Int J Clin Exp Med 2017;10(9):13616-13624
www.ijcem.com /ISSN:1940-5901/IJCEM0052741

Original Article

Changes in microparticles in intracoronary thrombi and peripheral arterial blood in patients with ST-segment elevation myocardial infarction

Tieci Yi[1], Jizhao Li[2,3], Lin Xue[1], Yanjun Gong[1], Lemin Zheng[2], Jianping Li[1], Yong Huo[1]

[1]Department of Cardiology, Peking University First Hospital, Beijing 100038, China; [2]School of Basic Medical Sciences, Peking University Health Science Center, Beijing 100191, China; [3]Beijing Unionluck Biological Technology Co., Ltd., Beijing 100142, China

Received March 12, 2017; Accepted June 20, 2017; Epub September 15, 2017; Published September 30, 2017

Abstract: Background: Acute ST-segment elevation myocardial infarction (STEMI) is one of the greatest threats to human health. Intracoronary thrombosis is the key pathophysiological process of STEMI. Microparticles (MPs) are closely related to thrombosis. However, the results of research on the relationship of MPs to myocardial infarction remain controversial. We assessed the systemic and intracoronary levels of MPs from cells of different origins in patients with STEMI and explored the possible role of MPs in the progression of intracoronary thrombosis. Methods: The study included 32 patients with STEMI and 10 control patients. Arterial blood was collected from both groups, and intracoronary thrombus samples were obtained from the STEMI group. The levels of MPs derived from endothelial cells, platelets, and leukocytes (positive for CD144, CD41b, and CD45, respectively) were determined by flow cytometry. Results: In the peripheral arterial blood, endothelial-derived $CD144^+$ MPs were increased in patients with STEMI, while platelet- and leukocyte-derived MPs showed no significant differences between patients and controls. In patients with STEMI, platelet-derived $CD41^+$ MPs were significantly higher in the intracoronary aspirates than in the peripheral arterialblood, butendothelial- and leukocyte-derived MPs showed no such differences. Conclusions: Changes in MPs in the intracoronary thrombi and peripheral blood in patients with STEMI suggest that MPs may play an important role in the development of intracoronary thrombosis and myocardial infarction. Further studies are needed to better understand the specific role of MPs in myocardial infarction.

Keywords: Microparticles, ST-segment elevation myocardial infarction, intracoronary thrombosis, peripheral arterial blood

Introduction

Acute ST-segment elevation myocardial infarction (STEMI) is currently one of the most troublesome public health problems. Inflammation, endothelial dysfunction, and intracoronary thrombosis are pivotal processes of STEMI.

Circulating microparticles (MPs) are membrane vesicles that have been shed as a result of apoptosis or activation of several cell types in response to various stimuli. They are present in low concentrations in normal plasma. However, increased levels of MPs are generated under various conditions such as platelet activation, direct vascular endothelial damage, thrombin activity on the cell surface, and C5b-9 activation. Studies have shown that MPs participate in the processes of inflammation, vascular dysfunction, coagulation, and thrombosis. Additionally, the levels of procoagulant MPs are increased in patients with acute coronary syndrome (ACS) [1-4]. During the past few years, several studies have focused on changes in MPs within infarct-related arteries in patients with STEMI [5-7]. However, the results of these studies are controversial. In the present study, we measured the levels of MPs in the culprit vessel and peripheral arterial plasma in 32 Chinese patients with STEMI and compared these levels with those in the peripheral blood of 10 patients without coronary heart disease (CHD) to further explore the role of MPs in STEMI.

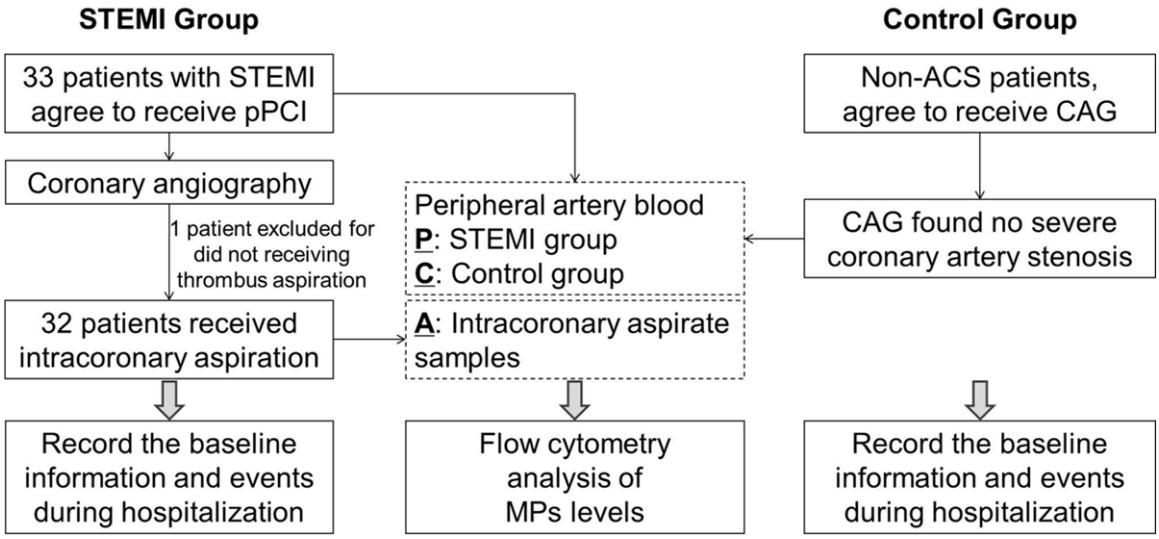

Figure 1. Trial profile. STEMI, ST-segment elevation myocardial infarction; CAG, coronary angiography; pPCI, primary percutaneous coronary intervention; MP, microparticles; ACS, acute coronary syndrome.

Patients and methods

Study population

We consecutively recruited patients with STEMI who received primary percutaneous coronary intervention (PCI) from October 2012 to March 2013 at Peking University First Hospital. STEMI was defined according to the criteria of the World Health Organization [8]. Patients with indications for primary PCI underwent aspiration using a manual aspiration catheter. Patients with chronic kidney disease (serum creatinine concentration of >2.0 mg/dL), a history of liver disease, recent (within 3 months) major trauma, arterial or venous thromboembolic disease, active infection, and/or a history of inflammatory or connective tissue disorders were excluded. Patients who received thrombolysis before PCI were also excluded. During the same period of time, 10 patients without severe coronary artery stenosis (no coronary artery showed narrowing of >50%), as proven by coronary angiography, were recruited as controls.

The study protocol was approved by the Ethics Committee of Peking University First Hospital and was performed in compliance with Food and Drug Administration guidelines. Written informed consent was obtained from each patient after the procedure had been fully explained.

Study procedure and blood sampling

All patients with STEMI were treated according to current guidelines. Primary PCI was performed by an experienced team. A loading dose of 300 mg of aspirin and 600 mg of clopidogrel was given to patients before the procedure. The doses of heparin and tirofiban were at the operator's discretion. After the sheath was inserted into the femoral or radial artery, a first 5-mL blood sample was obtained from a peripheral artery through the vascular sheath. When the guiding catheter had arrived at the predetermined position, an aspiration catheter (6 F, 145 cm; Invatec Italia S.r.l., Castel Mella, Italy) was advanced through the culprit lesion, and aspiration was performed while withdrawing the aspiration catheter. A 5-mL sample of aspirated atherothrombotic material was collected. Balloon angioplasty and stent implantation were then performed. All in-hospital clinical events were recorded. In the control group, only a 5-mL peripheral arterial blood sample from the punctured artery was collected. All samples were drawn into evacuated blood collection tubes with sodium citrate (0.109 M). Platelet-rich plasma was obtained as a supernatant after centrifugation at 1500×*g* for 15 minutes at room temperature. Platelet-poor plasma was then immediately obtained by a second centrifugation of the blood fraction at 13,000×*g* for 2 minutes. The platelet-poor plasma was then

Table 1. Demographic characteristics of study population

	STEMI (n=32)	Control (n=10)	*P* value
Males, n (%)	27 (84.4)	6 (60)	0.18
Age, years (mean ± SD)	62.1±13.2	59.6±8.3	0.58
Coronary heart disease			
OMI, n (%)	3 (9.4)	0 (0)	1.00
PCI, n (%)	5 (15.6)	0 (0)	0.32
CABG, n (%)	1 (3.1)	0 (0)	1.00
Stroke, n (%)	6 (18.8)	0 (0)	0.31
Diabetes mellitus, n (%)	12 (37.5)	2 (20.0)	0.45
Hypertension, n (%)	20 (62.5)	7 (70.0)	1.00
Dyslipidemia, n (%)	17 (53.1)	3 (30.0)	0.28
Current smokers, n (%)	14 (43.8)	3 (30.0)	0.49
Family history, n (%)	19 (59.4)	6 (60.0)	1.00
Drugs taken before admission			
Aspirin, n (%)	4 (12.5)	0 (0)	0.56
Clopidegrel, n (%)	1 (3.1)	0 (0)	1.00
ACEI/ARB, n (%)	8 (25)	4 (40)	0.43
β-Blocker, n (%)	3 (9.4)	1 (10)	1.00
Statins, n (%)	3 (9.4)	0 (0)	1.00
Total ischemic time, h (median, IQR)	4.50 (2.63, 8.83)	-	-

A *P* value of <0.05 was considered statistically significant. STEMI, ST-segment elevation myocardial infarction; SD, standard deviation; IQR, interquartile range; OMI, old myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; ACEI, angiotensin-converting enzyme inhibitor; ARB, adrenergic receptor blocker.

stored in a frozen state at -80°C. The hemoglobin level (g/L) and white blood cell count (n/mL) were measured at admission.

Microparticles assay

The frozen samples were thawed for 15 minutes at 37°C prior to analysis. A 50-μL sample of platelet-poor plasma was then co-incubated for 20 minutes at room temperature with 4 μL of phycoerythrin-conjugated monoclonal antibody toCD144 (BD560410), 4 μL of PerCp-Cy5.5-conjugated monoclonal antibody toCD45 (Biolegend 304028), and 4 μL of fluorescein isothiocyanate-conjugated monoclonal antibody toCD41b (BD 555469). MPs were then counted with a flow cytometer (Gallios Flow Cytometer; Beckman Coulter, Brea, CA). Forward and side scatter were set as triggers as determined by the scatter properties of Megamix beads (Biocytex, Marseille, France). In the present study, endothelial-derived MPs (EMPs), platelet-derived MPs (PMPs), and leukocyte-derived MPs (LMPs) were defined as MPs positively labeled with CD144, CD41b, and CD45, respectively.

Statistical analysis

The Shapiro-Wilk test was performed to determine whether continuous data were normally distributed. Normally distributed continuous data are presented as mean ± standard deviation, and non-normally distributed continuous variables are presented as median and interquartile range. However, to allow for the use of parametric techniques, logarithmic transformation was used to approximate a normal distribution of non-normally distributed continuous variables. Differences in normally distributed continuous variables were analyzed using the test, and non-normally distributed continuous variables were analyzed using the Mann-Whitney U-test. Differences in categorical variables were analyzed using the chi-square test. A two-tailed *P* value of <0.05 was considered statistically significant. All statistical analyses were performed with SPSS version 20.0 (IBM Corp., Armonk, NY).

Results

Baseline characteristics

As shown in **Figure 1**, 33 patients with STEMI and 10 control patients were recruited. One patient was excluded from the STEMI group because intracoronary aspiration was not performed. Thus, 32 patients with STEMI were included in the final analysis. The baseline characteristics of both groups are listed in **Table 1**. There were no significant differences between the two groups in age, sex, cardiovascular disease history (history of myocardial infarction, coronary artery bypass grafting, PCI, or stroke), cardiovascular disease risk factors (smoking, diabetes, hypertension, dyslipidemia, and family history), or drugs taken before the onset of STEMI. Additionally, as shown in **Table 2**, both groups had similar blood pres-

Table 2. Clinical characteristics of study population before primary percutaneous coronary intervention

	STEMI (n=32)	Control (n=10)	*P* value
HR, bpm	78.6±22.4	65.8±6.8	0.09
SBP, mmHg	126.6±31.6	143.0±19.6	0.13
DBP, mmHg	78.0±21.1	83.0±9.4	0.47
Creatinine, umol/L	79.2±23.9	72.9±17.1	0.44
BUN, mmol/L	5.78±1.93	6.09±2.00	0.67
Hemoglobin, g/L	144.8±30.5	133.8±13.6	0.30
Leukocytes, $\times 10^9$/L	8.67±3.13	5.61±1.15	0.00
Platelet, $\times 10^9$/L	182.4±64.6	188.2±56.7	0.81
Glucose, mmol/L	9.49±4.05	6.77±1.98	0.05
BNP, pg/mL	89.5±81.7	55.2±26.5	0.07
Blood lipid			
Triglyceride, mmol/L	1.72±0.94	1.68±1.48	0.92
TCHO, mmol/L	4.64±1.38	4.21±1.16	0.38
HDL-c, mmol/L	1.01±0.31	1.09±0.24	0.48
LDL-c, mmol/L	2.98±0.90	2.32±0.70	0.04
FIB, g/L	2.75±0.93	2.77±0.64	0.95
D-Dimmer, mg/L	0.24±0.51	0.16±0.24	0.68

Data are expressed as mean ± standard deviation. A *P* value of <0.05 was considered statistically significant. STEMI, ST-segment elevation myocardial infarction; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; BUN, blood urea nitrogen; BNP, brain natriuretic peptide; TCHO, total cholesterol; HDL-c, high-density lipoproteincholesterol; LDL-c, low-density lipoproteincholesterol; FIB, fibrinogen.

sures, hemoglobin concentrations, platelet counts, and serum creatinine concentrations. Consistent with the results of previous studies [9-11], the levels of serum glucose, leukocytes, and low-density lipoproteincholesterol were significantly higher in patients with STEMI at admission. The heart rate and brain natriuretic peptide concentration tended to be higher in the STEMI than control group.

MP levels

The levels of MPs derived from each cell origin in the peripheral arterial blood and intracoronary aspirated material are shown in **Table 3** and **Figure 2**.

The level of $CD144^+$ EMPs in both the peripheral arterial blood and intracoronary thrombotic material was significantly higher in patients with STEMI than in controls. However, we observed no significant difference in the level of $CD144^+$ EMPs between the peripheral arterial blood and intracoronary aspirated material in patients with STEMI.

The level of $CD41b^+$ PMPs in the peripheral arterial blood was not significantly different between patients with STEMI and controls. However, $CD41b^+$ PMPs were significantly higher in the intracoronary aspirated material than in the peripheral arterial blood of patients with STEMI.

The levels of $CD45^+$ LMPs were quite similar among the three groups of samples. $CD45^+$ LMPs were highest in the aspirated atherothrombotic material and lowest in the peripheral arterial blood of patients with STEMI, but there was no statistically significant difference among them.

Discussion

Previous studies have suggested a potential role of circulating MPs in endothelial dysfunction, platelet activation, coagulation, and thrombosis [12-14], but no consensus has been reached regarding the relationship between MPs and myocardial infarction. The level of MPs in the intracoronary thrombosis has rarely been studied. In addition, the specific roles of distinct populations of circulating MPs are unknown. The main results of our study are as follows.

$CD144^+$ EMPs were elevated in the circulation of patients with STEMI

EMPs released from activated or apoptotic vascular endothelial cells (ECs) are an important marker of endothelial dysfunction. Previous studies have shown that EMPs are highly procoagulant and closely involved in the process of thrombosis. First, EMPs carry ultra-large von Willebrand factor, stimulate platelet aggregation, and improve the stability of platelet aggregation [15]. Additionally, EMPs can increase the expression of tissue factor on monocytes and induce tissue factor-dependent procoagulant activity [16]. At the same time, EMPs are the carrier of tissue factor in the circulation [17], which has been proven essential for the sustainable development of a fibrin thrombus [18]. Moreover, EMPs are an important source of phosphatidylserine, which acts as an indispensable membrane surface component for coagulation complex formation [13]. EMPs

Table 3. Levels of microparticle

Microparticles (n/μL)	Control (C) (n=10)	STEMI (n=32)		*P* value P VS C#	*P* value A VS P$
		Peripheral arterial blood (P)	Aspirate material (A)		
CD144+ EMPs※	143.0 (110.5, 196.3)	282.5 (135.0, 395.0)	244.5 (118.8, 557.3)	0.039	0.475
CD41b+ PMPs※	6198.0 (2998.8, 7333.8)	3507.5 (2647.0, 7035.3)	7491.0 (4026.3, 11230.3)	0.423	0.006
CD45+ LMPs※	874.5 (403.5, 1045.0)	747.5 (578.3, 955.3)	822.0 (700.0, 978.5)	0.652	0.194

※Data are expressed as median (interquartile range); #Tested with the Mann-Whitney U test; $Tested with the paired t-test. A *P* value of <0.05 was considered statistically significant. EMPs, endothelial-derived microparticles; PMPs, platelet-derived microparticles; LMPs: leukocyte-derived microparticles.

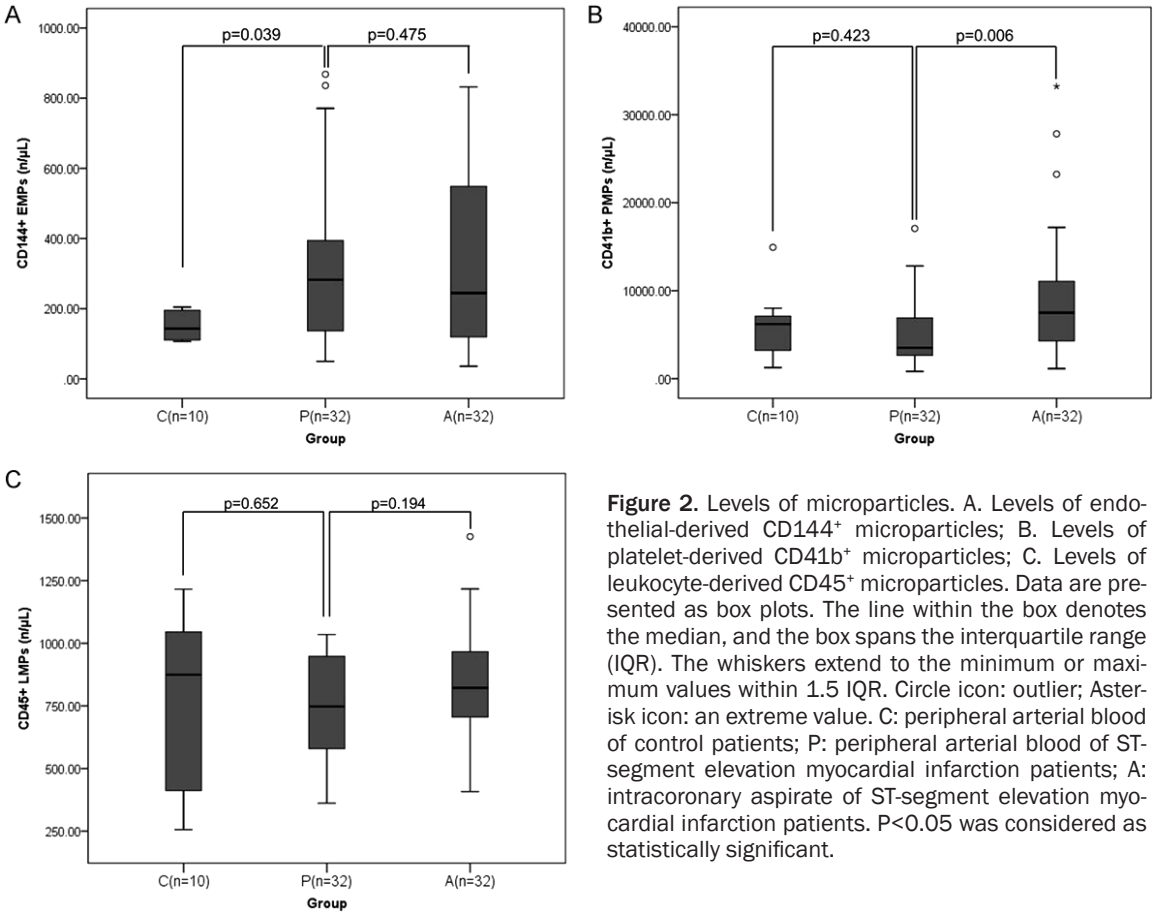

Figure 2. Levels of microparticles. A. Levels of endothelial-derived CD144+ microparticles; B. Levels of platelet-derived CD41b+ microparticles; C. Levels of leukocyte-derived CD45+ microparticles. Data are presented as box plots. The line within the box denotes the median, and the box spans the interquartile range (IQR). The whiskers extend to the minimum or maximum values within 1.5 IQR. Circle icon: outlier; Asterisk icon: an extreme value. C: peripheral arterial blood of control patients; P: peripheral arterial blood of ST-segment elevation myocardial infarction patients; A: intracoronary aspirate of ST-segment elevation myocardial infarction patients. P<0.05 was considered as statistically significant.

clearly have significant contributions to the process of thrombosis.

However, the effect of EMPs on the development of STEMI remains unclear. Several studies have focused on the changes in EMP levels in patients with CHD and ACS. These studies have shown that EMPs are significantly higher in patients with CHD than in patients with no history of vascular occlusive disorders. CD31+ EMPs are also higher in patients with ACS than in patients with stable angina and are associated with the development of high-risk angiographic lesions including eccentric type II lesions, multiple irregular lesions, and lesions with thrombi [1, 3]. In agreement with these results, we found that the level of circulating CD144+ EMPs was significantly higher in patients with STEMI than in patients with normal coronary arteries. These results are consistent with our previous knowledge that EC dysfunction is a basic pathogenetic factor in STEMI. Considering the procoagulant capacity of EMPs, they might be an important contributor to the systemic hypercoagulable states that are present in patients at risk of STEMI.

In the present study, we found no significant difference in the CD144+ EMP levels between the intracoronary aspirates and peripheral arte-

Table 4. Changes in levels of MPs in patients with STEMI in various studies

		Peripheral Blood*	Intracoronary Thrombus¶
EMPs	$CD31^+$ EMPs [5]	→	↑
	$CD42b^+$ EMPs [5]	↑	→
	$CD31^+/CD42^-$ EMPs [6]		↑
	$CD105^+$ EMPs [7]		↑
	CD 144^+ EMPs	↑	→
PMPs	$CD146^+$ PMPs [5]	→	↗ §1
	$CD31^+/CD42^+$ PMPs [6]		↑
	$CD42b^+$ PMPs [7]		↗ §2
	$CD41b^+$ PMPs	→	↑
LMPs	$CD11a^+$ LMPs [5]	→	→
	$CD11a^+$ LMPs [7]		↑
	$CD45^+$ LMPs	→	→

*Changes in MP levels in the peripheral blood of patients with STEMI compared with controls; ¶Changes in MP levels in the intracoronary aspirates compared with peripheral blood in patients with STEMI; §1The increase in $CD146^+$ PMPs in the intracoronary thrombus is on the borderline of statistical significance (P=0.052); §2The increase in $CD42b^+$ PMPs in the intracoronary thrombus is on the borderline of statistical significance (P=0.052). EMPs, endothelial-derived microparticles; PMPs, platelet-derived microparticles; LMPs, leukocyte-derived microparticles.

rial blood of patients with STEMI. As shown in **Table 4**, the changes in EMPs seem to differ among studies. Min et al. [5] found that $CD42b^+$ EMPs were elevated in the peripheral blood of patients with STEMI but were not further increased in the intracoronary thrombus, while $CD31^+$ EMPs were significantly elevated in the intracoronary aspirates. Porto et al. [6] reached similar results for $CD31^+$ EMPs. Morel et al. [7] also found that $CD105^+$ EMPs were increased in the occluded coronary artery. One of the reasons for these inconsistent conclusions is that ECs in different states can release phenotypically and quantitatively distinct EMPs. Previous studies have proven that EMPs released by apoptotic ECs are mainly positive for constitutive markers such as CD31. In contrast, during EC activation, inducible markers are markedly increased on EMPs [19]. Because ECs are systemically activated in patients with STEMI, it is reasonable to presume that EMPs positive for inducible markers (CD144, CD42b) are increased equally in both the peripheral blood and intracoronary aspirated material, while EMPs positive for constitutive markers (CD31, CD105) are only increased in the intracoronary samples, indicating apoptosis of ECs in the obstructed artery. However, the clinical significance of a certain type of EMPs remains unclear.

PMPs were elevated in aspirates from the culprit coronary artery

PMPs, which are a result of platelet activation and/or apoptosis and represent the largest MP population in the circulation, play a critical role in the processes of coagulation and thrombosis. Circulating PMPs are associated with atherothrombotic events in patients with CHD [20]. PMPs bind to the forming thrombus, specifically to the fibrin, and promote coagulation [21]. PMPs can propagate thrombin and fibrin production [22]. The PMP level was correlated with the thrombus weight and tissue factor activity in an experimental mouse model of venous thrombosis [23]. Like other MPs, PMPs can also provide a membrane surface for the coagulation process.

In the present study, the levels of $CD41b^+$ PMPs were significantly higher in the material aspirated from culprit coronary arteries than in the peripheral arterial blood of patients with STEMI. Other studies have obtained similar results (see **Table 3**) [5-7]. Moreover, Porto et al. [6] reported that the intracoronary $CD31^+/CD42^+$ PMP level was positively related to the thrombus score and corrected Thrombolysis in Myocardial Infraction frame count and inversely related to the myocardial blush grade and Quantitative Blush Evaluator score. These findings further verify that locally elevated PMPs may have an important role in the dynamic process of coronary atherothrombosis in patients with STEMI.

Furthermore, as shown in **Table 3**, all studies showed that the levels of PMPs in the peripheral blood of patients with STEMI were similar to those in the control patients. This suggests that the locally elevated PMPs in the intracoronary aspirates were the result of PMPs concentrating at the site of thrombosis in the culprit coronary artery. According to current knowledge, the possible sources of the locally elevated PMPs include those released from the ruptured atherosclerotic plaque, those produced by aggregated platelets in the culprit artery, or a gathering of circulating PMPs [18, 24-26]. Further research is needed to clarify the exact cause of this phenomenon.

$CD45^+$ LMPs were not significantly changed in patients with STEMI

Some inflammatory markers, such as high-sensitivity C-reactive protein, have been proven to be independent predictors of cardiovascular events. LMPs are also a marker of inflammation. Circulating LMPs can be upregulated by inflammatory stimulation *in vivo* and time-dependently activate the c-Jun NH2-terminal kinase signaling pathway in ECs [27]. At the same time, LMPs derived from polymorphonuclearneutrophils can express activated integrin $\alpha_M\beta_2$ and act as effective activators of platelets [28]. In patients with ACS, $CD11b^+$ LMPs can serve as independent markers of severe coronary lesions and as risk factors for recurrent cardiovascular events after stenting [29].

The levels of $CD11a^+$ LMPs in the peripheral blood are reportedly not higher in patients with ACS than in patients with stable coronary disease or those without coronary disease [1]. Min et al. [5] also found no significant difference in the level of circulating $CD11a^+$ LMPs between patients with STEMI and patients with normal coronary arteries. Our results regarding $CD45^+$ LMPs are in agreement with these previous results. There are several possible reasons for these seemingly surprising results. First, in these studies, the control patients were not healthy volunteers but patients undergoing coronary angiography for other reasons such as unexplained chest pain. As seen in **Table 1**, the morbidity rates associated with diabetes, hypertension, dyslipidemia, and smoking were similar between the STEMI and control groups in these studies. These risk factors can elevate the LMP levels. Second, according to recent guidelines, patients with STEMI were treated much more aggressively than control patients. For example, loading doses of statins and antiplatelet drugs were routinely given to patients with STEMI before the procedure. Previous studies have proven that these therapies may change the level of LMPs [30-33]. These factors may eliminate the differences between the two groups and influence the result of the comparison of the two groups.

In the present study, the level of $CD45^+$ LMPs in the intracoronary thrombus was similar to that in the peripheral circulation in patients with STEMI. This finding is consistent with the findings of Min et al. [5], who found no significant elevation in the level of $CD11a^+$ LMPs in the intracoronary aspirations from the culprit coronary artery. However, Morel et al. [7] observed a significant rise in $CD11a^+$ LMPs in close proximity to the intracoronary thrombus among patients with STEMI. Regardless, the sample size of the latter study is relatively small (12 patients with STEMI), and further study and verification are needed.

In conclusion, our study revealed that in patients with STEMI, $CD144^+$ EMPs were significantly increased in the systemic circulation and $CD41b^+$ PMPs were only increased within the culprit coronary artery, while the level of $CD45^+$ LMPs was not significantly changed. These findings suggest that MPs may take part in the process of coronary atherothrombosis in patients with STEMI. However, further studies are needed to clarify the specific mechanisms and explore the possible application of MPs in the diagnosis and treatment of STEMI.

Acknowledgements

The faculty in the cardiovascular laboratory of Peking University First Hospital provided great help in the collection of samples. This study was supported by the National Natural Science Foundation of China (No. 81470025).

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Jianping Li, Department of Cardiology, Peking University First Hospital, No. 8 Xishiku Street, Xicheng District, Beijing 100038, China. Tel: +86-10-8357 5728; E-mail: lijianping@medmail.com.cn

References

[1] Mallat Z, Benamer H, Hugel B, Benessiano J, Steg PG, Freyssinet JM and Tedgui A. Elevated levels of shed membrane microparticles with procoagulant potential in the peripheral circulating blood of patients with acute coronary syndromes. Circulation 2000; 101: 841-843.

[2] Bernal-Mizrachi L, Jy W, Fierro C, Macdonough R, Velazques HA, Purow J, Jimenez JJ, Horstman LL, Ferreira A, de Marchena E and Ahn YS. Endothelial microparticles correlate with high-risk angiographic lesions in acute coronary syndromes. Int J Cardiol 2004; 97: 439-446.

[3] Bernal-Mizrachi L, Jy W, Jimenez JJ, Pastor J, Mauro LM, Horstman LL, de Marchena E and

Ahn YS. High levels of circulating endothelial microparticles in patients with acute coronary syndromes. Am Heart J 2003; 145: 962-970.

[4] Morel O, Hugel B, Jesel L, Mallat Z, Lanza F, Douchet MP, Zupan M, Chauvin M, Cazenave JP, Tedgui A, Freyssinet JM and Toti F. Circulating procoagulant microparticles and soluble GPV in myocardial infarction treated by primary percutaneous transluminal coronary angioplasty. A possible role for GPIIb-IIIa antagonists. J Thromb Haemost 2004; 2: 1118-1126.

[5] Min PK, Kim JY, Chung KH, Lee BK, Cho M, Lee DL, Hong SY, Choi EY, Yoon YW, Hong BK, Rim SJ and Kwon HM. Local increase in microparticles from the aspirate of culprit coronary arteries in patients with ST-segment elevation myocardial infarction. Atherosclerosis 2013; 227: 323-328.

[6] Porto I, Biasucci LM, De Maria GL, Leone AM, Niccoli G, Burzotta F, Trani C, Tritarelli A, Vergallo R, Liuzzo G and Crea F. Intracoronary microparticles and microvascular obstruction in patients with ST elevation myocardial infarction undergoing primary percutaneous intervention. Eur Heart J 2012; 33: 2928-2938.

[7] Morel O, Pereira B, Averous G, Faure A, Jesel L, Germain P, Grunebaum L, Ohlmann P, Freyssinet JM, Bareiss P and Toti F. Increased levels of procoagulant tissue factor-bearing microparticles within the occluded coronary artery of patients with ST-segment elevation myocardial infarction: role of endothelial damage and leukocyte activation. Atherosclerosis 2009; 204: 636-641.

[8] Thygesen K, Alpert JS and White HD. Universal definition of myocardial infarction. J Am Coll Cardiol 2007; 50: 2173-2195.

[9] Pres D, Gasior M, Strojek K, Gierlotka M, Hawranek M, Lekston A, Wilczek K, Tajstra M, Gumprecht J and Polonski L. Blood glucose level on admission determines in-hospital and long-term mortality in patients with ST-segment elevation myocardial infarction complicated by cardiogenic shock treated with percutaneous coronary intervention. Kardiol Pol 2010; 68: 743-751.

[10] Di Stefano R, Di Bello V, Barsotti MC, Grigoratos C, Armani C, Dell'Omodarme M, Carpi A and Balbarini A. Inflammatory markers and cardiac function in acute coronary syndrome: difference in ST-segment elevation myocardial infarction (STEMI) and in non-STEMI models. Biomed Pharmacother 2009; 63: 773-780.

[11] Zhang YC, Wei JJ, Wang F, Chen MT and Zhang MZ. Elevated levels of oxidized low-density lipoprotein correlate positively with C-reactive protein in patients with acute coronary syndrome. Cell Biochem Biophys 2012; 62: 365-372.

[12] Thomas GM, Panicot-Dubois L, Lacroix R, Dignat-George F, Lombardo D and Dubois C. Cancer cell-derived microparticles bearing P-selectin glycoprotein ligand 1 accelerate thrombus formation in vivo. J Exp Med 2009; 206: 1913-1927.

[13] Owens AR and Mackman N. Microparticles in hemostasis and thrombosis. Circ Res 2011; 108: 1284-1297.

[14] Barry OP, Pratico D, Lawson JA and FitzGerald GA. Transcellular activation of platelets and endothelial cells by bioactive lipids in platelet microparticles. J Clin Invest 1997; 99: 2118-2127.

[15] Jy W, Jimenez JJ, Mauro LM, Horstman LL, Cheng P, Ahn ER, Bidot CJ and Ahn YS. Endothelial microparticles induce formation of platelet aggregates via a von Willebrand factor/ristocetin dependent pathway, rendering them resistant to dissociation. J Thromb Haemost 2005; 3: 1301-1308.

[16] Sabatier F, Roux V, Anfosso F, Camoin L, Sampol J and Dignat-George F. Interaction of endothelial microparticles with monocytic cells in vitro induces tissue factor-dependent procoagulant activity. Blood 2002; 99: 3962-3970.

[17] Shet AS, Aras O, Gupta K, Hass MJ, Rausch DJ, Saba N, Koopmeiners L, Key NS and Hebbel RP. Sickle blood contains tissue factor-positive microparticles derived from endothelial cells and monocytes. Blood 2003; 102: 2678-2683.

[18] Gross PL, Furie BC, Merrill-Skoloff G, Chou J and Furie B. Leukocyte-versus microparticle-mediated tissue factor transfer during arteriolar thrombus development. J Leukoc Biol 2005; 78: 1318-1326.

[19] Jimenez JJ, Jy W, Mauro LM, Soderland C, Horstman LL and Ahn YS. Endothelial cells release phenotypically and quantitatively distinct microparticles in activation and apoptosis. Thromb Res 2003; 109: 175-180.

[20] Namba M, Tanaka A, Shimada K, Ozeki Y, Uehata S, Sakamoto T, Nishida Y, Nomura S and Yoshikawa J. Circulating platelet-derived microparticles are associated with atherothrombotic events: a marker for vulnerable blood. Arterioscler Thromb Vasc Biol 2007; 27: 255-256.

[21] Siljander P, Carpen O and Lassila R. Platelet-derived microparticles associate with fibrin during thrombosis. Blood 1996; 87: 4651-4663.

[22] Aleman MM, Gardiner C, Harrison P and Wolberg AS. Differential contributions of monocyte- and platelet-derived microparticles towards thrombin generation and fibrin formation and stability. J Thromb Haemost 2011; 9: 2251-2261.

[23] Ramacciotti E, Hawley AE, Farris DM, Ballard NE, Wrobleski SK, Myers DJ, Henke PK and Wakefield TW. Leukocyte- and platelet-derived microparticles correlate with thrombus weight and tissue factor activity in an experimental mouse model of venous thrombosis. Thromb Haemost 2009; 101: 748-754.

[24] Ghosh A, Li W, Febbraio M, Espinola RG, McCrae KR, Cockrell E and Silverstein RL. Platelet CD36 mediates interactions with endothelial cell-derived microparticles and contributes to thrombosis in mice. J Clin Invest 2008; 118: 1934-1943.

[25] Leroyer AS, Isobe H, Leseche G, Castier Y, Wassef M, Mallat Z, Binder BR, Tedgui A and Boulanger CM. Cellular origins and thrombogenic activity of microparticles isolated from human atherosclerotic plaques. J Am Coll Cardiol 2007; 49: 772-777.

[26] Reininger AJ, Bernlochner I, Penz SM, Ravanat C, Smethurst P, Farndale RW, Gachet C, Brandl R and Siess W. A 2-step mechanism of arterial thrombus formation induced by human atherosclerotic plaques. J Am Coll Cardiol 2010; 55: 1147-1158.

[27] Mesri M and Altieri DC. Leukocyte microparticles stimulate endothelial cell cytokine release and tissue factor induction in a JNK1 signaling pathway. J Biol Chem 1999; 274: 23111-23118.

[28] Pluskota E, Woody NM, Szpak D, Ballantyne CM, Soloviev DA, Simon DI and Plow EF. Expression, activation, and function of integrin alphaMbeta2 (Mac-1) on neutrophil-derived microparticles. Blood 2008; 112: 2327-2335.

[29] Faille D, Frere C, Cuisset T, Quilici J, Moro PJ, Morange PE, Bonnet JL and Alessi MC. CD11b+ leukocyte microparticles are associated with high-risk angiographic lesions and recurrent cardiovascular events in acute coronary syndromes. J Thromb Haemost 2011; 9: 1870-1873.

[30] Pfister SL. Role of platelet microparticles in the production of thromboxane by rabbit pulmonary artery. Hypertension 2004; 43: 428-433.

[31] Tramontano AF, O'Leary J, Black AD, Muniyappa R, Cutaia MV and El-Sherif N. Statin decreases endothelial microparticle release from human coronary artery endothelial cells: implication for the Rho-kinase pathway. Biochem Biophys Res Commun 2004; 320: 34-38.

[32] Nomura S, Shouzu A, Omoto S, Nishikawa M and Iwasaka T. Effects of losartan and simvastatin on monocyte-derived microparticles in hypertensive patients with and without type 2 diabetes mellitus. Clin Appl Thromb Hemost 2004; 10: 133-141.

[33] Lechner D and Weltermann A. Circulating tissue factor-exposing microparticles. Thromb Res 2008; 122 Suppl 1: S47-S54.