Mean platelet volume as an inflammatory marker in acute exacerbation of chronic obstructive pulmonary disease

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Background Mean platelet volume (MPV) is affected by inflammation in many conditions, such as in inflammatory bowel diseases, rheumatoid arthritis, and ankylosing spondylitis. Conflicting reports exist about its value in stable and exacerbating chronic obstructive pulmonary disease (COPD).

Objective The aim of the present study was to find out whether there was a significant change in the MPV during acute exacerbation of COPD compared with smokers and healthy controls.

Patients and methods The study was carried out on 135 adult patients of both sexes (77 men and 58 women), who presented to Alexandria Main University Hospital. Patients were categorized into three groups of 45 patients each; patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) made up group I, healthy smokers without COPD made up group II, and healthy controls made up group III.

Results MPV values were 8.34 ± 0.95 and 9.28 ± 0.67 fl in patients with acute exacerbation of COPD and in smokers, respectively. MPV values in the control group were 9.12 ± 0.60 fl. MPV values were significantly lower in patients of acute exacerbation than in smokers and controls (both, $P < 0.001$). A positive correlation was found between MPV and measured forced expiratory volume at first second (FEV_1), C-reactive protein, and total leukocytic count in total sample.

Conclusion MPV was found to be decreased in acute exacerbations of COPD compared with smokers and healthy controls. Evaluation of MPV in COPD exacerbation may indicate systemic inflammation. Thus, MPV may be used as a negative acute-phase reactant in COPD exacerbation. *Egypt J Broncho* 2016 10:46–51

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Introduction

Chronic obstructive pulmonary disease (COPD), a common preventable and treatable disease [1], is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases [2]. Exacerbation and comorbidities contribute to the overall severity in individual patients [1]. Inhaled cigarette smoke and other noxious particles cause lung inflammation, which results in the induction of parenchymal tissue destruction and disruption of normal repair and defense mechanisms and fibrosis of small airways. These pathological changes lead to air trapping and progressive airflow limitation, in turn to breathlessness and other characteristic symptoms of COPD [1,2]. Exacerbations of COPD are accompanied with both airflow limitation and a marked increase of inflammation and inflammatory markers as C-reactive protein (CRP) [3].

Mean platelet volume (MPV) is a marker of platelet activation [4], and is affected by the aging of platelets and varies according to the balance between production and destruction. In several inflammatory clinical conditions, the degree of inflammation and changes in MPV appear to be correlated; however, the impact of this is controversial [5,6].

MPV is an important cardiovascular risk predicting factor in adults. MPV has a predictive value for the appearance of stroke and acute myocardial infarction. It is also increased in diabetes, rheumatologic, and systemic and inflammatory diseases such as inflammatory bowel diseases, rheumatoid arthritis, ankylosing spondylitis psoriasis, and familial Mediterranean fever [7–13].

Few studies showed elevated MPV value in stable COPD [14,15]. During acute exacerbation of COPD, proinflammatory cytokines and acute-phase reactants suppress the size of platelets by interfering with megakaryopoiesis and subsequent release of small-size platelets from bone marrow [16]. Cigarette smoking has been associated with an increased MPV; in addition, smoking cessation has been shown to lead to decreased MPV [17].

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The variation of MPV in exacerbations and in smoking status was not sufficiently examined, and so we measured MPV during exacerbations and in non-COPD smokers and compared both with well-matched controls.

Patients and methods

Patients

From January 2015 to June 2015, we enrolled 135 participants, who were divided into three groups of 45 participants each. Group I included 45 patients with the diagnosis of COPD exacerbation and were admitted to our emergency room or outpatient clinics at the Department of Chest Diseases, Alexandria Faculty of Medicine (Egypt). Group II and Group III included 45 participants each, who were smoker controls and healthy controls, respectively. The study was approved by the Ethics Committee of the Faculty of Medicine, Alexandria University.

COPD was diagnosed according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, on the basis of past smoking history, clinical evaluation, and spirometry, showing irreversible airflow obstruction. These data were either provided by the patient (medical report, spirometry report, or drug prescription written by a chest physician) or previously kept in the hospital records. An exacerbation of COPD was defined as sustained (≥48 h) worsening of dyspnea, cough, or sputum production leading to an increase in the use of maintenance medications and/or supplementation with additional medications [1].

Patients who had acute cerebrovascular event, acute coronary syndrome, hematological disease, bowel inflammatory disease, rheumatological disease, liver disease, renal disease, thrombocytopenia, and pregnant women were excluded from the study.

Study design

Informed written consent was taken from all eligible patients/participants. For groups I and II, medical history was recorded and spirometry was carried out. Complete blood cell count (CBC), CRP, arterial blood gases (ABG), and MPV measurements were taken at first administration of medications for exacerbation. The control group (group III) included 45 age-matched healthy controls without a smoking history. CBC, CRP, and MPV were measured for healthy controls; spirometry and ABG were not carried out for this group.

Spirometry

A spirometer (CHESTGRAPH HI-701; Chest M.I. Inc., Hongo, Bunkyo-Ku-Tokyo, Japan) was used for all assessments. A laboratory technician demonstrated each respiratory maneuver for each participant before testing. Patients were instructed to perform forced expirations until three acceptable measurements were obtained according to the European Respiratory Society criteria [18]. Each recorded result was expressed as a percentage of the predicted value for that parameter. Predicted values were calculated according to the system developed by Quanjer *et al.* [19].

Laboratory measurements

CBCs were measured by an automatic blood counter (ADVIA 2120 Haematology System, Bayer Health Care, Diagnostics Division, Tarrytown, NY, USA). The expected MPV values in our laboratory ranged between 6.0 and 11.0 fl. CBC and CRP were recorded for patients with COPD exacerbation and smokers.

Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS software package (IBM SPSS Statistics for Windows, Version 20.0., IBM Corp., Armonk, NY). Qualitative data were described as number and percentage. Quantitative data were described as range (minimum and maximum), mean, SD, and median. Comparison between different groups regarding categorical variables was performed using the χ^2-test. The distributions of quantitative variables were tested for normality using the Kolmogorov–Smirnov test, Shapiro–Wilk test, and D'Agostino test. If it revealed normal data distribution, parametric tests were carried out. If the data were abnormally distributed, nonparametric tests were used. For normally distributed data, comparison between the two groups was conducted using the independent *t*-test, whereas for more than two groups, the *F*-test (analysis of variance) and post-hoc test (least significant difference) were carried out for pair-wise comparison; for abnormally distributed data, comparison between two groups were performed using the Mann–Whitney test. Correlations between two quantitative variables were assessed using Spearman's coefficients regarding normality of the data. Significance of the obtained results was judged at the 5% level.

Results

Patients' demographics, medical history, laboratory results, and spirometric data are shown in Table 1. MPV values were 8.34 ± 0.95, 9.28 ± 0.67, and 9.12 ± 0.60 fl for groups I, II, and III, respectively (Fig. 1). MPV values for group I were significantly lower than those for smokers or for controls (for both, $P < 0.001$). There was no statistically significant difference in MPV values between group II and group III ($P = 0.309$).

Table 1: Demographics, functional parameters, and laboratory results of patients of exacerbations of COPD, smokers and controls

Parameters	Group (I) (n = 45)	Group (II) (n = 45)	Group (III) (n = 45)	Test of significance	P
Age y	56.67 ± 10.64	56.0 ± 8.58	53.09 ± 8.57	F=1.878	0.157
Sex m/f	26/13	24/21	27/18	χ^2=0.423	0.809
HTN (n)	35	34	28	χ^2=3.150	0.235
DM (n)	23	22	25	χ^2=0.415	0.812
Mean BP. (mmHg)	116.11 ± 13	116.06 ± 11	115.39 ± 15	F=0.040	0.961
HR (beat/min)	99.89 ± 9	79.56 ± 11	78.33 ± 10.28	F=58.186*	<0.001*
RR (respiratory rate)	30.89 ± 1.67	16.16 ± 2.45	15.87 ± 2.31	F=705.317*	<0.001*
Temperature (Celsius)	38.03 ± 0.67	36.92 ± 0.29	36.96 ± 0.23	F=91.886*	<0.001*
MPV (fL)	8.34 ± 0.95	9.28 ± 0.67	9.12 ± 0.60	F=20.192	<0.001*
CRP (mg/dl)	54.73 ± 14.08	2.13 ± 1.0	1.38 ± 0.55	F=633.351	<0.001*
WBC (cell/ul)	12.06 ± 2.72	7.0 ± 2.10	6.38 ± 1.34	F=96.212	<0.001*
pH	7.40 ± 0.04	7.41 ± 0.05	—	t=1.601	0.113
HCO_3 (meq/l)	29.42 ± 2.51	23.53 ± 1.71	—	t=13.002*	<0.001*
PaO_2 (mmHg)	75.01 ± 6.49	93.73 ± 3.81	—	t=16.697*	<0.001*
$PaCO_2$ (mmHg)	49.27 ± 4.07	36.42 ± 3.54	—	t=15.976*	<0.001*
Hb (gm/dl)	12.53 ± 1.55	12.57 ± 1.34	12.43 ± 1.55	F=0.101	0.904
Platelets (cell/ul)	259.16 ± 54.48	272.38 ± 58.55	278.67 ± 55.40	F=1.415	0.247
FEV_1 (ml)	1.23 ± 0.77	3.64 ± 0.78	—	t=217.116*	<0.001*
FEV_1 % predicted	38.14 ± 17.13	93.94 ± 11.72	—	t=18.031*	<0.001*
FVC (ml)	2.16 ± 0.89	4.42 ± 0.95	—	Z= 7.438*	<0.001*
FVC % predicted	51.65 ± 17.33	89.55 ± 10.52	—	t=157.341*	<0.001*
FEV_1/FVC	53.33 ± 13.14	83.47 ± 7.18	—	t=182.385*	<0.001*

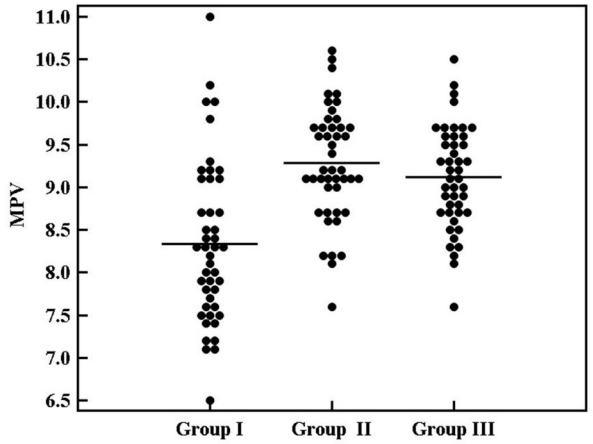
Data are presented as mean ± standard deviation, Abbreviations: COPD = chronic obstructive pulmonary disease; HTN = systemic hypertension; DM = Diabetes Mellitus; BP = Blood Pressure; HR = Heart Rate; RR = Respiratory rate; MPV = mean platelet volume; CRP = C-reactive protein; WBC = white blood cell; HCO_3 = serum bicarbonate; PaO_2 = partial arterial oxygen tension; $PaCO_2$ = partial arterial carbon dioxide tension; Hb = hemoglobin, FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; * : Statistically significant at $P \leq 0.05$

Table 2: Correlation between MPV and both CRP and WBCs in each group

	MPV					
	Group I		Group II		Group III	
	R	P	R	P	R	P
CRP	0.047	0.759	–0.304	0.542	–0.007	0.963
WBC	0.029	0.852	–0.234	0.122	–0.073	0.632

r: Pearson coefficient; * : Statistically significant at $P \leq 0.05$

Fig. 1



Comparison between the studied groups according to mean platelet volume (MPV) (in fl).

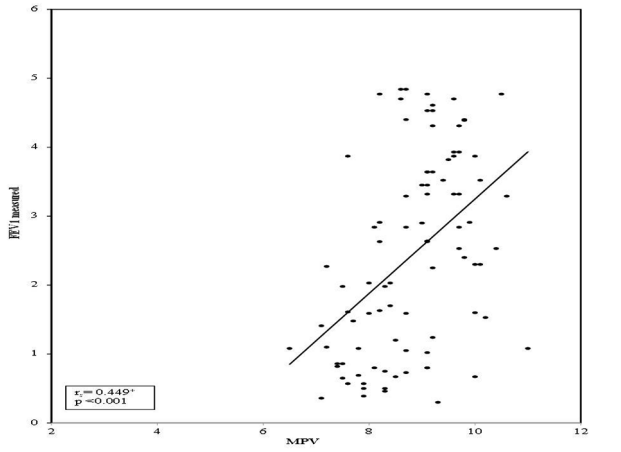
A significant negative correlation was found between MPV and both CRP and white blood cell (WBC) (r = -0.446, P < 0.001 for CRP and r = –0.405, P < 0.001 for WBC), as shown in Table 2. Of note, no significant correlation was found between MPV and CRP for patients within each individual group (r_s = 0.047, P = 0.759 in group I, r_s = –0.304, P = 0.542 in group II, and r_s = –0.007, P = 0.963 in group III) and again no significant correlation was found between MPV and WBCs for patients within each individual group (r_s = 0.029, P = 0.852 in group I, r_s = –0.234, P = 0.122 in group II, and r_s = –0.073, P = 0.632 in group III).

There was a significant positive correlation between FEV_1 and MPV for total sample (r = 0.449, $P \leq 0.001$) (Fig. 2), although there were no correlations between FEV_1 and MPV levels in exacerbation group or for smokers (r = 0.174, P = 0.252 and r = –0.116, P = 0.447, respectively), as shown in Table 3.

Discussion

During exacerbation of COPD, more hyperinflation and gas trapping take place. This is associated with reduced expiratory flow leading to an increase in dyspnea [20] and worsening of V_A/Q abnormalities

Fig. 2



Correlation between mean platelet volume (MPV) (in fl) and FEV_1 (in ml) measured for total sample.

Table 3: Correlation between MPV and FEV1 measured for total sample (*n* = 90)

	MPV	
	R	*P*
FEV1 measured	0.449*	<0.001*

* : Statistically significant at $P \leq 0.05$

with resultant hypoxemia. Sinus tachycardia may be due to breathlessness, hypoxia, or bronchodilator therapy. These findings have been reported in many studies and reviews in the literature [21,22]. Similarly, we found mean heart rate, mean respiratory rate, and temperature of patients with AECOPD significantly higher than those in group II and III ($P_1 < 0.001$, $P_2 < 0.001$; $P_1 < 0.001$, $P_2 < 0.001$; and $P_1 = 0.040$, $P_2 = 0.002$, respectively).

A main finding in our study was significantly lower MPV values in patients with AECOPD compared with healthy smokers and controls (both, $P < 0.001$), with no significant difference between group II and group III ($P < 0.309$). It is widely known that because of systemic inflammation observed during the exacerbation of COPD, overproduction of inflammatory mediators such as CRP, tumor necrosis factor-α, and other proinflammatory cytokines takes place [23,24]. This results in the suppression of platelet size because of an interference with megakaryopoiesis and the subsequent release of small-size platelets from the bone marrow [16,25,26].

In agreement with our study, studies by Ulasli *et al.* [27] and Wang *et al.* [28] measured MPV, CRP, and pulmonary function testing (PFT) for a group of patients with COPD and for age-matched healthy controls and compared these parameters for patients during the stable period and during the exacerbation of COPD. In their study, Ulasli *et al.* [27] demonstrated that patients with COPD exacerbation had lower MPV compared with healthy controls (8.6 ± 1.0 and 9.3 ± 0.8 fl, respectively, $P = 0.001$). A study by Wang *et al.* [28] also reported lower MPV in patients with AECOPD than in healthy controls (9.5 ± 0.9 and 10.4 ± 1.1 fl, respectively, $P = 0.001$). MPV increased once patients recovered from their exacerbation of COPD (stable COPD) in both studies (9.3 ± 1.4 and 9.8 ± 0.9 fl, respectively, $P = 0.001$ for both).

Nevertheless, hypoxia, pulmonary artery hypertension, and thrombosis lead to bone marrow stimulation resulting in the secretion of larger platelets. Furthermore, this may result in an increased sequestration of smaller platelets with larger platelets remaining in the circulation [29,30]. This may lend support to several studies [14,15,31,32] that showed increased MPV during stable period of COPD in comparison with the exacerbation period or with healthy controls.

In contrast, in a study by Biljak *et al.* [33], platelet count, MPV, and classical markers of systemic inflammation (CRP, WBC count, and the relative proportion of segmented neutrophils) for COPD patients were determined. They compared them with those measured for healthy controls and found out that MPV was reduced in stable COPD patients compared with the control group. This study has been criticized [27] as the control group was not age-matched and had variable smoking status.

There is an increase in platelet reactivity in COPD patients, which may be associated with increased protein oxidation of platelets [34–36]. Platelet activation in COPD patients is associated with hypoxia through the induction of changes in platelet structure [37]. This leads to an increased activation of cyclooxygenase-1 with thromboxane formation and increased platelet aggregation in hypoxemic COPD patients [38]. In addition, clotting activation may promote platelet activation and increase thromboxane production [39]. The above-mentioned facts may explain the significant positive correlation between MPV and measured FEV_1 ($P = 0.001$) regardless of the underlying condition; this can be interpreted as follows: the more the airway obstruction, the lower the MPV.

However, a study by Cui *et al.* [32] found a significant negative correlation between MPV and predicted FEV_1 ($P = 0.0001$), suggesting higher MPV in more severe obstruction. This was stated for stable COPD patients rather than during exacerbation. They included a very selected population of very old male patients (mean age was 86.03 years).

We failed to find any correlation between MPV and FEV_1 for patients within each individual group. In their respective studies, Steiropoulos *et al.* [31], Biljak *et al.* [33], and Ulasli *et al.* [27] noted that MPV did not correlate with any indices of COPD severity. Among patients with COPD, MPV did not differ significantly between GOLD stages. Certainly, this may be, at least in part, because of the small number of patients within each group. Conflicting reports regarding the relationship between MPV and COPD severity 'stage' necessitates conduction of more research at this point.

It is important to say that we found no influence of smoking on MPV. This finding was reported in many studies [33,40].

Not surprisingly, reduced lung function was associated with increased levels of systemic inflammatory markers such as CRP and leukocytic count, which may have important pathophysiological and therapeutic implications for those with stable COPD [25]. Both CRP and WBC in our study were found significantly higher in patients during AECOPD than in patients in group II and III. The same finding was reported in many similar studies [27,28,33].

In a study conducted locally in our institution, Helmy *et al.* [41] enrolled 50 adult patients with AECOPD, who were admitted to the ICU. Serum CRP and interleukin (IL)-6 levels were measured on admission; the primary endpoint was any-cause mortality during the ICU stay or 28 days after discharge; lengths of ICU and hospital stay besides complications encountered were recorded. The study reported elevated levels of CRP (97.55 ± 32.53 mg/dl) in the patients. These higher levels of CRP in comparison with our study may be attributed to the inclusion of mechanically ventilated COPD patients with more severe condition, and hence more elevated levels of CRP as a marker of inflammation were expected.

Elevated inflammatory cytokines such as CRP and IL-6 in patients with COPD play important role in oxidative stress, which lead to platelet activation, and influence megakaryopoiesis and platelet volume [26]. Platelet aggregation is accelerated by hypercapnia and hypoxemia [29]. The above-mentioned facts may explain the significant negative correlation between MPV and CRP and WBC (for both, $P < 0.00001$) in our study, and thus MPV can be considered as a negative inflammatory marker for COPD.

Similarly, a study by Wang *et al.* [28] found significant negative correlation between MPV and both CRP and WBC in patients with exacerbation of COPD ($P < 0.001$ and 0.002, respectively). However, a study by Biljak *et al.* [33] found negative but not significant correlation between MPV and both CRP and WBC ($P = 0.120$ and 0.037, respectively).

Nevertheless, we did not find any correlation between MPV and CRP in patients within each individual group. Certainly, this may be, at least in part, because of the small number of patients within each group. In their study, Ulasli *et al.* [27] noted that MPV did not correlate with CRP and WBC; however, they found a negative significant correlation between MPV and neutrophil percentage ($P = 0.013$).

ABG analysis is an important parameter in acute exacerbation of COPD and provides the best clues as to acuteness and severity of disease and determines the need of ventilator support. Gas entrapping, gas exchange abnormalities, and reduced ventilatory drive in exacerbation of COPD lead to CO_2 retention when it is combined with reduced ventilation because of a high work of breathing because of severe obstruction and hyperinflation coupled with ventilator muscle impairment. The abnormalities in alveolar ventilation and a reduced pulmonary vascular bed further worsen the V_A/Q abnormalities that lead to hypoxemia; in addition, gradual destruction of alveolar septae of pulmonary capillary bed leads to a decrease ability to oxygenate blood. Hypercapnia in turn leads to respiratory acidosis, which leads to an increased serum HCO_3 level as a response to acidosis [31–33].

Not surprisingly, we found that arterial bicarbonate (HCO_3) level was elevated significantly in AECOPD patients compared with smokers ($P < 0.001$). Mean arterial partial oxygen tension (PaO_2) was significantly lower in AECOPD patients than in smokers ($P < 0.001$), and the mean partial pressure of arterial carbon dioxide ($PaCO_2$) was significantly higher in AECOPD than in smokers ($P < 0.001$). These findings were recorded in many studies and reviews in the literature [22,34].

There were several limitations to our study. The number of participants enrolled in the study was relatively small. We did not, as well, classify patients according to severity. Furthermore, smoking habits of our patients were self-reported; the measurement of nicotine level would be much more reliable. PFT and MPV should have been assessed after stabilization of exacerbated COPD patients. Comparison of MPV and CRP to other inflammatory markers, such as IL-6, IL-8, etc., would have solidified our results. At last, the current study was conducted in a single center rather than in multicenters.

In conclusion, MPV is decreased in acute exacerbations of COPD compared with smokers and healthy

controls. Evaluation of MPV in COPD exacerbation may indicate systemic inflammation. Thus, MPV may be used as a negative acute-phase reactant in COPD exacerbation.

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Conflicts of interest
There are no conflicts of interest.

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