Association of Platelet-Monocyte Aggregates with Platelet Activation, Systemic Inflammation, and Myocardial Injury in Patients with Non-ST Elevation Acute Coronary Syndromes

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Summary

Background: Platelet-monocyte aggregates (PMA) and C-reactive protein (CRP) are increased in unstable coronary disease. The interrelation of PMA with platelet activation, systemic inflammation, and their association with markers of myocardial injury has not been studied extensively.

Hypothesis: The study was undertaken to evaluate the association of CRP, PMA, and cardiac troponin I (cTnI) in patients admitted with non-ST elevation acute coronary syndromes (NSTEMI-ACS).

Methods: In all, 69 consecutive patients with NSTEMI-ACS, 58 patients with stable angina pectoris (SAP), and 46 control patients without coronary artery disease were selected; PMA, sP-selectin, sCD40L, interleukin (IL)-6, CRP, and cTnI concentrations were measured in these patients at the time of admission. Patients with NSTEMI-ACS were classified into two groups: those with troponin normal (cTnI < 0.06 ng/ml) and those with troponin elevation (cTnI ≥ 0.06 ng/ml). Their risk for clinical in-hospital cardiac events (death and nonfatal myocardial infarction) was analyzed.

Results: Compared with SAP and control, patients with NSTEMI-ACS exhibited higher levels of PMA, sP-selectin, sCD40L, IL-6, and CRP. All these parameters were found to be higher ($p < 0.001$) in patients with troponin elevation than in those with normal troponin. There was a significant relationship between PMA and CRP ($r = 0.628$, $p < 0.001$) and cTnI ($r = 0.557$, $p < 0.001$) in patients with NSTEMI-ACS. Logistic analysis further demonstrated that the presence of elevated PMA, CRP, and cTnI levels each confers and increases risk of future cardiac events.

Conclusions: Levels of PMA and CRP were significantly increased in patients with NSTEMI-ACS, especially in those with troponin elevation. This increase is strongly related to the risk of in-hospital cardiac events. A panel of PMA, CRP, and cTnI may provide important information additional to current laboratory data for the treatment of NSTEMI-ACS.

Key words: acute coronary syndromes, platelet-monocyte aggregates, inflammation, troponin-I

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Introduction

Acute coronary syndromes (ACS), which are the surrogate of major adverse events, result from destabilization, disruption, or rupture of the atherosclerotic plaque.¹ An atherosclerotic plaque is not merely a lipid-rich physical blockage, but rather consists of a mix of cytokines, adhesion molecules, chemokines, collagens, and enzymes secreted from multiple cell types.² Inflammation is believed to play a decisive initial and perpetuating role in the thrombotic transformation of this

plaque,^{3,4} and platelet activation is central to the formation of thrombus.⁵ This increased state of inflammation is mainly paralleled by activation of platelets with surface-exposing P-selectin, which tethers the platelet to monocyte via P-selectin glycoprotein ligand-1 (PSGL-1) to form platelet-monocyte aggregates (PMA). The close interaction between monocytes and platelets leads to leukocyte activation and cell-adhesion molecule expression, and activates the release of enzymes such as Matrix Metalloproteinases (MMPs), which degrade the subendothelial basement membrane, leading to subsequent plaque rupture or thrombogenicity.⁶ Monocyte-platelet aggregates have been shown to be an early marker of acute myocardial infarction (MI) and to cause complications after percutaneous coronary intervention (PCI).^{7–9}

Because the outcome of ACS is highly dependent on inflammation and thrombosis, it is assumed that measurement of these two processes will allow better assessment of plaque instability. An established link between inflammation and thrombosis in ACS is the formation of PMA.¹⁰ Elevated levels of C-reactive protein (CRP) are a marker of systemic inflammation. Increased troponin is an indicator of myocardial injury associated with vascular embolization caused by thrombosis. However, the interrelation between PMA and platelet activation, systemic inflammation and myocardial injury, with clinical characteristics in the setting of non-ST elevation acute coronary syndrome (NSTEMI-ACS) has not been previously investigated. This study sought to establish whether PMA level could be a new risk factor in patients with NSTEMI-ACS and tried to show the relationship between inflammation and PMA formation which may lead to myocardial injury. We also assessed the association between these markers and clinical events in patients with NSTEMI-ACS and discuss their roles in the development of ACS.

Methods

Study Patients

From April 2004 to April 2005, we studied 127 patients with angiographically verified coronary artery disease—69 with ACS and 58 with stable angina pectoris (SAP)—who had effort-induced angina (Canadian Cardiovascular Society functional class I and II) without any worsening of symptoms within 6 months. Patients who had NSTEMI-ACS were included if the current diagnosis was unstable angina or non-ST-elevation MI based on typical electrocardiographic changes (ST-T segment depression and/or T-wave inversion) and/or elevation of troponin I. Forty-six age- and gender-matched patients presenting with recurrent chest pain, who had normal coronary arteries confirmed by angiography, were selected as control. All subjects gave written informed consent to the study protocol, which was approved by the

Ethics Committee of the Second Affiliated Hospital of Zhejiang University. Patients with Prinzmetal's angina and angina secondary to extracardiac conditions, as well as patients with renal disease, hepatic disease, inflammatory disease, hematologic disorders, autoimmune disorders, and those on treatment with immunosuppressive agents were also excluded.

Blood Collection and Laboratory Test

Whole blood from all patients was obtained immediately after admission and was drawn with a 21-G needle and a light tourniquet, and then gently added to the collection tube containing buffered sodium citrate (BD Vacuum Becton-Dickinson, Franklin Lakes, N.J., USA). The protocol was set by our laboratory, and instrument setups, adjustments, and valid controls were performed as previously described.¹¹ The sample was analyzed by flow cytometry. Data analysis was performed with CellQuest software (Becton-Dickinson). Platelet-monocyte aggregates were defined as monocytes positive (CD14-PE) for platelet binding (CD42a-FITC), and values are expressed as the percentage of aggregated monocytes.

Venous blood samples from the patients were obtained on admission: nine parts freshly obtained blood was mixed with one sodium citrate (BD Vacutainers, Becton Dickinson). Platelet-free plasma was obtained by centrifugation 1500 G for 10 min for determination of soluble P-selectin (sP-selectin), soluble CD40L (sCD40L), IL-6. Other freshly obtained blood was immediately added to the collection tube with no additive (BD Vacutainers). Serum was prepared for measurement of CRP, cardiac troponin-I (cTnI), and so forth. Serum and plasma specimens were frozen and stored at -70°C until analysis. All assays were performed according to the manufacturer's instructions and analyzed by the following methods: sP-selectin, sCD40L, and IL-6 were measured simultaneously using a beads-based multiplex assay (human cardiovascular 7plex flowcytomix, purchased from Bender MedSystems Co. Ltd., Burlingame, Calif., USA). C-reactive protein was determined by a highly sensitive, latex-enhanced, turbidimetric immunoassay with a low detection limit of 0.25 mg/l (IMMAGE, BeckmanCoulter; Reagent from Orion Diagn Co. Ltd., Vantaa, Finland). Cardiac troponin I was measured by chemiluminescence immunoassay (ACCESS2 and Reagent AccuTnI from Beckman Coulter) and the results were reported as nanograms per milliliter, with interpretation of cutoff values (0.06 ng/ml) based on the manufacturer's recommendations (CV < 10%), and a low detection limit of 0.01 ng/ml.

Clinical Data and Cardiac Events

The clinical data collected for this study included history, physical examination, presence or absence and

characteristics of chest pain, laboratory data, electrocardiographic (ECG) and angiographic findings, and final diagnosis. The primary endpoint of the study was major cardiac events defined as the combination of cardiac death and nonfatal myocardial (re-)infarction. Myocardial infarction was defined according to the current guidelines.¹² Follow-up was performed in-hospital by record review.

Statistical Analysis

Continuous variables are expressed as mean $\pm$ standard deviation and were compared using unpaired Student's *t*-tests or one-way analysis of variance (ANOVA) for parameter data and the Kruskal-Wallis test for non-parametric data. Discontinuous variables were compared using the chi-square test. Correlation between the continuous variables was evaluated by Spearman's *r*, when appropriate, and logistic regression was also used to analyze the relationship between these indicators and ACS. Two tailed *p* values <0.05 were considered statistically significant. All calculations were performed using the Standard Package for Social Science 12.0 (SPSS, Inc., Chicago, Ill., USA).

Results

Demographic and Clinical Characteristic Data

Baseline clinical characteristics of the study patients are listed in Table 1. All patients with SAP and NSTEMI-ACS were using various combinations of aspirin, nitrates, calcium antagonists, and/or beta blocker; of the control patients, 41% also used aspirin or nitrates in less than 1 week; 43% of patients with SAP, 55% of patients with NSTEMI-ACS, and 23% of the control were receiving long-term therapy with statins according to National Cholesterol Education Program-Adult Treatment Panel (NCEP-ATP) III guidelines.¹³ In all patients with NSTEMI-ACS, therapy with clopidogrel, aspirin, and low-molecular weight heparin was introduced immediately after blood sampling on admission. If anginal attack was not controlled by these medications, patients were scheduled for emergency coronary revascularization. No statistically significant differences were evident between the SAP and NSTEMI-ACS groups with respect to age, gender, and other traditional atherosclerotic risk factors. Of the study patients with NSTEMI-ACS, 25 had troponin elevation and 44 had normal troponin; their clinical characteristics are summarized in Table 2. There were no statistically significant differences between the two groups with regard to age, gender, creatinine, and other traditional atherosclerotic risk factors, including number of vessels disease ($p > 0.05$), but ST-segment depression was statistically significant more often in patients with troponin elevation than in those with normal troponin.

Levels of Platelet Activation, System Inflammation, and Myocardial Injury Markers

Patients with NSTEMI-ACS showed a high level of PMA ($35.7 \pm 11.5\%$) compared with patients with SAP and control patients (22.8 ± 5.5 and $12.3 \pm 3.3\%$, respectively, $p < 0.01$). Patients who had NSTEMI-ACS also had significantly higher concentrations of sCD40L, sP-selectin, IL-6, and CRP compared with the SAP and control groups. However, the level of platelet activation related to biomarkers such as sCD40L and sP-selectin showed no difference between the SAP and control groups (Table 1). Levels of PMA, sP-selectin, sCD40L, IL-6, and CRP in patients with troponin elevation were significantly higher than those in patients with normal troponin ($p < 0.05$) (Table 2).

Relationship among Platelet-Monocyte Aggregates, C-Reactive Protein, and Cardiac Troponin-I in Patients with Non-ST Elevation Acute Coronary Syndromes

There was a high level of PMA associated with CRP elevation (35.5 ± 9.97 vs. 29.1 ± 4.99 ; $p = 0.002$), cTnI elevation (40.0 ± 10.9 vs. 30.6 ± 5.80 ; $p = 0.001$), and ST-segment depression (34.9 ± 10.5 vs. 30.6 ± 5.78 ; $p = 0.040$). We found no correlation between age, gender, and PMA, and no association between clinical data (including number of coronary lesions) and PMA ($p > 0.05$) (Table 3). There was a positive relationship between PMA and CRP ($r = 0.628$, $p < 0.001$, Fig. 1), and cardiac troponin I ($r = 0.557$, $p < 0.001$; Fig. 2) in patients with NSTEMI-ACS.

Predictive Value of These Markers for in-Hospital Clinical Cardiac Events

In all, 13 cardiac events (including cardiac death/nonfatal new MI) in 69 patients with NSTEMI-ACS were recorded and reviewed in hospital. To elucidate the

FIG. 1 Correlation between C-reactive protein (CRP) and platelet-monocyte aggregates (PMAs) in patients with non-ST elevation acute coronary syndromes.

TABLE 1 Baseline characteristics of the study subjects

	Control (n = 46)	SAP (n = 58)	NSTE-ACS (n = 69)
Age (years)	63.7 ± 9.2	65.1 ± 8.4	65.8 ± 10.2
Sex (male) %	56.5 (26)	65.5 (38)	63.8 (44)
Diabetes %	13.0 (6)	18.5 (10)	17.4 (12)
Hypertension %	39.1 (18)	46.6 (27)	42.0 (29)
Hyperlipidemia %	56.5 (26)	60.3 (35)	59.4 (41)
sCD40L (ng/ml)	4.3 ± 3.3	5.4 ± 4.3	8.3 ± 4.8 ^{a,b}
sP-selectin (ng/ml)	38.2 ± 16.6	46.5 ± 12.6	80.7 ± 56.3 ^{a,b}
IL-6 (pg/ml)	29.8 ± 28.0	98.4 ± 80.1 ^a	215.4 ± 119.6 ^a
CRP (mg/l)	0.80 ± 0.49	1.49 ± 1.3 ^a	5.01 ± 5.21 ^{a,b}
cTnI (ng/ml)	0.011 ± 0.005	0.023 ± 0.012	0.188 ± 0.143 ^a
PMA (%)	12.3 ± 3.3	22.8 ± 5.5 ^a	35.7 ± 11.5 ^{a,b}

Values are mean ± standard deviation, or % (no.) of patients.

^a p < 0.01 vs. control.

^b p < 0.01 vs. SAP.

Abbreviations: SAP = stable angina pectoris, NSTE-ACS = non-ST elevation acute coronary syndrome, IL = inter leukin, CRP = C-reactive protein, cTnI = cardiac troponin I, PMA = platelet monocyte aggregates.

TABLE 2 Clinical characteristics of the patients with non-ST elevation acute coronary syndrome

	cTnI <0.06 ng/ml (n = 44)	cTnI ≥ 0.06 ng/ml (n = 25)	p Value
Age (years)	64.9 ± 8.3	68.2 ± 19.5	0.51
Sex (male) %	65.9 (25)	76.0 (19)	0.50
Diabetes %	15.9 (7)	20.0 (5)	0.83
Hypertension %	43.2 (19)	40.0 (10)	0.64
Hyperlipidemia %	59.1 (26)	60.0 (15)	0.89
ST-segment depression	45.4 (20)	60.0 (15)	0.036
Triple-vessel disease %	34.1 (15)	40 (10)	0.60
sCD40L (ng/ml)	8.12 ± 4.33	8.58 ± 5.96	0.048
sP-sel (ng/ml)	76.5 ± 12.1	85.5 ± 21.6	0.025
IL-6 (pg/ml)	167.0 ± 103.7	275.3 ± 136.6	0.001
CRP (mg/l)	2.78 ± 1.51	7.07 ± 3.26	0.001
PMA (%)	30.6 ± 5.80	40.0 ± 10.9	0.001

Data are mean value ± standard deviation, or % (no.) of patients.

Abbreviation as in Table 1.

FIG. 2 Relationship between troponin I (cTnI) and platelet-monocyte aggregates (PMAs) in patients with non-ST elevation acute coronary syndromes.

potential predictive value by markers of PMA, CRP, and cTnI for clinical cardiac events, we divided the study participants based on concentrations of markers above versus equal to or below the following thresholds: PMA, 22.2% (99th percentile of control); cTnI, 0.06 ng/ml;¹⁴ and CRP, 3mg/l.¹⁵ As the variables of age and gender were stratified and adjusted to intrinsic individual variables, logistic regression analysis revealed that PMA, CRP, and cTnI were strongly related to the risk of cardiac events, and their odds ratio (OR) values and 95% confidence interval (CI) were 3.639 (95% CI 1.511–5.862, p = 0.002), 2.235 (1.392–4.268, p = 0.011), and 2.312 (1.324–4.580, p = 0.046), respectively.

Discussion

The main finding of our study was the documentation, for peripheral blood samples, of an increase in

TABLE 3 Relationship of platelet monocyte aggregate valves, as a continuous variable, with traditional atherosclerotic risk factors and biochemical markers in patients with non-ST elevation acute coronary syndrome

	PMA(%)	p Value
Age (>65 years)		0.802
Yes	33.0 ± 9.02	
No	32.5 ± 8.48	
Gender		0.596
Men	33.2 ± 9.67	
Women	32.1 ± 7.01	
Diabetes		0.325
Yes	33.3 ± 8.96	
No	30.6 ± 8.01	
Hypertension		0.620
Yes	32.2 ± 9.53	
No	33.2 ± 8.25	
Hyperlipidemia		0.395
Yes	33.6 ± 8.11	
No	31.7 ± 9.66	
ST-segment depression		0.040
Yes	34.9 ± 10.5	
No	30.6 ± 5.78	
Triple-vessel disease		0.395
Yes	34.3 ± 11.1	
No	31.9 ± 7.16	
CRP (≥3 mg/l)		0.002
Yes	35.5 ± 9.97	
No	29.1 ± 4.99	
cTnI (≥0.06 ng/ml)		0.001
Yes	40.0 ± 10.9	
No	30.6 ± 5.80	

Abbreviations as in Table 1.

markers of platelet activation, systemic inflammation, and myocardial injury linked to patients with NEST-ACS. Especially augmentation of the PMA was more pronounced in patients with troponin elevation, and these markers can predict the risk of future cardiac events in patients with NEST-ACS. Recent discoveries have led investigators to believe that PMA bridge thrombosis and inflammation,¹⁰ which further increase the instability of plaques and aggravate the clinical symptoms of patients with ACS. Several studies have indicated that higher PMA levels are associated with the presence of atherosclerotic disease and the development of ACS.⁷⁻⁹ Our data agree with this finding.

Previous Studies

The study by Furman *et al.* first showed that circulating PMA are an early marker of acute MI;⁸ however, markers of system inflammation and platelet activation were not measured. Our study found that levels of sP-selectin, sCD40L, PMA, IL-6, and CRP were increased in subsequent events from stable to unstable angine pectoris and were significantly elevated in patients with NSTEMI (troponin elevation). Such results indicate that

patients with SAP had a lesser extent of platelet activation and systemic inflammation than patients with ACS, suggesting that high levels of platelet activation may be an important phenomenon in the pathogenesis and clinical outcome of ACS, with a better reflection on plaque instability and ongoing vascular thrombosis and inflammation.

Markers of Platelet Activation, Inflammatory Mediators, and Troponin-I

Our data show that higher levels of IL-6, CRP, sP-selectin, sCD40L, and PMA, and the presence of ST-segment depression in patients with troponin elevation, compared with those with normal troponin, also suggest that soluble and local markers of platelet activation and inflammatory activity may be directly associated to myocardial ischemia and myocardial injury. The surprising finding in the present study is that there was a positive relationship among PMA, CRP, and cTnI in patients with NEST-ACS. We also found that PMA were associated with CRP elevation (35.5 ± 9.97 vs. 29.1 ± 4.99 , $p = 0.002$), cTnI elevation (40.0 ± 10.9 vs. 30.6 ± 5.80 , $p = 0.001$), and ST-segment depression (34.9 ± 10.5 vs. 30.6 ± 5.78 , $p = 0.040$). The study confirms that PMA may provide clues regarding the extent of basal platelet activation and may also predict the severity of the inflammatory response in patients with NSTEMI-ACS. As a result, we conclude that levels of PMA can be increased by inflammation, and that higher troponin-I concentrations are a consequence of increased inflammation and platelets activity in patients with NSTEMI-ACS.

Association between Platelet-Monocyte Aggregates, C-Reactive Protein, and Cardiac Troponin-I with in-Hospital Cardiac Events

In recent years, the arterial inflammation hypothesis has focused attention on explaining the pathogenesis and progression of atherosclerosis as well as of acute coronary events.¹⁶ Several studies have shown the prognostic value of CRP in ACS.¹⁷⁻¹⁹ The mechanism behind inflammation marker elevation in patients with worse prognosis is not clear. We first demonstrated that levels of PMA were significantly associated with CRP, which are inflammatory markers in atherosclerotic development and plaque instability. Furthermore, PMA levels were associated with cTnI, which are an indicator of myocardial injury associated with vascular embolization caused by thrombosis. In addition, our logistic regression analysis demonstrated that high levels of PMA, CRP, and cTnI each showed an increased risk for ACS. Ray's study demonstrated that increased levels of PMA may predict patients to be at risk for troponin elevation following PCI and can identify those most likely to benefit from abciximab treatment; this further confirmed our hypothesis that PMA can be a possible clinically therapeutic target

for ACS.²⁰ We conclude that PMA may be involved in myocardial injury development in patients with NSTEMI-ACS.

Clinical and Research Implications

Platelet activation is more common and more clinically relevant with regard to ACS, PCI, and coronary artery bypass surgery. We found that higher levels of PMA correlated with other markers of CRP and troponin to show an increased risk for future cardiac events, but a direct comparison with troponin levels would be necessary to establish the true diagnostic utility of this measurement. Its use is possibly more important as a marker for risk stratification in patients with acute MI. Perhaps equally important, the PMA represent a potential new therapeutic target for limiting thrombotic and inflammatory responses in ACS. Since there is a close relationship among platelet activation, systemic inflammation, and myocardial injury, which can provide overall information about the pathophysiologic state within the coronary artery and ischemic outcome, we envision a panel of inflammatory mediators, together with markers of platelet activation and myocyte necrosis, as part of a multimarker cassette that will unravel the pathophysiologic mechanism of the ACS in a given patient, direct risk stratification, and determine the most effective therapeutic interventions.

Study Limitations

This study documents the concomitant elevation of inflammation mediators, makers of platelet activation and myocardial injury, as well as significant correlations in the course of NSTEMI-ACS, using a single blood level drawn shortly after admission. It is also only a small clinical observational study with major differences between groups. Such associations need to be evaluated in a larger population to determine potential clinical significance. It is likely that serially determined blood concentrations would yield more information regarding changes of these markers over time.

Conclusions

The levels of PMA and system inflammation were significantly increased in patients with NSTEMI-ACS, especially in those with troponin elevation; this is strongly related to the risk of in-hospital cardiac events. Evaluation of inflammation, platelet activation, and myocardial injury together may provide important information additional to current laboratory data for defining high-risk patients with NSTEMI-ACS and reveal new insights into ACS as an example of exacerbation of atherosclerosis. Future studies should be directed at understanding the role of PMA in vascular disease, which cutoffs could

be useful for diagnosis, risk stratification, and making therapeutic decisions to inhibit their formation.

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