Early Changes in Platelet Size and Number in Patients with Acute Coronary Syndrome

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Abstract

A strong relationship exists between acute coronary syndrome (ACS) and platelets (PLTs) volume. Mean platelet volume (MPV) is a parameter of PLT functions and a marker for increased PLT activation. The aim of this study was to determine early changes in number of total PLT and MPV in different manifestation of ACS and to find out predictive value of MPV in the spectrum of ACS. This was a prospective study. One hundred thirty-four ACS patients were enrolled, 76 of them finished the study. PLT and MPV in patients with unstable angina, non-ST elevation, and ST elevation myocardial infarctions were determined on arrival and 1, 3, 72 hours, and 7 days after the admission to hospital. There was decrease in PLT and MPV in all three groups after 3 hours of arrival in hospital in comparison with admission values. In the later time period (72 hours and 7 days), there was an increase in PLT and MPV only in patients with acute myocardial infarction (AMI). We have revealed completely new dynamics in early changes in MPV and PLT count in patients with AMI. Biphasic changes were found in early phase after admission to the hospital. Fast response in these parameters raises new questions about their origin.

Keywords

- ▶ mean platelet volume
- ▶ platelet count
- ▶ large platelets
- ▶ platelet activation
- ▶ platelet function
- ▶ acute coronary syndrome
- ▶ early changes

Acute coronary syndromes (ACSs) are the set of signs and symptoms due to rupture of a plaque and formation of platelet (PLT)-rich coronary thrombus. The thrombus leads to partial or complete coronary artery occlusion, which in turn, leads to myocardial ischemia and clinical manifestation ranging from unstable angina (UA) to acute myocardial infarction (AMI).

PLTs and especially, large PLTs play a pivotal role in both initiation and propagation of ACS.^{1,2} Mean platelet volume (MPV) is an important indicator of PLT activation.³ Large PLTs are more active and have higher thrombotic potential.^{4,5} They are also denser, have higher thromboxane A₂ levels,

and express more glycoprotein Ib and IIb/IIIa receptors which enables them to aggregate more rapidly with collagen than smaller PLTs.⁶ In the recent years, numerous studies have been published, recognizing MPV as a predictor of cardiovascular disease and long-term mortality in patients who suffered from ACS.^{7–9} Increased mortality was found when the MPV increased over time after coronary revascularization.¹⁰ However, the role of changes in MPV in early phase after the ACS has not been previously evaluated. Our aim was to study dynamic changes in total number of PLTs and MPV in patients with UA and AMI (non-ST elevation myocardial infarction [NSTEMI] and ST elevation myocardial infarction [STEMI]) on arrival and 1, 3, 72 hours, and 7 days after the admission to hospital.

* These authors contributed equally to this study.

Methods

Study Design

This is a prospective hospital-based study. All experimental procedures were conducted in accordance of the declaration of Helsinki, and were approved by the Ethics Committee of the School of Medicine, University of Split.

Study Population

Overall, 134 patients recruited over a period of 6 months, and 73 patients at the end were enrolled in the study. Namely, out of a total of 137 patients admitted in the Coronary Care Unit suspected on ACS, 19 patients were excluded from the study because diagnosis was not confirmed. Five patients were excluded due to premature death, and further 39 patients were excluded due to incomplete data, most commonly failure to take any of five scheduled blood samples.

The following three groups were studied:

Group 1: UA group included 23 patients. UA group was defined as rest pain occurring within 48 hours without recent myocardial infarction, no evidence of major myocardial necrosis (no troponin I rise) and electrocardiographic evidence of transient ST segment depression or T-wave inversion.

Group 2: NSTEMI group included 25 patients. NSTEMI group was defined as typical angina pain lasting ≥ 30 minutes, with increase in levels of cardiac enzymes (troponin I levels) and electrocardiographic evidence of transient ST segment depression or T-wave inversion.

Group 3: STEMI group included 26 patients. STEMI group was defined as typical angina pain lasting ≥ 30 minutes, with increase in levels of cardiac enzymes (troponin I levels) and electrocardiographic evidence of elevation of the ST segment of ≥ 1 mm in two or more consecutive leads. In this group, 20 patients were recruited for the urgent percutaneous coronary intervention obtained within 1 hour of admission to the hospital.

Patient on oral anticoagulants or with thrombocytopenia were excluded. The patients received the regular therapy for ACS on admission. All patients received the aspirin, clopidogrel, and heparin; however, all without known effect on PLT size. Additional medication included angiotensin-converting enzyme inhibitors, β blockers, nitrates, statin, and diuretic agents depending on patients' clinical findings (e.g., blood pressure, heart rate).

Blood samples (2 mL) for PLT analysis were collected in dipotassium EDTA tubes on arrival, and 1, 3, 72 hours, and 7 days after admission to the hospital. Samples were analyzed within 2 hours of venipuncture due to well-known swelling of the PLTs in EDTA tubes. An extra blood was collected on admission for troponin I and glucose levels and for lipid profile. They were determined by standard methods with internal and external quality controls.

Statistical analysis was performed using Stat Soft 8 statistical package (StatSoft, Tulsa, OK). Continuous data were expressed as mean $\pm$ standard deviation and categorical data as percentage.

Comparisons between parameters in first 3 hours of admission and after 72 hours and 7 days were first tested with nonparametric Friedman's analysis of variance. In case

Table 1 Distribution of risk factors in all the patients

Groups	UA (23)	NSTEMI (25)	STEMI (26)	p-Value
Age (SD)	69.7 (9.1)	73.3 (11.5)	66.6 (11.4)	NS
Sex (male vs. female)	13 vs 7	18 vs 7	17 vs 9	NS
Hypertension (%)	17 (73)	17 (68)	16 (61)	NS
Diabetes mellitus (%)	9 (39)	11 (44)	8 (30)	NS
Current smokers (%)	8 (34)	8 (32)	10 (38)	NS
Hyperlipidemia (%)	16 (69)	17 (68)	16 (61)	NS

Abbreviations: NS, not significant; NSTEMI, non-ST elevation myocardial infarction; SD, standard deviation; STEMI, ST elevation myocardial infarction; UA, unstable angina.

Note: Chi-square test was used for categorical variables.

of a significant difference, the Wilcoxon signed-rank test was applied for the particular comparison. Chi-square test was used for categorical variables.

Results

A total of 76 patients recruited in our coronary unit represent our study population. Patients were divided in three groups (UA, NSTEMI, and STEMI groups), and there was no statistically significant difference in age, hypertension, type 2 diabetes mellitus, smoking, and hyperlipidemia status among all three groups ($\rightarrow$ **Table 1**). The number of females in NSTEMI group was lower ($\rightarrow$ **Table 1**).

Platelets Change

PLT count: There was significant decrease in total number of PLTs in all three groups after 3 hours of arrival in hospital in comparison with admission values (UA group: $p = 0.0007$; NSTEMI group: $p = 0.05$; and STEMI group: $p = 0.005$). After 72 hours and 7 days of arrival, there was an increase in total number of PLTs in NSTEMI and STEMI groups, in comparison with the lowest values achieved at 3 hours after admission, although significant levels were accomplished only in STEMI group in a period of 7 days after an admission to hospital ($p = 0.02$) ($\rightarrow$ **Fig. 1**).

MPV values: There was decrease, albeit not significant, in the number of large PLTs in all three groups after 3 hours of arrival in hospital in comparison with admission values (UA group: $p = 0.1$; NSTEMI group: $p = 0.2$; and STEMI group: $p = 0.1$). After 72 hours and 7 days of arrival, there was an increase in MPV, in comparison with the lowest values achieved at 3 hours after admission, in NSTEMI and STEMI groups. Significant levels were accomplished in NSTEMI group (7 days after an admission to hospital for 5.3%, $p = 0.008$) and in STEMI group (72 hours after an admission to hospital for 5%, $p = 0.001$; 7 days after an admission to hospital for 7.5%, $p = 0.00008$) ($\rightarrow$ **Fig. 2**).

Fig. 1 Platelet (PLT) count, presented as a mean $\pm$ standard deviation on admission, and at 1, 3, 72 hours, and 7 days after. *Values are statistically significant ($p < 0.05$) compared with the admission values (a) and lowest values achieved at 3 hours after (b).

Discussion

This is the first study to investigate early changes in number of total PLTs and MPV in different manifestation of ACS. Biphasic changes in MPV and PLT count in patients with AMI were found in early phase after admission to the hospital. The MPV and PLT counts decreased in early phase (first 3 hours) of all three manifestations of ACS. However, in the later phase (3 and 7 days after ACS), an increase in MPV and PLT counts was observed in NSTEMI and STEMI groups. In UA group, there was no increase in MPV and PLT counts in the later phase.

Most studies reported that increased MPV predates an ACS event rather than results from it, but no one followed early dynamics of MPV and PLT. In our study, we were surprised with a decrease in MPV in early phase (1 and 3 hours after admission to hospital) of ACS in all three groups. Martin et al found that PLT size remained elevated at 6 weeks

after hospital discharge and they concluded that increases in MPV are chronic rather than acute.¹¹ Our findings suggest acute changes as well. Moreover, it could even be three phases of MPV changes if we know that first values are obtained from the patients on admission to hospital when they have already been suffering pain. In studies previously conducted, it was shown that in control subjects or even patients with stable coronary artery disease, MPV was significantly lower than in ACS group.^{7,8,12} In accordance with these findings, we can assume that in all three included groups with ACS in our study, values of MPV obtained on admission are reflection of the acute coronary incident and pain which they are suffering, and they cannot be taken as a baseline values because they are probably higher than they would be in baseline condition.

The reduction in number of large PLTs in early phase of ACS could indicate consumption of PLTs for thrombus formation, especially more reactive large PLTs, during acute phase of ACS. Increase in MPV after 3 and 7 days, observed in our study in STEMI and NSTEMI groups, is in concordance with previous findings of association between MPV and long-term mortality.^{9,10,13,14} As larger PLTs are hemostatically more active, the presence of larger PLTs is probably a risk factor for developing coronary thrombosis and myocardial infarction. In the largest trial to date, investigators reported that, following a myocardial infarction, MPV was an independent risk factor for recurrent ischemia or death.^{14,15} A recent study in setting of STEMI suggested that MPV may have a role in guiding therapy because only subjects with elevated MPV had a mortality reduction from abciximab.¹⁶

This biphasic or even three phased dynamic changes in MPV in STEMI and NSTEMI groups suggest that they are probably distributed from some exchangeable reservoir in terms of acute stressful situation. Previous reports have suggested that the change in distribution of PLT volume arises at thrombopoiesis.¹¹ However, the life span of PLTs is about 8 days and more than 90% of the PLT population whose distribution was measured after myocardial infarction were circulating before the vascular occlusion occurred. It is almost impossible that observed fast changes, early decrease and increase in MPV, are only the consequence of changes in bone marrow megakaryocyte production. Moreover, although large PLTs have been thought to be young PLTs, it is now generally accepted that PLTs do not change in size as they age in the circulation.¹⁷ Bakovic et al reported that low-dose epinephrine infusion caused spleen contraction and an increase in MPV, in conditions of decreased blood pressure.¹⁸ The human spleen retains one-third of body PLTs, and MPV of the cells from human spleen is approximately 20% greater than MPV of circulating PLTs. Thus, the spleen could be a dynamic reservoir of large PLTs, and could be responsible for fast changes in number of circulating large PLTs in acute stressful situations.

Several studies have reported that increases in PLT volume are associated with decreases in PLT count.¹⁶ On the contrary, there is a study which found that PLT volume and count both increase during stimulated thrombopoiesis.¹⁹ The relationship between MPV and PLT counts is not completely understood. However, most studies found no significant association

Fig. 2 Mean platelet volume (MPV), presented as a mean $\pm$ standard deviation on admission, and at 1, 3, 72 hours, and 7 days after. *Values are statistically significant ($p < 0.05$) compared with the admission values (a) and lowest values achieved at 3 hours after (b).

between increased PLT count and incidents of ACS, restenosis, or long-term mortality.^{15,20} In our study, PLT count revealed the same dynamic of changes as MPV, supporting an idea about their ejection from possible spleen reservoir.

At the end, we have to highlight that, in our study, there was no significant difference in number of patients with comorbidities between different ACS groups, which could have an influence on MPV. The drugs used for treating were evenly distributed within the study groups.

Study Limitations

The major limitation of the study is relatively low number of patients who manage to finish the study. Notwithstanding, measurement of MPV in and after acute phase could provide important data about the PLT function in ACS.

Conclusion

We have revealed completely new dynamics in early changes in MPV and total PLT count in patients with ACS. Fast response in these parameters raises new questions about their origin. Further studies with spleen volume measurements should be done to clarify these findings.

Conflict of Interest

None declared.

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