ($P < 0.01$).

DISCUSSION

ED, one of the most prevalent sexual diseases affecting physical and psychosocial health, is now considered to be a major health problem for the male population.[13,26] Organic disease plays a dominant role in the pathogenesis of ED, in which vascular factors are the underlying cause in most ED patients.[27] The evidence is accumulating that arteriogenic ED, as a harbinger of CVD, is an independent marker of CVD risk and may reveal the presence of subclinical vascular disease in a man who otherwise has no expression of coronary artery disease.[28]

The vascular endothelium is a monolayer of cells arranged on the luminal surface of the blood vessel. It is a direct interface between the components of circulating blood and local tissue and it regulates local blood vessel function in a paracrine and endocrine manner,[29] affecting vascular tone, cell adhesiveness, coagulation, inflammation, and permeability.[30] Substances synthesized and released by the endothelium play important roles in platelet aggregation.[31] We suggest that endothelial damage affects vascular function and the damage to penile vasculature endothelial cells may contribute to the occurrence in arteriogenic ED.

Atherosclerotic occlusion in the cavernous artery is responsible for the occurrence of vascular ED, and platelet function had been found to be associated with the atherothrombotic process and involved in the inflammatory vascular response and in arterial and venous thrombosis.[15] In addition, platelets have an essential role in the pathogenesis of vascular ED, contributing to thrombus formation or positioning after plaque rupture,[32] and the activation of platelets based on atherosclerosis in the penile artery have been altered in the early period. During the last 10 years, many new facts about the relationship between ED and platelet activity have been determined. However, studies have focused on vasculogenic ED without distinguishing between arterial ED, venous leakage, or a combination of both.

The effect of increased platelet activity on vascular ED has been noted in several studies. PC, MPV, and PDW are key platelet activity parameters that represent platelet production speed and hemostasis,[33] of which MPV is representative of platelet function, state, and platelet size, and indirectly reflects platelet activity. The relationship between vasculogenic ED and platelet parameters is becoming more important.

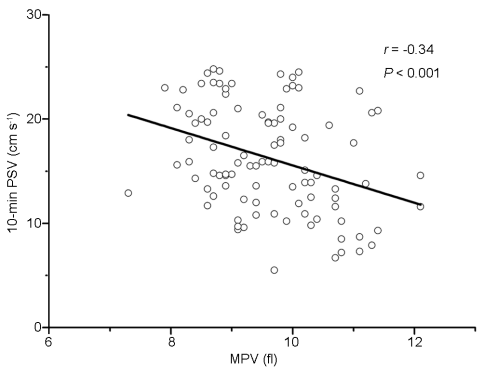

Figure 2: Spearman correlation coefficient (*r*) and linear regression line between MPV and 10-min PSV levels. MPV: mean platelet volume; PSV: peak systolic velocity.

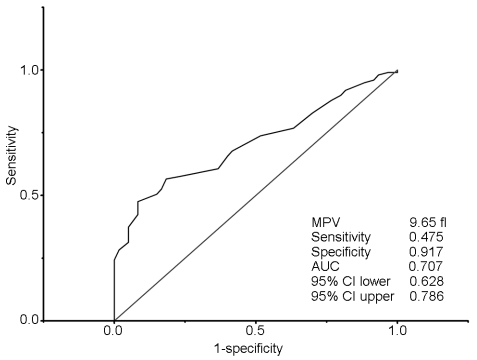

Figure 3: Receiver operating characteristic curve of MPV for predicting arteriogenic erectile dysfunction. MPV: mean platelet volume; AUC: area under the curve; CI: confidence interval.

Large platelets are metabolically and biologically more active than small platelets, wherein an increased platelet volume has an enhanced capability to aggregate in response to adenosine diphosphate (ADP) and produce more thromboxane A_2.[34]

In the current study, increased MPV can be incorporated into a set of emerging risk factors involved in ED pathogenesis. We aimed to investigate the association between the platelet volume and patients diagnosed with vasculogenic ED. Aldemir *et al*.[35] reported that MPV increased significantly in patients with vasculogenic ED, while the PC was not different between the two groups. Conversely, our findings illustrated that PC and MPV in arteriogenic ED patients were significantly higher than those with venous leakage and controls. However, there was no statistically significant difference between the venous and control groups. Thus, platelet activation in arteriogenic ED may be related to alterations in the coagulation process between the platelets and arterial endothelial cells. Guo *et al*.[36] suggested that platelet activation compensates for platelets consumed continuously during arteriogenic ED development, resulting in an increase in the PC to compensate for the consumption of platelets. Similar to our study, Otunctemur *et al*.[37] compared vasculogenic ED patients and a healthy control group and, in addition to MPV and PC, eosinophil count (EC) was also included in the examination. Although MPV values and the PC were significantly higher in the vasculogenic ED group, there was no difference in EC between the two groups. Our results are in partial agreement with the research performed by Otunctemur *et al*.[37] and Ren *et al*.[38] However, the MPV level was detected to be increased in all studies including the present study, especially where we distinguished arteriogenic ED from vasculogenic ED. The area under the ROC curve for the MPV was 0.707, but there was no statistically diagnostic value for the PC (AUC = 0.414). Based on this information and the results of our study, platelets may play an essential role in the pathogenesis of arterial ED. MPV may be more clinically useful for assessing and managing arteriogenic ED with subclinical CVD. Therefore, vascular endothelial cell damage accompanied by platelet activation may be the main mechanism of arteriogenic ED.

pDUS is an important measure that is used to determine vascular ED. PSV is an index of penile hemodynamics, and it plays an important role in assessing the vascular status of patients with ED.[39] Our results indicate that MPV was negatively correlated with 10-min PSV. Moreover, PDW was negatively correlated with 10-min PSV, but there was no statistically significant difference among the three groups. Therefore, MPV, a measure of the platelet size that is available in the blood, is increasingly recognized as a more important marker of platelet activity compared with PDW.[40] The cut-off value of MPV was 9.65 fl with a sensitivity of 47.5% and a specificity of 91.7%. Although the diagnostic sensitivity of arterial ED with MPV did not meet the requirements, the specificity is acceptable. The results are significant because only patients with arterial dysfunction based on pDUS testing have significant differences. These results suggest that MPV is a prediction marker for arterial ED that can be used to partially identify ED using pDUS. Platelet parameter testing, especially MPV, is a marker of platelet size that is easily measured using automated blood counters and they are routinely available at a relatively low cost. In most patients, platelet parameter testing can also help to reduce trauma caused by intracavernous drug injections.

This study had some limitations. The results of this study should be interpreted with caution. First, the relatively small sample size may restrict the generalizability of the results. Second, the platelet parameters for each lab test result might show slightly different values. Third, patients with arterial ED have different susceptibility to drugs injected into the penis. Fourth, we did not perform cavernosometry or cavernosography and repeated hemodynamic assessments to ensure the accuracy of the diagnosis. To the best of our knowledge, additional studies about the severity of arterial ED are required.

CONCLUSION

MPV values, which demonstrate thrombocyte activity, were found to be significantly higher in ED patients compared with healthy subjects, and MPV in arteriogenic ED patients was larger compared with nonarteriogenic ED patients. Thus, MPV could potentially be monitored as a useful marker to predict and diagnose arteriogenic ED. However, these data were obtained in a limited number of ED patients, and our results should be confirmed by additional studies. Additional large-scale studies are required to clarify whether high MPV values in ED patients are associated with the severity of arteriogenic ED.

AUTHOR CONTRIBUTIONS

MZY and GMY participated in the design, coordination of the study, and directed others to conduct the experimental investigation. XSW conceived the idea and drafted the manuscript. XSW and ZYX revised the manuscript. LQG and YG performed the statistical analysis. ZHX, ML, ZM, and JYZ collected the data. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

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