Predictive value of serum collagen biomarkers on the outcome of acute myocardial infarction treated with percutaneous coronary intervention

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Aims. This study was designed to investigate the predictive value of serum collagen biomarkers on the outcomes of acute ST-elevation myocardial infarction (STEMI) treated with percutaneous coronary intervention (PCI).

Methods. Two hundred and ten patients with STEMI were successfully treated with PCI within 6 hrs of the onset of chest pain. The levels of serum procollagen type I carboxyterminal peptide (PICP) and procollagen type III peptide (PIIINP) were measured by enzyme-linked immunosorbent assay (ELISA) before, 3 and 6 months after PCI. Left ventricular ejection fraction was assessed by echocardiography at 3 and 6 months after PCI. The composite endpoints were death by any cause, recurrent myocardial infarction, heart failure or stroke.

Results. At the end of the 12-month follow up, 29 patients (13.8%) experienced an end point. The level of serum PICP in patients with an end point was higher than in patients without an end point 7 days (19.45 ± 2.17 vs 14.95 ± 3.07 ng/mL, $P < 0.05$) or 3 months after the PCI (29.87 ± 3.02 vs 22.14 ± 3.33 ng/mL, $P < 0.05$). The serum PIIINP level in patients with an end point was also higher than those without 7 days after PCI (59.34 ± 4.23 vs 48.78 ± 4.23 ng/mL, $P < 0.05$). Multivariate logistic regression analysis showed day 7 (OR=2.170, 95% CI 1.583-4.345, $P=0.01$) and 3-month serum PICP (OR=2.340, 95% CI 1.431-4.650, $P=0.01$) were independent predictors of composite end points.

Conclusions. Persistent elevation of serum collagen marker PICP three months after PCI predicts an adverse outcome for patients with acute ST-elevation myocardial infarction.

Key words: myocardial infarction, percutaneous coronary intervention, procollagen type I carboxyterminal peptide, left ventricular function

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INTRODUCTION

Acute ST-segment elevation myocardial infarction (STEMI) is a leading cause of morbidity and mortality. Early revascularization with percutaneous coronary intervention (PCI) or thrombolytic therapy is associated with significant clinical benefits, such as reduction in the size of infarction, improvement in left ventricular function and decreases in mortality¹⁻³.

Ventricular remodeling is a major determining factor for the post-infarct ventricular function and the long-term prognosis following acute MI (ref.⁴). Type I collagen is a major component of myocardial extracellular matrix and plays a key role in ventricular remodeling⁴. Carboxy-terminal peptide of type I procollagen (PICP), a serum biomarker of myocardial type I collagen synthesis, was elevated within the first few days following acute MI (ref.^{5,6}). The other type of collagen that is associated with ventricular remodeling is collagen type III, which is a fibrillar constituent of granulation tissues. The amino-terminal propeptide of type III procollagen (PIIINP), a serum biomarker of myocardial biosynthesis of type III collagen, is associated with poor left ventricular function and high mortality following MI (ref.⁷).

Several earlier clinical observations in a small number of patients have found that coronary revascularization with PCI or thrombolytic therapy within the first 12 h of symptom onset diminished MI-induced PICP or PIIINP elevation^{8,9}. Although the reduction in PICP or PIIINP may represent less ventricular remodeling or dysfunction, the predictive value of post-PCI PICP and PIIINP on left ventricular function remains controversial^{8,9}. In the present study, we investigated the relations between post-PCI levels of serum PICP and PIIINP and the clinical outcome in patients with STEMI.

PATIENTS AND METHODS

Patient selection

This study was approved by the institutional review board of Liaocheng People's Hospital. Informed written consent was obtained from all participants. Between January 2009 and November 2011, 210 consecutive patients (157 males, mean age 62.1 ± 6.3 years) with new onset STEMI and presented within 6 h of the onset of chest pain were recruited into this study. In the same period, 364 patients with one or more of the following

criteria were excluded: a) previous Q-wave MI; b) previous diagnosis of congestive heart failure or cardiomyopathy; c) severe valvular heart disease or severe left ventricular dysfunction (New York Heart Association Function class IV) on admission; d) chronic renal dysfunction; e) refusal to participate in this study; f) unsuccessful PCI.

The diagnosis of ST-elevation MI was based on typical angina chest pain, ST segment elevation on body surface ECG, and positive a troponin test.

Study Protocol

On admission, all patients received aspirin, clopidogrel and lipid-lowering drugs as standard management. All proceeded with PCI within 6 h of the onset of chest pain. PCI was performed using standard techniques. The selection of catheters, stents and adjunctive therapies was left to the discretion of the operators. Coronary angiography was performed through the right femoral approach. Stent (drug-eluting stent or bare metal stent) was implanted and direct stenting was allowed if suitable culprit lesion was visualized^{6,9}. Success of PCI was defined as TIMI flow grade 2 or 3 and residual stenosis < 50% at the culprit coronary artery.

Measurement of PICP and PIIINP

PICP and PIIINP were measured from venous blood samples collected before PCI, 7 days and 3 months after PCI. The post-PCI blood samples were collected between 8-9 am each morning. All samples were centrifuged immediately at 3000 rpm for 10 min and plasma samples were stored at -70 °C until assay. PICP and PIIINP were measured by enzymelinked immunosorbent assay (ELISA) (Fanbang Biotech, Dalian, China). The interassay coefficient of variation (CVs) for PICP and PIIINP were 1.2% and 1.6% at mean values of 1.7 ng/mL and 1.6 pg/mL, respectively, and the intraassay coefficients of variation were 1.4% and 2.3% at mean values of 1.4 ng/mL and 1.3 pg/mL, respectively.

Echocardiographic studies

The left ventricular function was assessed with two-dimensional and Doppler echocardiographic studies performed 3, 6 and 12 months after PCI (ViViD7 cardiac ultrasound unit, 2.5-MHz transducer, GE, PA, USA). The examiner of the echocardiography was not aware of the patient's clinical data. Left ventricular ejection fraction was measured from the apical views by Simpson's biplane method. The mean of 3 measurements was used.

Follow-up

Patients were followed-up monthly for 12 months after MI in our cardiology clinics. Data on medication compliance after discharge and occurrence of end points were recorded. Primary endpoint was death due to any cause. The secondary endpoints were recurrent MI, PCI or coronary artery bypass grafting (CABG), readmission for heart failure and stroke.

Statistical analysis

SPSS 13.0 was used for statistical analysis. Quantitative variables are expressed as mean $\pm$ SD. Categorical data were compared by Fisher's exact test. Comparisons of numerical data between groups were conducted by student t tests. ANOVA was used to compare the data collected from day 7, 3, and 6 months. Pearson correlation analysis was performed to assess the relations between the serum levels of PICP and PIIINP and the left ventricular ejection fraction. Multivariate logistic regression analysis was performed to identify predictors of adverse cardiac events. A *P* value < 0.05 was considered statistically significant.

RESULTS

General finding

PCI was successful in all patients. There were no mortalities during hospitalization and patients were discharged after an average of 3.2 ± 2.1 days of post-procedural hospital stay.

All patients completed the follow-up. One or more end points were observed in 29 patients (13.8%). Four patients (1.9%) died of sudden cardiac death between 6 to 12 months after the discharge. Eight patients (3.8%) required target lesion revascularization. Recurrent non-fatal MI occurred in 6 (2.9%), and newly developed heart failure required hospitalization was found in 9 (4.3%). Stroke was found in 2 (1.0%) patients.

As shown in Table 1, there was no statistically significant difference between patients with or without end points in age, sex, baseline cardiovascular risk factors, locations of MI and the number of coronary arteries involved at the initial presentation. The mean systolic blood pressure in patients with an end point was higher than in the patients without an end point (*P*=0.02). There was no statistically significant difference in the post-PCI pharmacological therapies between the two groups (*P*>0.05).

Left ventricular function in patients with and without an end point

There was no statistically significant difference in the left ventricular ejection fraction between patients with and without an end point at 3-month follow up ($53.4 \pm 6.8\%$ vs $58.7 \pm 8.5\%$, *P*>0.05). However, the mean left ventricular ejection fraction in patients with an end point was lower than in the patients without an end point at 6 months ($51.4 \pm 6.6\%$ vs $59.6 \pm 7.2\%$, *P*<0.05) and 12-month ($51.5 \pm 9.1\%$ vs $57.2 \pm 9.4\%$, *P*<0.05) follow-up. Pearson correlation analysis showed that the level of PICP at day 7 (*r*= -0.630, *P*=0.001) and at 3 months (*r*= -0.671, *P*=0.001) were negatively associated with left ventricular ejection fraction measured at 6 months following PCI. There was no statistically significant correlation between PIIINP and the post-PCI left ventricular ejection fraction (*P*>0.05).

Table 1. Comparison of baseline characteristics.

	With end points (n=29)	Without end points (n=181)	<i>P</i>
Age (yrs)	64.6 ± 10.0	62.7 ± 9.4	NS
Sex (male, %)	18 (62.1%)	114 (63.0%)	NS
Hypertension (%)	12 (41.3%)	79 (43.6%)	NS
SBP (mmHg)	139.2 ± 12.0	121.8 ± 10.4	0.02
DBP (mmHg)	80.6 ± 9.8	79.5 ± 10.2	NS
Diabetes (%)	9 (31.0%)	55 (30.4%)	NS
Anterior MI (%)	20 (68.9%)	124 (68.5%)	NS
Inferior MI (%)	9 (31.1%)	57 (31.5%)	NS
Coronary lesions			NS
Single vessel	12 (41.3%)	76 (42.0%)	
Double vessel	9 (31.0%)	54 (29.8%)	
Three vessel	8 (27.6%)	51 (28.2%)	
Post-PCI therapies			
Aspirin (%)	18 (100%)	32 (100%)	NS
Clopidogrel (%)	29 (100%)	181 (100%)	NS
ACEI/ARB (%)	28 (96.6%)	176 (97.2%)	NS
Beta-blockers (%)	26 (89.7%)	164 (90.6%)	NS
Statins	29 (100%)	181 (100%)	NS

MI, myocardial infarction; SBP and DBP, systolic and diastolic blood pressure; PCI: percutaneous coronary intervention; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; NS, no significance.

Table 2. Comparison of PICP and PIIINP between the two groups.

	PICP (ng/mL)	PIIINP (pg/mL)
With an end point (n=29)		
Pre-PCI	11.01±2.19	32.21±4.02*
Day 7	19.45±2.17**▲	59.34±4.23**▲
3-month	29.87±3.02*▲	49.67±6.93*
6-month	15.04±3.29*	36.87±7.45*
Without an end point (n=181)		
Pre-PCI	10.76±2.60	30.44±4.96
Day 7	14.95±3.07**	48.78±4.23**
3-month	22.14±3.33*	40.93±6.94
6-month	13.56±2.53	31.57±5.68*

** $P < 0.01$ compared with the before percutaneous coronary intervention (PCI) value in the same group; * $P < 0.05$, compared with Day 7 in the same group; ▲ $P < 0.05$, compared with the patients without an end point.

Comparison of PICP and PIIINP in patients with and without an end point

As shown in Table 2, in patients with and without an end point, the day 7 serum PICP and PIIINP were higher than the pre-PCI levels within each group ($P < 0.001$). The mean level of serum PICP at 3-month was higher than that at day 7 in the two groups ($P < 0.05$). At the end of 6 months, the mean level of PICP in patients with an end point was lower than at the day 7 ($P < 0.05$). In patients without an end point, there was no statistically significant difference in the mean PICP level between day 7 and 6 months ($P > 0.05$).

In both groups, the mean PIIINP level 6 months after the PCI was lower than that at day 7 ($P < 0.05$). The mean

day 7 level of PIIINP in patients with an end point was higher than in the patients without ($P < 0.05$).

Predictive value of PICP and PIIINP on composite end points

Multivariate logistic regression analysis revealed that the predictors of adverse cardiovascular events were age (OR=2.612, 95% CI, 1.315-4.850, $P=0.01$), left ventricular ejection fraction 3 months after PCI (OR=3.820, 95% CI 1.9522-6.479, $P < 0.001$), day 7 (OR=2.170, 95% CI 1.583-4.345, $P=0.01$) and 3-month level of serum PICP (OR=2.340, 95% CI 1.431-4.650, $P=0.01$). PIIINP was not an independent predictor of the composite end point ($P > 0.05$).

DISCUSSION

The main findings of this study are: a) There was an elevation in the serum PICP and PIIINP within the first three months of PCI in patients with STEMI; b) The day 7 and 3-month levels of PICP and PIIINP in patients who suffered from a major adverse cardiovascular event were higher than in patients without a major cardiovascular event 12 months after the PCI; c) Together with age and post-PCI left ventricular ejection fraction, the serum levels of PICP 7 days and 3 months after the PCI are an independent predictor of adverse cardiovascular events. These results suggest that post-PCI levels of PICP may be used to assess patient's risk and to facilitate post-procedural monitoring and management.

Postinfarction left ventricular remodeling is a complex process. Infarct expansion, which results in ventricular dilatation and thinning of the wall in the first few hours of MI, involves the degradation of the intermyocyte collagen struts triggered by serine proteases and matrix metalloproteinases¹⁰. Serum levels of PICP, an indicator for myocyte collagen degradation or turnover, were found to closely relate to left ventricular function and the prognosis of MI (ref.¹¹). Matrix metalloproteinase-1, an enzyme responsible for extracellular collagen degradation and remodeling, was also elevated in the first two weeks following MI (ref.¹²). Matrix metalloproteinase-1 measured 7 days and at 2 weeks of the MI was negatively correlated with the left ventricular ejection fraction¹². In the present study, the serum PICP was elevated in patients with or without an end point, and the mean serum PICP levels at 3 months were higher than on day 7, suggesting the collagen turnover may have reached its peak approximately 3 months after the onset of MI. In patients with an end point, the mean left ventricular ejection fraction at 6 months was lower than in patients without a major adverse cardiovascular event. There was a negative correlation between the day 7 and 3-month serum PICP levels and the left ventricular ejection fraction 6 months after the PCI. Serum PICP levels measured 7 days and 3 months after PCI predicted the major adverse cardiovascular events 12 months after the PCI. These results indicate that a high level of serum PICP following successful PCI is associated with ventricular remodeling and deterioration of left ventricular function, and adverse cardiovascular outcomes.

The value of serum PIIINP in predicting the prognosis of MI is uncertain. Primary coronary revascularization within 6 h of MI was associated with a greater reduction of PICP than the revascularization performed more than 12 days after the MI (ref.⁹). However, the early coronary revascularization was not associated with a greater reduction in serum PIIINP (ref.⁹). A recent study on 233 patients with acute MI also failed to show any longitudinal changes or predictive values of serum PIIINP (ref.¹³). In the present study, although serum PIIINP levels were elevated following MI and PCI, they were not correlated with the left ventricular ejection fraction 3 or 6 months after PCI. Post-PCI serum levels of PIIINP did not predict the adverse cardiovascular events 12 months after the

PCI. These results suggest that although serum PIIINP may reflect post-MI ventricular remodeling, it is not a reliable indicator for post-MI ventricular function or adverse clinical outcomes.

In conclusion, serum cardiac collagen biomarkers were elevated following acute ST-elevation MI. Successful PCI was associated with a reduction in serum PICP and PIIINP. Persistent elevation of serum PICP within the 3 months following PCI was associated with left ventricular dysfunction, and major adverse cardiovascular events 12 months after the PCI.

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