A Decreased Mean Platelet Volume Is Associated with Stable and Exacerbated Asthma

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Key Words

Asthma · Mean platelet volume · Systemic inflammation · Platelet activation · C-reactive protein

Abstract

Background: Systemic inflammation is related to disease progression in asthma. Activated platelets play a critical role in atherogenesis, inflammation, and atherothrombosis. The mean platelet volume (MPV) is an early marker of platelet activation. **Objectives:** The aim of this study is to clarify the relevance of MPV levels in patients with stable and exacerbated asthma. **Methods:** We investigated the peripheral blood cell count parameters, C-reactive protein (CRP), lung function parameters, and arterial blood gas in patients with asthma and control subjects. Eighty-five stable asthma patients and 85 asthmatics with exacerbations were investigated. Eighty-five controls matched for age, gender, body mass index (BMI), and smoking status were recruited. **Results:** Patients with exacerbated asthma had lower MPV and higher CRP levels and white blood cell (WBC) counts compared to patients with stable asthma and control subjects. Furthermore, the MPV was reduced in patients with stable asthma compared to control subjects. Negative correlations between MPV and CRP were present in stable and exacerbated asthma. Although there was no relationship between MPV

and WBC count in stable asthma, there was an inverse relationship between MPV and WBC count in exacerbated asthma. **Conclusions:** These findings show that patients with stable asthma had a lower MPV compared to controls and the MPV levels in asthmatic patients with exacerbations were lower compared to those in patients with stable asthma. Further investigations regarding the role of MPV in asthma may be beneficial in the search for therapeutic targets.

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Introduction

Asthma is an enormous public health problem resulting in a considerable burden and substantial costs. It is a chronic inflammatory condition characterized by the activation of large numbers of immune and inflammatory cells within the airways [1]. Recent studies have demonstrated that systemic inflammation is related to disease progression in asthma [2]. Some proinflammatory cytokines such as interleukin (IL)-6, tumor necrosis factor (TNF)- α , and C-reactive protein (CRP) are increased in patients with asthma [3, 4].

Mounting evidence indicates a pivotal role for platelets in various inflammatory diseases, including atherosclerosis, inflammation, atherothrombosis, and asthma.

Activated platelets play a key role in bronchial hyperresponsiveness, bronchoconstriction, airway inflammation, and airway remodeling. Plasma β -thromboglobulin and platelet factor-4, common markers of platelet activation *in vivo*, have been reported to be elevated in symptomatic asthmatic patients [5–8]. In addition, platelets express more P-selectin on their surface in asthmatic patients.

The mean platelet volume (MPV), a common measure of platelet size, could be used as an indicator of activated platelets [9]. Furthermore, the MPV is an inflammatory index in different diseases [10–15]. For example, some studies have found that MPV levels are elevated in cardiovascular disease, peripheral artery disease, and cerebrovascular disease [10, 11, 14]. In contrast, others have reported that MPV levels are reduced in rheumatoid arthritis and ulcerative colitis [12, 13, 15]. A recent study demonstrated that MPV levels could be used to predict the onset of venous thromboembolism and arterial thrombosis [16]. In addition, patients with asthma have an increased risk of hypertension, pulmonary embolism, coronary heart disease, heart failure, and all-cause mortality [17–20]. Although one previous study showed no changes in MPV in asthmatic children [21], the MPV levels in asthmatic adults have not been clearly examined. Clarification of the roles of MPV at different stages of asthma would have significant clinical implications for the therapeutic targets in the treatment of asthma.

The aim of the present study is to evaluate MPV levels in stable and exacerbated asthma. Obesity and cigarette smoking exert positive effects on the MPV, and weight loss and smoking cessation decrease MPV levels [22–25]. Therefore, control cases were matched for age, gender, body mass index (BMI), and smoking status in our study.

Methods and Materials

Patient Population

This study included 255 adults (aged >18 years, 114 males and 141 females) from June 2011 to June 2012. There were 170 patients with asthma and 85 controls without asthma. The exacerbated asthma patients (aged 40.6 ± 4.0 years; 42 males and 43 females) were consecutively enrolled in the Department of Respiratory Medicine of The First Affiliated Hospital. The stable-asthma patients (aged 39.4 ± 3.9 years; 35 males and 50 females) and controls (aged 40.5 ± 4.4 years; 37 males and 48 females) were recruited from the International Physical Examination and Healthy Center of The Second Affiliated Hospital. Control cases were matched for age, gender, BMI, and smoking status. All participants provided written informed consent. The study protocol was approved by the Ethics Committee of The First and Second Affiliated Hospitals of Harbin Medical University, PR China.

Clinical Examination

All of the subjects underwent a physical examination. Body weight was measured in light clothing, without shoes, to the nearest 0.5 kg. Height was measured to the nearest 0.5 cm. The BMI was calculated as weight (kg) divided by height (m^2).

Biochemical Measurements and Pulmonary Function Tests

Clinical data including smoking status, medical history, and medication use were recorded for each subject. Whole-blood samples were drawn in ethylenediaminetetraacetic acid (EDTA)-containing tubes after an 8-hour overnight fast and all samples were processed within 30 min of blood collection. Platelet counts, MPV, and platelet distribution widths were measured using an autoanalyzer (Sysmex XE-2100; Kobe, Japan). High-sensitivity CRP was assayed via the nephelometric method (Dade Behring, Marburg, Germany). Arterial blood samples were examined using a blood gas analyzer (GEM premier 3000; USA) while the subjects were breathed room air for at least 30 min. The forced expiratory volume in 1 s (FEV_1) and the forced vital capacity (FVC) were measured with a spirometer (Jaeger, Wurzburg, Germany) according to American Thoracic Society criteria. The spirometric measurements were analyzed 3 times and the best result was used in our study. The inter- and intra-assay coefficients of variation of all these assays were below 5%. Quality controls in our laboratory documented a good reproducibility of MPV measurements, with intra-assay and inter-assay coefficients of variation of 5%.

Diagnosis and Exclusion Criteria

We defined acute asthma exacerbation as the occurrence of any one of the following events: asthma-related emergency visits, asthma-related hospitalization, or at least 3 days of use of systematic corticosteroids [26]. Stable asthma was defined as no exacerbation in the past 8 weeks. Spirometry was performed before and after the inhalation of short-acting bronchodilators. The asthma diagnosis was confirmed by a positive finding of reversibility with a bronchodilator. A postbronchodilator spirometry was performed 10–15 min after the inhalation of 400 μ g albuterol. An increase in FEV_1 both >200 ml and 12% above the prebronchodilator FEV_1 was considered clinically important [27]. Chronic obstructive pulmonary disease (COPD) was diagnosed according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria. Differential diagnoses of asthma and COPD were based on a combination of the history, physical examination, and spirometry. Spirometry measures indicated that a ratio of FEV_1 to FVC <70% or less than the lower limit of normal improved to values within the normal range in response to bronchodilator use in patients with COPD.

Exclusion criteria included: patients with hematological disorders, autoimmune diseases, cancer, chronic lung diseases other than asthma, valvular diseases, coronary artery disease, systemic inflammatory diseases, acute respiratory failure, heart failure, hepatic failure, renal failure, and medical treatment with anticoagulant, statins, angiotensin-converting enzyme inhibitors, acetylic salicylic acid, clopidogrel, and systemic glucocorticoids during the previous 8 weeks.

Statistical Analysis

Data were expressed as means $\pm$ SD or medians (IQR) for continuous variables or percentages for categorical variables. Group comparisons were made using the ANOVA test for normally distributed data, the Kruskal-Wallis test for nonparametric data, and the χ^2 test for categorical data. Post hoc analyses using a two-tailed Tukey

Table 1. Clinical and laboratory characteristics of asthmatic patients and control subjects

Variables	Exacerbated asthma	Stable asthma	Control	p value
Patients, n	85	85	85	
Age, years	40.6±4.0	39.4±3.9	40.5±4.4	0.109
Male gender, %	49	41	44	0.539
BMI, kg/m ²	24.9±3.0	25.5±3.2	25.2±2.3	0.436
Smoking, pack-years	18.4±13.5	17.1±14.4	16.2±12.0	0.556
Smokers, n				
Current smokers	29	20	28	0.257
Ex-smokers	37	36	30	0.496
Nonsmokers	19	29	27	0.205
Inhaled corticosteroids, %	61	40	0	0.006 ^d
Long-acting β -agonists, %	49	42	0	0.356 ^d
Leukotriene antagonists, %	9	14	0	0.341 ^d
FEV ₁ , % predicted	63.6±11.3 ^a	68.6±16.6 ^b	94.4±6.8 ^c	<0.001
FEV ₁ /FVC, %	56.8±10.9 ^a	63.7±7.2 ^b	83.9±7.5 ^c	<0.001
FVC, % predicted	72.0±7.1 ^a	80.9±7.1 ^b	98.5±7.3 ^c	<0.001
PaO ₂ , mm Hg	67.4±8.6 ^a	80.3±7.8 ^b	87.5±9.3 ^c	<0.001
PaCO ₂ , mm Hg	31.6±5.9	33.7±8.3 ^b	39.1±4.4 ^c	<0.001
CRP, mg/l	11.8 (8.7–17.8) ^a	7.7 (4.8–10.7) ^b	2.5 (1.9–3.4) ^c	<0.001
WBC, ×10 ⁹ /l	12.0±2.2 ^a	8.3±1.2 ^b	6.6±1.3 ^c	<0.001
Platelets, ×10 ⁹ /l	298.5±82.6	287.6±75.2	273.3±71.7	0.101
MPV, fl	9.8±0.8 ^a	10.3±1.1 ^b	10.7±1.1 ^c	<0.001
PDW, %	12.1±0.76	12.2±1.06	12.4±1.14 ^c	0.039
Hemoglobin, g/dl	129.9±13.3	134.5±10.6	132.7±21.2	0.147

Data are presented as means ± SD or medians (IQR) or percentages. p values were calculated using a one-way ANOVA test or the Kruskal-Wallis H test or the χ^2 test.

^a Significant difference ($p < 0.05$) in the comparison of exacerbated and stable asthma using a post hoc Tukey test or a Mann-Whitney U test.

^b Significant difference ($p < 0.05$) in the comparison of stable asthma and control subjects using a post hoc Tukey test or a Mann-Whitney U test.

^c Significant difference ($p < 0.05$) in comparison of exacerbated asthma and control subjects using a post hoc Tukey test or a Mann-Whitney U test.

^d p value was obtained via a comparison of exacerbated and stable asthma using a χ^2 test.

HSD test were conducted to compare differences in normally distributed data between the groups. The Mann-Whitney U test was used to compare differences in nonparametric data between the groups. Correlations between MPV and clinical parameters were tested by partial correlation with age, BMI, and smoking as continuous variables and gender as a dichotomous variable. CRP was skewed and was normalized by logarithmic transformation. Differences and correlations were considered significant at $p < 0.05$, and all reported p values were two-tailed. Statistical analyses were conducted using SPSS version 17.0 software (SPSS Inc., Chicago, Ill., USA).

Results

The clinical characteristics of subjects with asthma and control subjects are reported in table 1. The groups were well matched with respect to age, gender, BMI and smoking status. Medication with inhaled corticosteroids was

more prevalent in the asthma group. However, there was no difference in terms of medication with long-acting β -agonists and leukotriene antagonists between the exacerbated-asthma group and the stable-asthma group. Significant differences in pulmonary function parameters (FEV₁, FVC, and FEV₁/FVC) were observed between the groups. The levels of MPV and platelet distribution widths tended to decline and the levels of WBC and CRP tended to increase as the pathogenic condition aggravated. There was no difference in hemoglobin and platelet counts between the patients and the matched controls.

The MPV levels in the exacerbated-asthma, stable-asthma, and control groups are shown in figure 1. The MPV levels were reduced both in the exacerbated-asthma group and in the stable-asthma group compared to controls (exacerbated asthma vs. controls, $p < 0.001$; stable asthma vs. controls, $p = 0.003$, post hoc Tukey test).

Fig. 1. Boxplot showing the MPV levels in the exacerbated-asthma, stable-asthma, and control groups. The top, bottom, and middle lines in each box correspond to the 75th (top quartile), 25th (bottom quartile), and 50th percentiles (median), respectively.

Table 2. Partial correlation of MPV with laboratory parameters after adjustment for age, gender, BMI, and smoking status

Variables	MPV (fL)	
	r	p value
Exacerbated asthma		
CRP (mg/l)	-0.428	<0.001
WBC ($\times 10^9/l$)	-0.265	0.017
Stable asthma		
CRP (mg/l)	0.300	0.007
WBC ($\times 10^9/l$)	0.154	0.171
Controls		
CRP (mg/l)	0.072	0.555
WBC ($\times 10^9/l$)	0.108	0.375

CRP was log-transformed for analysis.

Moreover, the MPV levels of patients with stable asthma were higher compared to those of asthmatic patients with an exacerbation ($p = 0.008$, post hoc Tukey test). The MPV values in the exacerbated-asthma, stable-asthma, and control groups were 9.8 ± 0.8 , 10.3 ± 1.1 , and 10.7 ± 1.1 fL, respectively.

CRP levels were increased both in exacerbated-asthma and in stable-asthma patients compared to controls ($p < 0.001$ for both). Furthermore, the CRP levels of patients with stable asthma were higher compared to those of asthmatic patients in exacerbation ($p < 0.001$, post hoc Tukey test).

The partial correlation coefficients of MPV with laboratory parameters after adjusting for age, gender, BMI, and smoking status are presented in table 2. The coefficient for MPV and logCRP was -0.300 ($p = 0.007$) in stable asthma. The correlation was similar in exacerbated asthma ($p < 0.001$) (fig. 2). Although there was no correlation between WBC count and MPV in patients with stable asthma, WBC count was negatively correlated with MPV in patients with exacerbated asthma ($r = -0.265$, $p = 0.017$).

The Pearson correlation coefficients of MPV and CRP with lung function parameters are presented in table 3. There was no difference in CRP and lung function parameters. There was a correlation between MPV and FVC in exacerbated asthma ($r = -0.216$, $p = 0.047$). However, the correlation between MPV and FVC in exacerbated asthma was not significantly different after adjusting age, gender, BMI, and smoking status using a partial correlation test ($r = -0.184$, $p = 0.098$). In addition, the levels of MPV in stable asthma and in control subjects were not related to lung function parameters.

Discussion

The main findings of our study are as follows: patients with stable asthma had lower MPV levels compared to healthy controls. The MPV levels in asthmatic patients with an exacerbation were lower compared to those in patients with stable asthma. Moreover, a reduced MPV was negatively related to the WBC count and CRP levels in exacerbated asthma.

The roles of platelets in asthma have been well documented in recent years [28]. Platelets are involved in bronchial hyperresponsiveness, bronchoconstriction, airway inflammation, and airway remodeling [29–31]. The processes of leukocyte infiltration and airway wall remodeling fail to occur without the participation of platelets in a murine model [32]. Furthermore, increased circulating platelet-leukocyte aggregates have been detected in allergic asthmatic patients after an antigen challenge [33]. Systemic inflammation is associated with neutrophilic airway inflammation in asthma [2]. The intensity of the systemic inflammation rises during exacerbations of asthma. Increased proinflammatory cytokines such as CRP, TNF- α , and IL-6 are elevated during asthma exacerbations [3, 4]. Furthermore, IL-6 influences megakaryocyte ploidy and platelet volumes [34]. Platelets may act as chaperones, stimulating chemotaxis and the extravasation process of leukocytes from the pulmonary microcirculation into the broncho-pulmonary airways [1]. Moreover, platelet ag-

Fig. 2. Partial correlation coefficients of MPV and logCRP after adjusting for age, gender, BMI, and smoking status. MPV is negatively associated with logCRP. **a** Partial correlation coefficient of MPV and logCRP in stable asthma. **b** Partial correlation coefficient of MPV and logCRP in exacerbated asthma.

Table 3. Correlation of MPV and CRP with lung function

Variables	MPV (fl)		CRP (mg/l)	
	r	p value	r	p value
Exacerbated asthma				
FEV ₁ (% predicted)	0.089	0.418	-0.118	0.282
FVC (% predicted)	-0.216	0.047	0.110	0.317
FEV ₁ /FVC (%)	-0.088	0.421	-0.047	0.668
Stable asthma				
FEV ₁ (% predicted)	-0.097	0.378	-0.010	0.926
FVC (% predicted)	0.033	0.764	-0.026	0.815
FEV ₁ /FVC (%)	-0.096	0.381	-0.157	0.152
Controls				
FEV ₁ (% predicted)	-0.014	0.902	-0.044	0.711
FVC (% predicted)	0.047	0.672	-0.043	0.716
FEV ₁ /FVC (%)	-0.173	0.112	0.049	0.676

CRP was log-transformed for analysis.

gregation is accelerated by hypercapnia and/or hypoxemia [35]. Platelet-activating factor and platelet-derived growth factor are key mediators for hypoxia-induced cell activation and cytokine release in the human lung [36]. A previous report demonstrated that platelet-derived systemic brain-derived neurotrophic factor, a key mediator of neuronal plasticity, is correlated with disease severity in asthma [37]. Elevated MPV levels are usually associated with an increased risk of cardiovascular disease [38]. Re-

cent studies have indicated that low levels of MPV are due to the consumption of activated or large platelets under high-grade inflammatory conditions and this is reversed during the course of anti-inflammatory therapy [39]. In allergic tissue inflammation, platelets migrate extravascularly to lung tissue either by themselves or via P-selectin associated with the eosinophil surface [7, 40]. Our results showed that a reduced MPV is negatively correlated to CRP only in acute exacerbations and not in the stable phase. These findings are consistent with the idea that decreased MPV may be due to the enhanced systemic inflammation in exacerbated asthma.

Systemic inflammation may be the main mechanism for the development and progression of atherosclerosis in asthma. Patients with asthma have increased risks of hypertension, pulmonary embolism, coronary heart disease, heart failure, and all-cause mortality [17–20]. Multifactorial complex interactions between platelets, endothelial cells, and leukocytes further stimulate the production of proinflammatory cytokines and accelerate the progression of atherosclerosis [41]. Therefore, evaluating the cardiovascular disease risk in asthma patients by employing reliable disease markers is of great clinical significance.

Previous studies have reported that soluble P-selectin and platelet-activating factor are involved in asthma [41]. While platelet surface P-selectin obviously reflects platelet activation [7] and eosinophil-bound P-selectin in asthma also appears to be derived from activated platelets

[42], soluble plasma P-selectin seems to be at least partly derived from activated endothelial cells or a perturbed vasculature in asthma [43]. Soluble P-selectin mediates interactions among platelets, leukocytes, and endothelial cells. P-selectin could activate eosinophil β_1 integrins both in vitro and in vivo, providing a mechanism for how platelet activation results in the extravasation recruitment of eosinophils [42]. Platelet-activating factor is able to aggregate and activate platelets and exerts extensive proinflammatory effects in asthma [44].

Our study indirectly confirmed these results using a simple, inexpensive marker of platelet activation in adult asthma. Moreover, our study revealed that a reduced MPV is negatively correlated with CRP in acute exacerbation. Consistent with this notion, there is considerable evidence suggesting a role for activated platelets as inflammatory cells [45]. Neutrophilic airway inflammation may contribute to corticosteroid resistance in asthma [46]. In addition, recent studies have showed that platelet depletion resulted in a significant inhibition of allergen-induced airway hyperresponsiveness, and it was found to be more effective in suppressing airway remodeling processes than the administration of a glucocorticosteroid [47]. Previous studies showed that there were no changes in MPV levels and no negative associations between MPV and CRP in asthmatic children [21], but a genome-wide association study revealed that there are different mechanisms in childhood asthma and adult asthma [48–51]. Further investigations on the role of activated platelets in asthma may be beneficial in the search for therapeutic targets.

Comorbidities are important factors that influence changes in MPV [52]. Some studies have demonstrated that MPV is associated with smoking, obesity, diabetes, coronary artery disease, peripheral arterial disease, and heart failure [12]. Therefore, we selected the matched patients and ruled out the influence of comorbidities in our

study. However, activated platelets play a critical role in the development of inflammation in asthma. Antiasthmatic medication keeps asthma under clinical control mainly through anti-inflammatory properties and maybe affect MPV values. Further studies are warranted to determine the effects of antiasthmatic drugs on MPV.

Some limitations of our study are worth noting. Firstly, a number of chronic allergic conditions (e.g. chronic urticaria and nasal polyposis) can influence changes in MPV [53, 54]. Future studies are needed to address this issue. Secondly, inaccurate measurement of platelet indices can result in misinterpretation of prothrombotic changes [55]. An artefactual increase in MPV may be due to the use of EDTA. Platelet swelling caused by EDTA in test tubes can be minimized by the rapid processing of samples [39]. Furthermore, a standardized method needs to be set up to accurately measure platelet parameters [56]. Thirdly, this study lacks information about airway inflammation. Phenotyping of asthma allows the identification of responders to targeted therapy. Finally, there is no information about genetic contributions to platelet activation. Gene polymorphisms exert a cumulative effect on platelet activation and increase the risk of negative outcomes in thrombotic disorders [57].

In conclusion, our study shows that asthmatic patients has a lower MPV compared to healthy controls, and the MPV levels in asthmatic patients with exacerbations were lower compared to those in patients with stable asthma. Further investigations on the role of MPV in asthma may be beneficial in the search for therapeutic targets.

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