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ARTICLE

The Relationship Between the Level of Serum ESM-1 and Lp-PLA2 in Patients With Acute ST-Segment Elevation Myocardial Infarction

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Acute ST-segment elevation myocardial infarction (STEMI) is the most lethal coronary heart disease with vascular endothelium dysfunction and inflammation in the disease development process. Endothelial cell-specific molecule 1 (ESM-1) and lipoprotein-associated phospholipase A2 (Lp-PLA2) are important for the diagnosis and characterization of STEMI. To date, no studies have reported the correlation between ESM-1 and Lp-PLA2 levels in patients with STEMI, which may be an important predictor of the fatal disease. To measure the level of serum ESM-1 and Lp-PLA2, and to evaluate the relationship and the clinical significance of these two biomarkers in patients with acute STEMI, 37 inpatients with acute STEMI were sequentially enrolled in the research group and 24 study objects with normal coronary artery function were included in the control group. The measurement of the relative parameters was done by enzyme-linked immunosorbent assay using blood samples taken from the median cubital vein while the inpatients were enrolled. The levels of serum SEM-1 and Lp-PLA2 were significantly higher in patients with acute STEMI than in study objects with normal coronary artery function ($P < 0.05$). A significant correlation of serum SEM-1 and Lp-PLA2 was observed, leading to close linearity ($r^2 = 0.8131$, $P < 0.0001$). In conclusion, the endothelium dysfunction factor ESM-1 and inflammatory factor Lp-PLA2 are significantly higher and correlated in patients with acute STEMI. These two factors could be novel and effective biomarkers for acute STEMI diagnosis and evaluation.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Acute ST-segment elevation myocardial infarction (STEMI) is the most lethal coronary heart disease with vascular endothelium dysfunction and inflammation in the disease development process. Endothelial cell-specific molecule 1 (ESM-1) and lipoprotein-associated phospholipase A2 (Lp-PLA2) are important for the diagnosis and characterization of STEMI.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ In this research, we examined the serum levels of ESM-1 and Lp-PLA2 in patients with STEMI. In addition, the levels of these two biomarkers were compared to reveal their intrinsic correlation.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ The levels of serum SEM-1 and Lp-PLA2 were significantly higher in patients with acute STEMI than in study objects with normal coronary artery function ($P < 0.05$). A significant correlation of serum SEM-1 and Lp-PLA2 was observed, leading to close linearity ($r^2 = 0.8131$, $P < 0.0001$).

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ This is the first study to identify a significant correlation between EMS-1 and Lp-PLA2 in patients with STEMI. These two factors could be novel biomarkers for the diagnosis and evaluation of the disease. Measures should be taken based on the changes of these biomarkers in time to give proper therapy and reduce the mortality.

Acute ST-segment elevation myocardial infarction (STEMI) is one of the most fatal coronary heart disease (CHD) results from occlusion of an epicardial coronary artery due to the rupture of an atherosclerotic plaque.[1,2] The disease process of STEMI is fast with poor prognosis[3] and high lethality rate.[2] Besides the atherosclerotic plaque rupture and superimposed thrombosis, the ischemia-reperfusion injury holds the primary responsibility for the myocardial injury.[4] The coronary artery ischemia-reperfusion injury manifests as microvascular dysfunction, primarily by increased capillary

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permeability and edema,[5,6] and coronary microembolization of atherosclerotic particular debris.[7] Currently, primary percutaneous coronary intervention is crucial for patients with STEMI to improve myocardial salvage and prevent reperfusion injury.[8] However, efforts toward the prediction and staging of STEMI was never ceased.[9] Some built scoring systems based on the validation and integration of different risk factors.[10] Others may want to seek the way by analyzing the critical biomarkers related to the pathogenesis of STEMI to predict and diagnose the disease.

In recent years, endothelial cell-specific molecule 1 (ESM-1) was recognized as an important endothelial marker,[11] which may be involved in the pathogenesis of atherosclerosis and lead to endothelial dysfunction.[12] The serum ESM-1 level was suggested to be a novel biomarker for the diagnosis, evaluation,[12,13] or even staging[14] of acute STEMI. However, Aparci *et al*.[15] suggest that the measurement of serum ESM-1 alone is not sufficient for the characterization of endothelial dysfunction. The defining of endothelial dysfunction requires more inflammatory factors examination.[15] Lipoprotein-associated phospholipase A2 (Lp-PLA2) is reported to be involved in the development of atherosclerosis.[16–18] The inhibitory of Lp-PLA2 could be effective for the regulation of atherosclerosis.[19] Yang *et al*.[20] reported that serum Lp-PLA2 and ischemia-modified albumin are predictive of the degree of myocardial ischemia in patients with acute coronary syndrome. Lp-PLA2 is also reported to be a predictor of STEMI.[21,22] EMS-1 is considered to be an indicator of endothelial dysfunction and Lp-PLA2 is deemed to be an inflammatory factor mediating the atherosclerotic plaque formation. Therefore, it can be speculated that there may be some correlation between the two. However, the relationship between these two biomarkers is not yet clear. To date, there is still no study reporting about the correlation of ESM-1 and Lp-PLA2 levels in patients with STEMI, which could be an important predictor of this lethal disease.

In this research, we examined the serum levels of ESM-1 and Lp-PLA2 in patients with STEMI. The levels of these two biomarkers were compared to reveal their intrinsic correlation.

METHODS

Patients

The present study was approved by the Ethics Committee of the First Affiliated Hospital with Nanjing Medical University. All procedures performed in this study were in accordance with the ethical standards of the First Affiliated Hospital with Nanjing Medical University research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

The study was carried out in the inpatient department of cardiology, Xuzhou Central Hospital, where 37 patients with acute STEMI and 24 study objects with normal coronary artery function examined by coronary angiogram were enrolled in the study cohort between January and December 2018. Among the patients with acute STEMI were 23 men and 14 women aged from 30 to 75 years.

The inclusion criteria were: patients within 12 hours of onset who had elevated troponin levels along with at least one of the following states: (1) chest pain > 30 minutes; (2) two or more limb lead ST-segment elevated ≥ 0.1 mv or chest lead ST-segment elevated ≥ 0.2 mv in the electrocardiogram, with emerging left bundle branch block; (3) abnormal Q waves shown in the electrocardiogram; (4) emerging imagological myocardium viability or wall motion abnormality; and (5) intracoronary thrombosis detected by coronary arteriography or autopsy. The exclusion criteria were: (i) patients with cardiac function staging from the New York Heart Association (NYHA) class III to IV in combination of acute or chronic infection, or immune system disease, such as rheumatism, carcinoma, diabetes, hepatopathy, or renal disease; (ii) patients who had been proceeded to CHD percutaneous coronary intervention surgery; and (iii) patients with cerebrovascular or peripheral vessel disease.

Testing methods

ESM-1 concentration tests. All study subjects had 5 mL of blood samples taken from the median cubital vein immediately by the inpatient department. The blood samples were stored in a 4 centigrade-degree refrigerator to coagulate for 1 hour before centrifuging at 1,000× g for 15 minutes under the same temperature. The serum was transferred to an EP tube and stored in a −80 centigrade-degree refrigerator. The kits for ESM-1 enzyme-linked immunosorbent assay tests were purchased from Shanghai mlbio ESM-1 detection range: 0.2–12 ng/mL.

Lp-PLA2 concentration tests. When the patient was admitted to the hospital, 5 mL of median cubital vein blood was immediately taken, centrifuged at 1,000× g and 4°C for 15 minutes, and the serum was frozen at 80°C for examination. The kit was purchased from Nanjing Norman Biotechnology (Nanjing, Jiangsu, China). The concentration was measured by the fluorescein-enhanced immunochemiluminescence method, and the specific operation was performed according to the kit instructions. The minimum detection limit was ≤ 1 ng/mL.

Statistical analysis

The analysis of the general data was carried out on the SPSS version 23.0 platform (IBM, Armonk, NY). The χ^2 test or Fisher's exact test were used while the data was described as n/%. The measurement data is described by mean ± SD. The differential analysis of the measurement data was done by using the independent sample *t*-test if the two sets of data were in accordance with the normal distribution; the Mann-Whitney rank-sum test was used if the two sets of data were not in accordance with the normal distribution. Pearson's product-moment correlation was used for the correlation analysis between the data following the bivariate normal distribution.

RESULTS

Patients' baseline characteristics

The baseline characteristics of the study objects are listed in **Table 1**. The two groups of patients have similar status on age, body mass index, smoking habit, hypertension history, CHD family history, triglyceride level, and creatinine level. Significant higher troponin, total cholesterol level, low-density lipoprotein-cholesterol level, glutamic-oxaloacetic transaminase level, glutamic-pyruvic transaminase level, and troponin I level in patients

Table 1 Baseline characteristics of the two groups of study objects

Variables	STEMI (*N* = 37)	Control (*N* = 24)	$t/\chi^2/Z$	*P* value
Sex, male/female	23/14	15/9	0.001	0.979
Age, years	57.35 ± 11.55	57.21 ± 10.33	0.049	0.961
BMI, kg/m^2	24.91 ± 2.57	24.03 ± 2.06	1.476	0.145
Cardiovascular risk factors *n* (%)				
Smoking habit	16 (43.2)	8 (33.3)	0.599	0.439
Hypertension history	12 (32.4)	6 (25.0)	0.387	0.534
CHD family history	6 (16.2)	3 (12.5)	0.160	0.689
TC, mmol/L	4.61 ± 1.14	3.99 ± 1.07	2.022	0.048
LDL-C, mmol/L	3.22 ± 0.98	2.54 ± 0.93	2.573	0.013
TG, mmol/L	1.69 ± 0.71	1.42 ± 0.50	1.560	0.124
GOT, μ/L	190 (52.5 ~ 293.00)	18.0 (14.75 ~ 31.75)	5.668	0.000
GPT, μ/L	43 (29.00 ~ 66.50)	22.5(12.75 ~ 36.25)	3.371	0.001
Creatinine, μmol/L	54.31 ± 13.49	53.77 ± 15.55	0.140	0.889
Troponin I, ng/L	33.80 ± 4.32	0.03 ± 0.01	6.276	<0.001
Fasting blood glucose at 2 weeks after enrollment	5.13 ± 0.87	5.05 ± 0.62	0.391	0.698
2-hour postprandial at 2 weeks after enrollment	7.84 ± 2.04	7.59 ± 1.57	0.509	0.612

BMI, body mass index; CHD, coronary heart disease; GOT, glutamic-oxaloacetic transaminase; GPT, glutamic-pyruvic transaminase; LDL-C, low-density lipoprotein-cholesterol; STEMI, ST-segment elevation myocardial infarction; TC, total cholesterol; TG, triglyceride.

with acute STEMI than control group objects were detected. The increased level of serum troponin indicates the STEMI incident.

ESM-1 and Lp-PLA2 levels

Significantly higher levels of serum ESM-1 and Lp-PLA2 were detected in patients with acute STEMI than those who were included in the control group (**Table 2**, **Figure 1**). The serum ESM-1 of patients with STEMI is significantly higher than the control. The mean serum ESM-1 of the patients with acute STEMI was 1.23 ng/mL ranging from 1.07 ng/mL to 1.38 ng/mL. It is 1.6-fold higher than the control group (mean = 0.77 ng/mL, ranging from 0.59–0.89 ng/mL).

The serum Lp-PLA2 of the patients with STEMI is significantly higher than the control as well. The mean serum Lp-PLA1 level of the patients with acute STEMI is 236.23 ng/mL, whereas the mean serum Lp-PLA2 level of the control group is 156.54 ng/mL. The mean serum Lp-PLA2 level of patients with acute STEMI is 1.5-fold higher than those who have a normal cardiac function.

The correlation of the serum ESM-1 and Lp-PLA2 levels

A bivariate Spearman correlation analysis was done to study the relationship between the serum ESM-1 and Lp-PLA2 levels. A significant correlation of serum SEM-1 and Lp-PLA2 was observed, leading to close linearity (**Figure 2**, $r^2 = 0.8131$, $P < 0.0001$). A higher level of serum ESM-1 was detected while the patient had higher Lp-PLA2.

DISCUSSION

In this research, 37 patients with STEMI and 24 patients with normal coronary artery function confirmed by coronary angiogram were included in two study groups, respectively. Blood samples taken from the median cubital vein and the serum samples were collected for the bioassay. ESM-1 and Lp-PLA2 were measured and the correlation between these two biomarkers was analyzed. The serum ESM-1 level of the patients with STEMI is significantly higher than those without (1.23 ± 0.08 ng/mL vs. 0.77 ± 0.09 ng/mL, $P < 0.001$). The serum Lp-PLA2 of the patients with STEMI varies from 81 to 528 ng/mL, the mean value is 236.38 ± 124.47 ng/mL. It is significantly higher than those who are enrolled in the control group (156.54 ± 88.46, $P = 0.0085$). The correlation of the ESM-1 and Lp-PLA2 was also measured and the close linearity of these two parameters was observed ($r^2 = 0.8131$, $P < 0.0001$).

ESM-1 was recognized as an important endothelial marker.[11] Our previous research indicated that ESM-1 levels > 1.01 ng/mL were an independent indicator of major

Table 2 ESM-1 and Lp-PLA2 levels of the two groups of study objects

	STEMI (*N* = 37)	Control (*N* = 24)	*t*/*Z*	*P* value
ESM-1, ng/mL	1.23 ± 0.08	0.77 ± 0.09	21.82	<0.001
Lp-PLA2, ng/mL	174.00 (136.50 ~ 345.50)	125.00 (100.00 ~ 172.25)	–3.086	0.002

ESM-1, endothelial cell-specific molecule 1; Lp-PLA2, lipoprotein-associated phospholipase A2; STEMI, ST-segment elevation myocardial infarction.

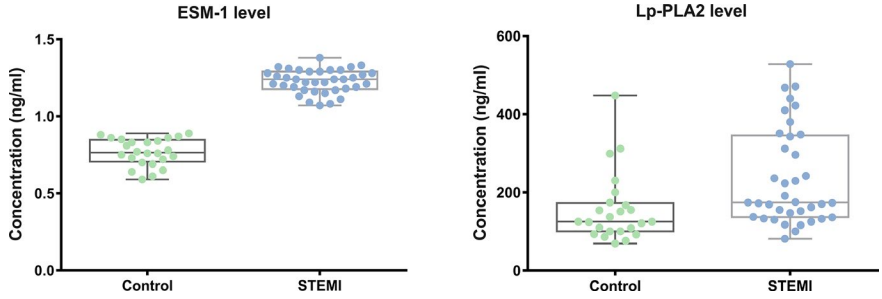

Figure 1 Serum endothelial cell-specific molecule 1 (ESM-1) and lipoprotein-associated phospholipase A2 (Lp-PLA2) levels of the two groups of study objects.

adverse cardiac events in patients with stress hyperglycemia having STEMI.[12] The correlation between EMS-1 and high-sensitivity C-reactive protein levels and the neutrophil to lymphocyte ratio was also revealed in our investigation.[13] In this study, a significantly higher serum ESM-1 was observed in patients with STEMI, which was consistent with our previous findings. The application of the ticagrelor enhanced the prognosis of STEMI and also lowered the ESM-1 level at the end of the treatment of 7 days.[23,24] All these studies suggested EMS-1 was an important biomarker and predictor of STEMI.

Lp-PLA2 is reported to be involved in the development of atherosclerosis.[16–18] The elevated serum Lp-PLA2 level of the patients with STEMI in our study is in accordance with the previous reports.[25,26] Stankovic *et al*.[21] discovered Lp-PLA2 was an independent predictor of 30-day major adverse cardiac event in patients with STEMI. Lp-PLA2 was also reported to be an independent predictor of high thrombus burden in patients with STEMI,[22] and manual thrombus aspiration could effectively reduce Lp-PLA2 level.[27] Yang *et al*.[20] reported that the Lp-PLA2 level provided a staging basis of the degree of risk of patients with STEMI.

The importance of EMS-1 and Lp-PLA2 to STEMI diagnosis and prediction has been recognized by various studies. EMS-1 is considered to be an indicator of endothelial dysfunction and Lp-PLA2 is, on the other hand, deemed to be an inflammatory factor mediating the atherosclerotic plaque formation. However, the relationship between these two biomarkers was never discussed. Our statistical analysis indicated that there is a linear relationship of the serum concentration between these two biomarkers (r^2 = 0.8131, $P < 0.0001$) in patients with STEMI. The higher expression of EMS-1 comes with a higher Lp-PLA2 in patients with STEMI. The mechanism of such a linkage is not clear, but we have our hypothesis. Lp-PLA2 is highly expressed in the atherosclerotic plaque.[28] We assume EMS-1 is also highly expressed in the plaque (no data supported). The two biomarkers are released while the rupture of the atherosclerotic plaque initiates and then pushes the final boundary of STEMI outburst.

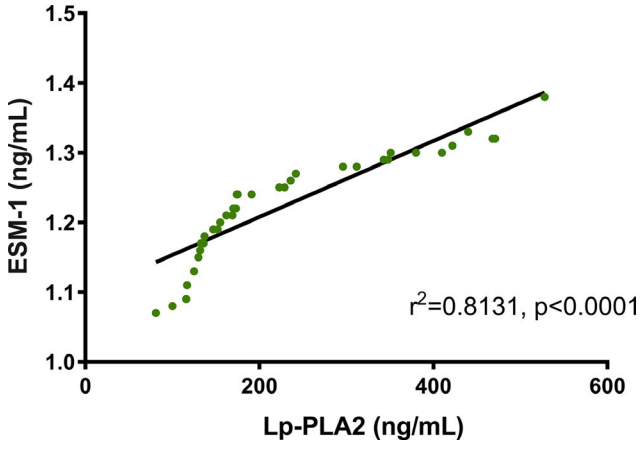

Figure 2 The correlation between serum endothelial cell-specific molecule 1 (ESM-1) and lipoprotein-associated phospholipase A2 (Lp-PLA2) levels.

Limitations

Although we made a great discovery of the relationship between EMS-1 and Lp-PLA2 in patients with STEMI, there are still some limitations of this research, including the sampling of the blood. Blood sampling within the coronary artery instead of the peripheral blood sampling might improve the accuracy of the ESM-1 and Lp-PLA2 level testing. Although the study was carried out giving a guarantee of patients' safety, it has a lot of limitations, such as safety and ethical issues. Therefore, further animal experiments are necessary to give deeper insight into the cell signaling pathway of STEMI, which might shed light on a more accurate prediction and staging of the disease.

CONCLUSION

Significantly higher serum ESM-1 and Lp-PLA2 levels were observed in patients with acute STEMI compared with those who had a normal myocardial function. The raised serum ESM-1 level and the elevated serum Lp-PLA2 level had a significant correlation suggesting an intrinsic interaction during the acute STEMI process. This is the first study to identify a significant correlation between EMS-1 and Lp-PLA2 in patients with STEMI. These two factors could be novel biomarkers for the diagnosis and evaluation of the disease. Measures should be taken based on the changes of these biomarkers in time to give proper therapy and reduce the mortality.

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