Cocaine use does not affect mean platelet volume

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Abstract: Increased mean platelet volume (MPV) is a marker of platelet activation. Platelet activation with cocaine use is not well studied. We wanted to investigate MPV levels in patients with cocaine-associated chest pain (CACP) as a marker of platelet activation. Retrospectively, MPV of 82 consecutive patients with CACP (group 1) with positive urine drug screen (UDS), without acute myocardial infarction (AMI) (group 1A) and with AMI with elevated troponin (group 1B), were included in the study. The control group (group 2) consisted of 89 consecutive patients admitted during the same time period with acute chest pain (ACP) who had negative UDS and negative cardiac markers with a normal cardiac stress test or normal coronary angiogram. Analysis showed no statistically significant difference of MPV between group 1, 8.46 ± 1.06 fL, versus group 2, 8.7 ± 1.07 fL; $p = 0.142$; and between group 1A, 8.46 ± 1.05 fL, and group 1B, 8.46 ± 1.09 fL; $p = 0.983$. By multiple linear regression analysis, MPV was not influenced by cocaine abuse ($R = 0.269$, $R^2 = 0.072$, adjusted $R^2 = -0.009$, $p = 0.562$). MPV is not elevated in patients with cocaine use even when they had AMI. Further studies may be necessary to investigate the role of platelet activation in patients with cocaine use and chest pain.

Keywords: mean platelet volume, cocaine use, platelet

Introduction

Cocaine is a naturally occurring substance found in South America's *Erythroxylum coca* plant that has been in use for more than 5000 years [1]. Cocaine, one of the most commonly used illicit drugs in United States, is associated with a wide spectrum of cardiovascular complications including myocardial infarction first reported in 1982 [2]. Every year, more than 500,000 patients present to hospital emergency department with cocaine-associated cardiovascular complications, most commonly chest pain [3]. Many cases of myocardial infarction have been reported in cocaine users who have normal coronaries [4]. The exact pathogenesis of cocaine-associated chest pain (CACP) and myocardial infarction is not clear in users with normal coronary anatomy but has been hypothesized to be due to coronary vasoconstriction, focal coronary vasospasm, increased oxygen demand, and transient coronary thrombosis [5]. Cocaine can also promote endothelial dysfunction in subjects with significant coronary artery disease (CAD) and facilitate thrombus formation in diseased vessels [5]. In patients with cocaine-induced myocardial infarction, platelet-rich coronary thrombi were observed which suggested activation of platelets [6]. Increased platelet factor 4, β-thromboglobulin in nasal cocaine users [7], and a delayed increase in platelet P-selectin expression in conscious dogs with cocaine infusion [8] also suggest platelet activation with cocaine. Despite these findings, the role of platelet activation in patients with CACP remains unclear.

Mean platelet volume (MPV) has been shown to be an indicator of platelet activity. Higher MPV values are seen in patients with myocardial infarction and unstable angina [9]. Larger platelets contain more dense granules, produce more thromboxane A2, and express more glycoprotein Ib and IIb/IIIa receptors [10]. However, there are no published studies on the effect of cocaine use on MPV. We hypothesized that, in patients with CACP, especially with acute coronary syndrome, MPV will be increased, and this may reflect platelet activation in CACP.

Materials and Methods

The study was a retrospective study. All patients seen in an urban university hospital between 2002 and 2010 were identified by cross-referencing the International Classification of Diseases, Ninth Revision (ICD-9), 970.81, 304.20, and 304.21 diagnostic codes in medical records' search for cocaine use and chest pain/acute coronary syndromes. Universal definition for myocardial infarction is used to define AMI [11]. Positive cardiac marker is defined as troponin level with at least one value above the 99th percentile of the upper reference limit. Patients were included in the study if they had a documented history of cocaine use with urine or blood toxicology screen that revealed cocaine or cocaine metabolites and chest pain *(Fig. 1)*. We included 82 consecutive cocaine-associated chest pain (CACP) patients (group 1) without myocardial infarction (group 1A, $n = 31$) and with myocardial infarction (group 1B, $n = 51$) who had positive blood or urine toxicology screen for cocaine in the study. We also reviewed the medical records of 89 consecutive patients with no known history of coronary artery disease and admitted during the same time period with acute chest pain (ACP), who had negative urine drug screen (UDS) and negative cardiac markers with a normal cardiac stress test and/or a normal coronary angiogram (group 2). Patients with CACP with no drug screen or negative drug screen and ACP patients with no drug screen were excluded in this study. In group 2, three patients had ST-elevation myocardial infarction; the rest had non-ST-elevation myocardial infarction. In this group, 24 patients had cardiac catheterization, and 9 of them required percutaneous intervention for obstructive CAD. Data collected included demographics, medical and cocaine use history, presenting characteristics, and diagnostic tests. Laboratory data were obtained from the time of admission by using the computerized database including platelet indices, platelet count, and white blood cell (WBC) count. As per the hospital's policy, blood samples were drawn by vein puncture and collected in standard sterile dipotassium EDTA tubes. Complete blood count analyses were performed in the same Coulter analyzer model LH within 1 h as a standard in our institution, and analyzer was routinely checked for quality control. The reference value for MPV ranged between 6.5 and 10.9 fL. The hospital's institutional review board approved this study.

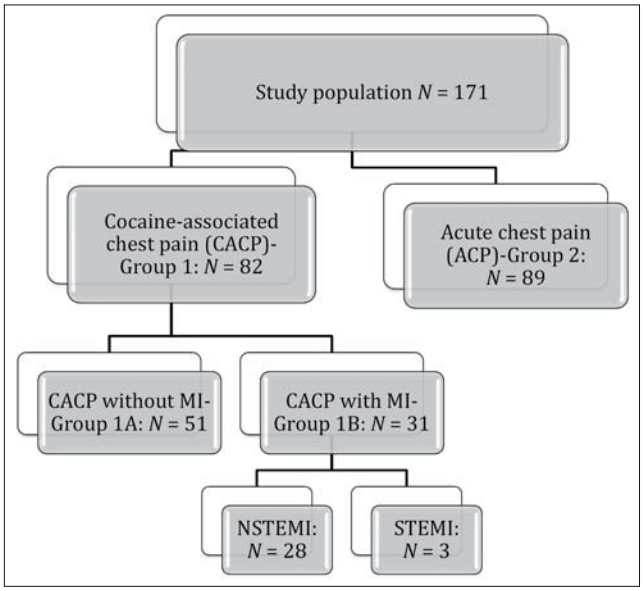

Fig. 1. Flow chart showing study design; cocaine-associated chest pain (CACP), acute chest pain (ACP), myocardial infarction (MI), non-ST elevation myocardial infarction (NSTEMI), ST elevation myocardial infarction (STEMI), *N*: number of patients

Statistical analysis

Data was analyzed with Statistical Package for Social Sciences version 10 (SPSS for Windows 17, Inc. Chicago, IL, USA). A p value of <0.05 was considered for statistical significance. The data was analyzed using an independent sample *t*-test, chi-square, and multiple linear regression analysis depending on the variables.

Results

The study population consisted of 171 patients, out of whom the CACP group (group 1) had 82 patients and 89 patients in the control group (group 2). The demographic and medical treatment characteristics of the two groups were studied and compared as shown in *Table I*, CACP versus control group. An independent sample *t*-test revealed that there was no statistically significant difference in MPV between CACP (group 1), 8.46 ± 1.06 fL, and control (group 2), 8.7 ± 1.07 fL; $p = 0.142$ *(Fig. 2)*. Since the two groups had significantly different composition in terms of their demographic and clinical characteristics, to define independent factors influencing MPV, multiple linear regression analysis was used with MPV being the dependent variable for the equation and Cocaine group, age, gender, race, hypertension, diabetes, hyperlipidemia, congestive heart failure, cerebrovascular accident, end stage renal disease, smoking, and alcohol as the independent variables. MPV was not influenced by cocaine abuse ($R = 0.269$, $R^2 = 0.072$, adjusted $R^2 = -0.009$, $p = 0.562$), despite controlling for the possible confounding factors. To study MPV levels within cocaine users with and without AMI, an independent sample *t*-test was done comparing MPV levels in group 1A (CACP but no AMI) and group 1B (CACP with AMI). There was no statistically significant difference in MPV between the groups (group 1A: 8.46 ± 1.05 fL, group 1B: 8.46 ± 1.09 fL;

Table I Clinical characteristics of the study population

		Total, $N = 171$						p
		CACP, group 1 ($n = 82$)			ACP, group 2 ($n = 89$)			
		Mean ± SD	Count	Column, n %	Mean ± SD	Count	Column, n %	
Age		48 ± 7.92			52 ± 11.32			0.018*
Sex	Female		22	26.8		47	52.8	0.001*
	Male		60	73.2		42	47.2	
Race	Non-Black		13	15.9		36	40.4	<0.001**
	Black		69	84.1		53	59.6	
Hypertension	No		22	27.2		19	21.3	0.376
	Yes		59	72.8		70	78.7	
Diabetes	No		66	81.5		55	61.8	0.005*
	Yes		15	18.5		34	38.2	
Dyslipidemia	No		51	63.0		47	52.8	0.181
	Yes		30	37.0		42	47.2	
Obesity	No		65	84.4		57	64.0	0.003*
	Yes		12	15.6		32	36.0	
Stroke	No		74	91.4		78	87.6	0.431
	Yes		7	8.6		11	12.4	
Peripheral arterial disease	No		78	96.3		88	98.9	0.268
	Yes		3	3.7		1	1.1	
End-stage renal disease	No		76	95.0		89	100.0	0.048*
	Yes		4	5.0		0	0.0	
Smoking	No		9	11.1		66	74.2	<0.001**
	Yes		72	88.9		23	25.8	
Alcohol	No		22	27.2		60	67.4	<0.001**
	Yes		59	72.8		29	32.6	
Platelet count		250.05 ± 98.94			254.84 ± 89.80			0.742
Hemoglobin		13.66 ± 2.52			14.03 ± 2.20			0.313

CACP = cocaine-associated chest pain, ACP = acute chest pain
Data are expressed as mean ± SD, as number of percentage
p value is comparing the group 1 with group 2
*$p < 0.05$
**$p < 0.001$

$p = 0.983$) *(Fig. 3)*. The medications that the patients started in emergency room were also compared between the groups; except β-blockers ($p < 0.001$), there was no difference between group 1 and group 2 *(Table II)*.

Discussion

Mean platelet volume is a simple method of platelet function easily available on the routine complete blood count panel. The change in MPV occurs quickly in response to platelet activation. Because of these features, MPV has been studied as an indicator of platelet activation, and increased MPV has been reported in patients with known CAD risk factors such as smoking, diabetes mellitus, obesity, hypertension, and increased cholesterol compared to healthy controls. Patients with unstable angina have also been reported to have increased MPV compared to patients with stable angina [12].

Cocaine causes acute increase in heart rate, systolic and diastolic blood pressure [13], vasoconstriction in coronary arteries [10], accelerated coronary atherosclerosis [15], and direct myocardial injury [16]. All of these can contribute to cocaine-associated chest pain and also may affect platelets directly or indirectly. Despite that, in our study, we did not find any significant difference in MPV between patients with CACP and patients presenting with ACP who were not cocaine users and had nega-

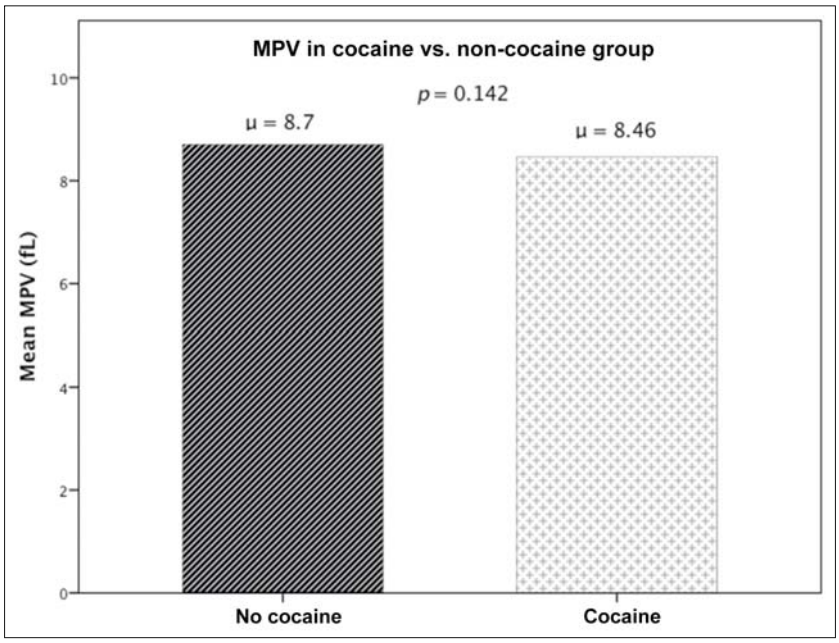

Fig. 2. Showing comparison of MPV between cocaine-associated chest pain and control group

tive UDS for cocaine. MPV levels were also not elevated in 51 of 82 patients with CACP who had AMI compared to ACP group. In fact, although there was no statistical significance, the mean MPV value in CACP patients was lower than the ACP group (8.46 ± 1.06 fL versus 8.7 ± 1.07 fL; $p = 0.142$). Of note, smoking and alcohol use were more common in the CACP group *(Table I)*; we know that smoking can increase MPV, but the effect of alcohol on MPV level is not well known. The medical treatment used was also similar in both groups except β-blockers which are less commonly used in CACP group *(Table II)*. In a recent study of hypertensive patients, 15–30 days after treatment with either selective or nonselective β-blockers, an increase in MPV with contraction of spleen has been reported [17]. Even then, in our study, MPV was lower in CACP group despite less β-blocker use.

Prognostic value of MPV also has been investigated in several studies. Patients with acute myocardial infarction (AMI) with an elevated MPV had a significantly higher

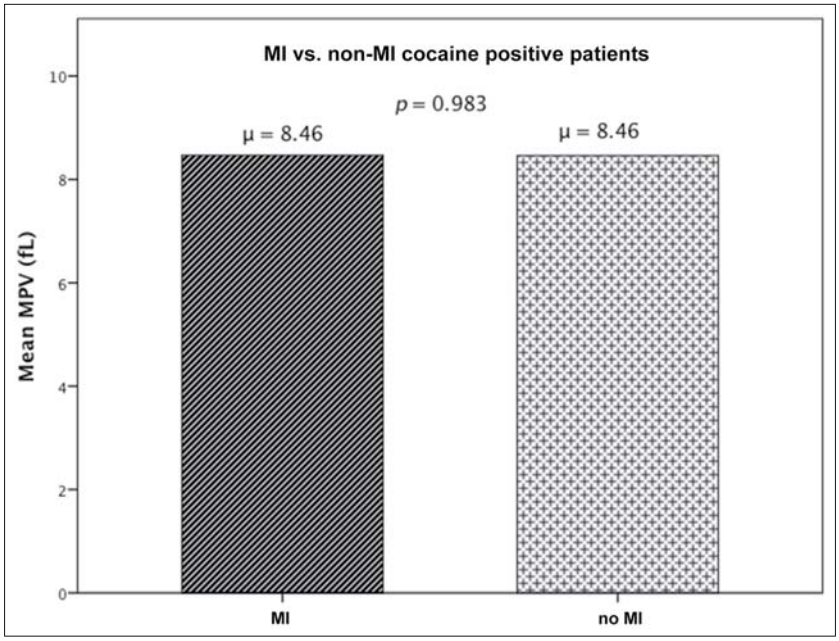

Fig. 3. MPV levels in cocaine-associated chest pain (CACP) but no acute myocardial infarction (AMI) and CACP with AMI

Table II Medical treatment characteristics of both groups

		CACP, group 1		ACP, group 2		*p*
		Count	Column, *n* %	Count	Column, *n* %	
Aspirin	No	12	14.8	8	9.0	0.239
	Yes	69	85.2	81	91.0	
P2y12 inhibitor	No	47	58.0	56	62.9	0.514
	Yes	34	42.0	33	37.1	
ACE inhibitor	No	18	22.2	14	15.7	0.276
	Yes	63	77.8	75	84.3	
Beta blocker	No	61	75.3	21	23.6	<0.001
	Yes	20	24.7	68	76.4	
Statins	No	27	33.3	19	21.3	0.079
	Yes	54	66.7	70	78.7	

p value is comparing the group 1 with group 2
CACP = cocaine-associated chest pain, ACP = acute chest pain
Data are expressed as count, as number of percentage
Statistically significant $p < 0.05$

risk of death compared to those with a normal MPV in these studies [9, 18, 19]. Mean platelet volume of more than 9 fL has also been shown to be associated with higher cardiovascular event rate in patients with coronary artery ectasia [20]. We do not know if lack of elevation in MPV in CACP patients even in those with AMI suggests a favorable outcome. More prospective studies will be needed for evaluation of prognostic significance of MPV levels in patients with cocaine-induced AMI.

Despite several studies, it is not very clear if MPV can be a used as a biomarker of platelet activity in an individual patient in clinical practice. There are methodological variables that may affect the MPV results, in addition to method of venipuncture, the degree of accuracy of filling, how the sampling tubes mixed, choice of anticoagulant used in tubes, and temperature at which MPV is analyzed [21]. MPV even differs in freshly produced platelets and in aging platelets [21]. All of this information brings up the question if the lack of difference in MPV levels in our study could be secondary to MPV being not a particularly sensitive marker of platelet activation. Perhaps other measures of overall platelet activation would have found a difference since there are some other studies suggestive of platelet activation with cocaine use. In a study of 14 healthy volunteers, Heesch et al. have shown an increase in platelet factor 4 and β-thromboglobulin 120 min after receiving intranasal cocaine [7]. Siegel et al. have shown elevated CRP, vWF, and fibrinogen in 10 cocaine-dependent users (6–20 uses of cocaine by inhalation per week over prior year; mean age, 41 + 6 years), compared to normal levels in 10 cocaine abusers (2–6 intranasal uses of cocaine per month over prior year; mean age, 26 + 4) with negative drug screen [22]. These studies were done in small number young volunteers without any symptoms. In contrast, our study population is older with significant symptoms and needed to be admitted to hospital.

Our study had limitations; it was a retrospective, single-center study, and the number of patients was limited. Body mass index can influence MPV, and this was not included in our analysis. MPV is known to increase over time in EDTA-anticoagulated samples, and the time delay between sample collection and laboratory analysis can affect MPV measurement. The recommended optimal measurement time for MPV is 120 min after the vein puncture. In our laboratory, the time interval is less than an hour, and this would have minimized the EDTA-induced platelet swelling effect in our study.

The control group did not consist of totally "healthy" people which is also a limitation of our study. In our study as a control group, we needed to include patients admitted at the same time interval who had negative urine drug screen (UDS), and to get as healthy as possible, we included patients with no known history of coronary artery disease and negative cardiac markers with a normal cardiac stress test and/or a normal coronary angiogram. As seen in *Table I*, smoking and alcohol were also statistically less consumed in control group compared to our study group.

Conclusions

MPV is not elevated in patients admitted with CACP whether they have AMI or not. Further studies may be necessary to investigate the role of platelet activation

with cocaine use and associated chest pain since MPV may not be a sensitive marker of platelet activation in this population.

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Conflict of interest: The authors declare no conflict of interest.

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