

Levels of pregnancy-associated plasma protein A in patients with coronary artery disease

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Abstract

Purpose: To investigate the levels of pregnancy-associated plasma protein A (PAPP-A) or insulin-like growth factor -1 (IGF-1) in patients with acute coronary syndrome.

Methods: Serum PAPP-A and IGF-1 was measured with biotin–tyramide-amplified enzyme immunoassay and Enzyme Linked Immuosorbent Assay, respectively, in patients with ST elevation acute myocardial infarction (STEMI, n=12), unstable angina (UAP, n=15), and stable angina (n=15). PAPP-A and IGF-1 was also measured in 16 healthy subjects (control group).

Results: The serum levels of PAPP-A in the STEMI (16.9±10.3 mIU/L) and UAP group (15.2±10.5 mIU/L) were higher than in the stable angina (8.5±3.1 mIU/L) or control group (8.4±2.0 mIU/L, $P<0.01$). The serum levels of IGF-1 in the STEMI (132.3±40.9 µg/L) and UAP group (127.3±36.0 µg/L) were also higher than in the stable angina (44.9±18.5 µg/L) or control group (67.7±24.5µg/L, $P<0.01$). There were no differences in serum levels of PAPP-A or IGF-1 among the single, double and three vessel lesion groups. The serum levels of PAPP-A (19.9±10.1 mIU/L) and IGF-1 (153.2±52.4 µg/L) after PCI were higher than those before PCI (15.1±10.0 mIU/L and 91.4±51.0 µg/L, respectively, $P<0.01$). A positive correlation was found between PAPP-A and IGF-1 levels in the STEMI and UAP group before PCI ($r=0.48$, $P<0.01$).

Conclusion: PAPP-A and IGF-1 are elevated in patients with acute coronary syndrome. They may be used as biomarkers for vulnerable plaques in patients with coronary artery disease. Whether post-PCI elevation of IGF-1 can be used to predict restenosis of coronary arteries remains to be seen.

Rupture of vulnerable plaque and subsequent thrombus formation in the coronary artery are considered to be responsible for the pathogenesis of the acute coronary syndrome.¹ Percutaneous coronary intervention (PCI) has become one of the main treatment measures for acute coronary syndrome.^{2,3} Successful PCI reduces the incidence of death, myocardial infarction and hospitalisation in patients with acute coronary syndrome.^{2,3} However, restenosis of targeted coronary arteries remains a major downside of PCI.^{2,3}

Recent studies have demonstrated that pregnancy-associated plasma protein-A (PAPP-A) is associated with the rupture of vulnerable plaque. It may play an important role in the occurrence and development of acute coronary syndrome.⁴ Several studies showed

that insulin-like growth factor-1 (IGF-1) is related to atherosclerosis and coronary artery disease.⁵ Some experimental studies have confirmed that PAPP-A and IGF-1 participate in the progress of restenosis after PCI.⁶ This study measured the serum levels of PAPP-A and IGF-1. At the same time, coronary angiography was performed in patients with coronary artery disease to investigate the relationship between PAPP-A, IGF-1 and the severity of coronary lesions, and the effect of PCI on PAPP-A, IGF-1.

Subjects and methods

Study Subjects

The study was approved by the institution review board of the First Affiliated Hospital of Zhengzhou University. Informed consent was obtained from all participants before the study.

Between January 2006 and October 2006, 42 patients (27 men, mean age 62.5 ± 12.5 yr, range 40-78) were recruited from the Department of Cardiology and the Department of Emergency Medicine the First Affiliated Hospital of Zhengzhou University. All patients had coronary artery disease confirmed by coronary angiography. Of the 42 patients, 12 were ST-elevation acute myocardial infarction (STEMI), 15 were unstable angina pectoris (UAP) and 15 were stable angina pectoris (SAP). PCI (angioplasty followed by stent implantation) was performed in 24 of these patients with STEMI and UAP. Sixteen healthy subjects (10 men, mean age 56.1 ± 10.3 yr, range 42-76) were also recruited for the measurement of serum PAPP-A and IGF-1.

STEMI was defined as prolonged chest pain accompanied by ischemic ST-T elevation. It was confirmed by elevated plasma creatine kinase-MB (CK-MB) of more than twice the upper limit of the normal range, and by a troponin-I level of > 0.5 ng/ml. UAP was defined as chest pain at rest with either ST-segment depression of at least 0.1 mV or T-wave inversion in two or more continuous electrocardiographic leads. There was no elevation of CK-MB or troponin-I.⁷

SAP was diagnosed as chest pain of at least six month's duration accompanied by evidence of severe coronary artery disease on coronary angiography and by the absence of clinically evident ischemic episodes during the week preceding arteriography.⁸

Angiographically, severe coronary artery disease was defined by the presence of one or more stenoses of at least 50% in any major coronary artery. Those who had a previous history of cardiomyopathy, valvular heart disease, tumor, inflammatory diseases, liver and renal dysfunction, cerebral vessels, and peripheral angiopathy were excluded from the study, as were those who were pregnant.

Both STEMI and UAP patients were managed with intravenous heparin before PCI. Thrombolytic therapy with streptokinase was used in the three STEMI patients who did not receive PCI. Other drugs used in all three groups of patients included beta-blockers, aspirin, nitrates, statins and angiotensin-converting enzyme inhibitors.

Measurements of PAPP-A and IGF-1

In patients with acute coronary events, venous blood was drawn within one hour of the onset of chest pain, and approximately 30 min before PCI. In patients with stable angina and underwent coronary angiogram or PCI, venous blood was drawn four hours before and four hours after coronary angiography or PCI. Within 30 min of blood collection, blood samples were centrifuged at 1600 revolutions/min per minute for 5 min. The abstracted serum was stored at -70°C . PAPP-A concentrations were determined by means of a biotin-tyramide-amplified enzyme immunoassay, as previously described,⁹ with a limit of detection of 0.03 mIU/L. Inter-observer variation of these measurements was less than 7%. Enzyme Linked Immunosorbent Assay (ELISA) was used to measure the serum levels of IGF-1 in patients with coronary artery disease and control group. IGF-1 concentration was measured by an IGF-I ELISA kit (Shanghai Senxiong Technology Industry Co. Ltd, Shanghai, China).

TABLE 1. Clinical characteristics of STEMI, UAP, SAP and the control group.

	STEMI group	UAP group	SAP group	Control group	<i>P</i>
n	12	15	15	16	
Age (yr)	62.58±12.53	58.3±11.74	58.07±9.18	56.0±10.30	0.52
Male (%)	7 (58.33)	10 (66.67)	10 (66.67)	10 (62.50)	0.82
Smoking history (%)	6 (50.00)	7 (46.47)	8 (53.33)	7 (43.75)	0.14
Hypertension (%)	6 (50.00)	8 (53.33)	7 (46.47)	7 (50.00)	0.96
Family history of CAD (%)	7 (58.33)	8 (53.33)	7 (46.47)	7 (43.75)	0.87
Diabetes (%)	5 (41.67)	7 (46.47)	7 (46.47)	7 (43.75)	0.84
Triglyceride (mmol/L)	1.58±0.53	1.80±0.83	1.65±1.01	1.86±0.99	0.82
Total cholesterol (mmol/L)	4.93±0.94	5.19±1.06	4.83±1.02	4.77±0.97	0.14
High-density lipoproteins (mmol/L)	1.08±0.19	1.25±0.55	1.22±0.47	1.14±0.22	0.80
Low-density lipoproteins (mmol/L)	2.94±0.75	3.03±1.24	2.96±0.75	2.82±0.81	0.53

CAD: coronary artery disease; STEMI: ST elevation myocardial infarction; UAP: unstable angina. SAP: stable angina.

Inter-observer variation of these measurements was less than 5%.

Statistical Analysis

Statistical analysis was performed with SPSS 10.0 software. Data were expressed as mean ± SD. Data between groups were compared by student *t* test. Categorical data was compared with Chi-square test. Comparison among the four groups was performed by analysis of variance of univariate (ANOVA). The relationship between serum levels of IGF-1 and PAPP-A was analyzed by univariate linear relation. Correlation coefficient was tested by *t*-test. *P*<0.05 was considered as statistical significant.

Results

Among the four groups, there was no significant difference in sex, age, smoking history, family history of coronary artery disease, diabetes, hypertension and blood cholesterol levels (Table 1).

Comparisons of the mean level of serum PAPP-A, IGF-1 between groups

The levels of PAPP-A and IGF-1 in the STEMI and UAP groups were higher than the SAP and control group (*P*<0.01). There was no difference in PAPP-A between the SAP and control groups (Table 2).

Relationship between PAPP-A, IGF-1 and severity of vascular lesions

The serum levels of PAPP-A and IGF-1 in single, double and three vessel disease group were higher than that in control group (*P*<0.05). However, there was no difference in the serum levels of PAPP-A and IGF-1 among the three patient groups (Table 3).

Comparisons of the serum levels of PAPP-A, IGF-1 before and after PCI

The serum levels of PAPP-A and IGF-1 after PCI were higher than that of before PCI (*P*<0.01)(Table 4).

Correlation between the levels of PAPP-A and IGF-1 in AMI and UAP group.

A positive correlation was found between the serum levels of PAPP-A and IGF-1 in STEMI and UAP group before PCI (*r*=0.48, *P*<0.01).

Discussion

The major findings of the this study are: 1) The serum levels of PAPP-A or IGF-1 in the STEMI and UAP group were higher than in the stable angina or in the health subjects; 2) The serum levels of PAPP-A or IGF-1 were similar between patients with stable angina and health subjects; 3) There were no differences in serum levels of PAPP-A or IGF-1 among patients

with single, double or three vessel lesions; 4) The post-PCI levels of PAPP-A or IGF-1 were higher than those before PCI; 5) Before PCI, the PAPP-A levels were positively correlated with IGF-1 in the STEMI and the UAP group.

These results provide further support to a recent study by Bayes-Genis and colleagues⁹, who also found that PAPP-A was abundantly expressed in plaque cells and extracellular matrix of ruptured or eroded unstable plaques of coronary arteries. They did not detect PAPP-A in the stable plaques,⁹ whereas in our study, only a very low level of PAPP-A was found in patients with stable angina and in health participants. The results indicate that increased levels of PAPP-A may reflect the instability of atherosclerotic plaques, and that PAPP-A may be used as a new biomarker for acute coronary syndrome.

Recent evidence suggests IGF-1 plays an important role in the development of atherosclerosis. Both IGF-1 and its receptor are highly expressed in the atherosclerotic lesions¹⁰ In unstable atherosclerotic plaques IGF-1 messenger RNA expression is greater than in the stable plaques¹⁰

The present study did not attempt to measure IGF-1 directly from the coronary lesions but the serum levels of IGF-1 in patients with unstable angina and ST elevation myocardial infarction were higher than in patients with stable angina or healthy subjects. In addition, a positive correlation was found between serum levels of IGF-1 and PAPP-A prior to PCI. These results suggest that similar to PAPP-A, IGF-1 is involved in the pathogenesis of acute coronary syndrome and may also be used as a biomarker for vulnerable plaques.

It is unclear how IGF-1 is also elevated in patients with acute coronary syndrome, but previous studies on human fibroblasts suggested that PAPP-A acts as the enzyme cleaving IGF-binding protein 4, an inhibitor of the action of IGF.¹¹ Therefore, PAPP-A may increase the availability of IGF-1. In addition, the vascular smooth muscle cells at the site of injury or vulnerable plaque may increase the expression of IGF-1.¹²

TABLE 2. Comparisons of the level of serum PAPP-A and IGF-1

	n	PAPP-A (mIU/L)	IGF-1 (µg/L)
STEMI group	12	16.9±10.3	132.3±40.9
UAP group	15	15.2±10.5	127.3±36.0
SAP group	15	8.5±3.1* [△]	44.9±18.5* [△]
Control group	16	8.4±2.0* [△]	67.7±24.5* [△]

STEMI: ST elevation myocardial infarction; UAP: unstable angina, SAP: stable angina.

Compare with STEMI group, * $P < 0.01$, Compared with UAP group, [△] $P < 0.01$.

TABLE 3. Comparisons of serum PAPP-A and IGF-1 in single, double and triple-vessel disease

	n	PAPP-A (mIU/L)	IGF-1 (µg/L)
Single vessel lesion group	2	15.09±10.15 *	91.54±49.04*
Triple-vessel lesion group	17	16.07±10.81*	90.46±51.08*
Double vessel lesion group	13	17.30±10.01*	92.40±50.02*
Control group	16	8.35±2.01	67.69±24.54
<i>P</i>		0.077	0.064

Compared with control group, * $P < 0.01$

TABLE 4. Comparisons of the serum level of PAPP-A and IGF-1 before and after PCI

Time	n	PAPP-A (mIU/L)	IGF-1 (µg/L)
Before PCI	24	15.1±10.0	91.4±51.0
After PCI	24	19.9±10.1	153.2±52.4
<i>P</i>		0.005	0.001

In the present study, the serum levels of PAPP-A and IGF-1 following PCI were higher than before PCI. Although there is no clear explanation for the post-PCI elevation in PAPP-A or IGF-1, it is likely that the mechanical injuries to the atheromatous plaques in the coronary arteries following angioplasty and stenting caused the release of these materials to the blood stream. The clinical importance of the post-PCI increase in PAPP-A and IGF-1 is unknown. Given the reported association between restenosis and IGF-1 in clinical and experimental settings, it is reasonable to hypothesize that patients who had high post-PCI levels of IGF-1 may have increased risk of coronary restenosis. However, this hypothesis can only be proven through long-term follow up in a large patient population.

In conclusion, this small study has demonstrated that, in patients with STEMI or unstable angina, there

is an increased serum level of PAPP-A and IGF-1. PCI elevates serum PAPP-A and IGF-1 even further. PAPP-A and IGF-1 may be used as biomarkers for vulnerable plaques in patients with coronary artery disease. Whether IGF-1 elevation post-PCI is associated with an increased risk of restenosis of coronary arteries remains to be determined.

Acknowledgments

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