ORIGINAL PAPER

Serum Periostin Levels in Acute Myocardial Infarction Patients: a 3-month Follow-up Study

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ABSTRACT

Background: Heart attack, acute myocardial infarction, are a major cause of morbidity and mortality in Western countries and are rapidly pandemic in developing and underdeveloped countries. Periostin concentration increases in the blood of patients after acute myocardial infarction and affects the process of cardiac remodeling leading to myocardial fibrosis. **Objective:** To evaluate the correlation between serum periostin levels and cardiac function and acute myocardial infarction patients' short-term prognosis (three months after onset).**Methods:** Fifty-two acute myocardial infarction patients were prospectively enrolled in the present study, and 52 controls were established. The levels of periostin of acute myocardial infarction patients at 5-7 days after the onset were measured using enzyme-linked immunosorbent assay. Other blood tests and echocardiography were performed during the patient's hospital stay. The correlation between periostin and TIMI, GRACE scores, body mass index, laboratory findings, and 3-month post- acute myocardial infarction data, including pro-B-type natriuretic peptide and echocardiographic parameters, were investigated. **Results:** Serum periostin levels increased significantly in acute myocardial infarction patients compared with normal controls. There was an association between serum periostin at diagnosis and cardiac function three months after acute myocardial infarction: serum periostin was in negative correlation with ejection fraction ($r = -0.31$, $p = 0.028$); positive association was found between serum periostin level and left ventricular end-diastolic diameter ($r = 0.38$, $p = 0.006$). **Conclusion:** Serum periostin levels increase in acute myocardial infarction, and serum periostin can be used to predict cardiac function three months after acute myocardial infarction.

Keywords: periostin, acute myocardial infarction, cardiac function.

1. BACKGROUND

Cardiovascular diseases, including acute myocardial infarction (AMI), are a major cause of morbidity and mortality in Western countries and are rapidly pandemic in developing and underdeveloped countries (1). AMI is a dangerous and rather common disease, and it is about 3 million people suffer from AMI every year in the world. This pathology tends to increase in Vietnam, and AMI is the leading cause of death among ischemic heart diseases (2). The number of deaths from AMI is still high: in a Europe country like Romania, AMI caused more than half a million deaths between 1994 and 2017, while in the United States, in a decade from 2012 to 2022, there were more than 1.5 million deaths related to AMI (3, 4).

Periostin (PN) was first detected in rats by Takeshita in 1993, then known as OSF-2 (Osteoblast Specific Factor 2), with a molecular weight of 90 kDa secreted by fibroblasts (5, 6). Periostin is produced by osteoblasts, fibroblasts, and the heart valve of human adults is also the site of secretion (7). Serum PN increases significantly after AMI, affecting cardiac remodeling, then chronic myocardial fibrosis. In the long term, it will lead to heart failure due to excessive remodeling, increasing cardiac fibrosis. Cardiomyoblast activation is a key step in the pathogenesis of heart failure, and periostin is likely to contribute to the increased endurance of these cells in heart failure, particularly by increasing the endurance of these cells in the post-infarction scar healing process (8).

Heart failure is a common complica-

Categorical variables		Mean±SD of PN (ng/mL)	p
Sex	Male (n = 27)	200.45±79.18	0.684
	Female (n = 25)	211.44±112.47	
Increasing systolic blood pressure (SBP)	+ (n = 35)	214.10 ±100.79	0.371
	0 (n = 17)	188.50±82.31	
Smoking	+ (n = 14)	190.18±75.49	0.483
	0 (n = 38)	211.47±102.59	
Diabetes	+ (n = 9)	236.28±123.68	0.297
	0 (n = 43)	199.34±89.40	

Table 1. The relationship between categorical variables and 1st serum PN.

Categorical variables		Mean±SD of PN (pg/mL)	p
TIMI	Low risk (n = 16)	2265.54±1076.59	0.815
	Medium risk (n = 14)	2039.23±654.73	
	High risk (n = 10)	2201.31±1180.06	
GRACE	Low risk (n = 8)	2313.56±1334.56	0.154
	Medium risk (n = 15)	1795.11±664.31	
	High risk (n = 17)	2433.88±928.18	

Table 2. The relationship between TIMI, GRACE scores (40 cases of non ST-elevation AMI), and 1st serum PN levels.

tion after AMI and significantly increases mortality risk (9). The frequency of heart failure 30 days after AMI was 13%, after infarction from 30 days to 1 year, and an average of 3.2 years after AMI was 32,6% và 12.6%, respectively (10). The improvement in survival after AMI predisposes the patient to subsequent ischemic heart disease, a major cause of heart failure (11).

The state of heart failure after AMI is currently a medical burden for patients, their families, and society. So that the prognosis of cardiac function after AMI is essential because it affects the choice of treatment as well as the subsequent follow-up, and biomarkers play an important role in prediction. PN has recently begun to be studied in that general trend, although the scale is still quite modest, and the number of studies is not much in some countries. However, with positive results from these researches, serum PN promising to be an effective and necessary factor in contributing to the prognosis of cardiac function after AMI.

2. OBJECTIVE

In this study, the serum levels of PN in AMI patients were calculated to evaluate the correlation between serum PN levels with cardiac function and short-term prognosis in AMI patients.

Continuous variables	Pearson correlation coefficient	p
Age (year)	- 0.07	0.603
BMI (Body Mass Index) (kg/m2)	0.13	0.358
Killip	- 0.03	0.859
Troponin Ths (ng/L)	- 0.11	0.503
Glucose (mmol/L)	0.08	0.599
Ure (mmol/L)	- 0.03	0.852
Creatinin (μmol/L)	0.15	0.281
Cholesterol (mmol/L)	0.04	0.805
HDL-c (HDL-cholesterol) (mmol/L)	- 0.11	0.431
Triglycerid (mmol/L)	- 0.08	0.583
WBC (White Blood Cell) (103/μL)	- 0.001	0.994
TIMI	- 0.04	0.804
GRACE	0.12	0.475
Smoking	- 0.10	0,483
Diabetes	0.15	0.297
Aspirin	-	-
Clopidogrel	-	-
Statin	-	-
Angiotensin II/ ACEi	-	-

Table 3. The relationship between continuous variables and PN in the first time.

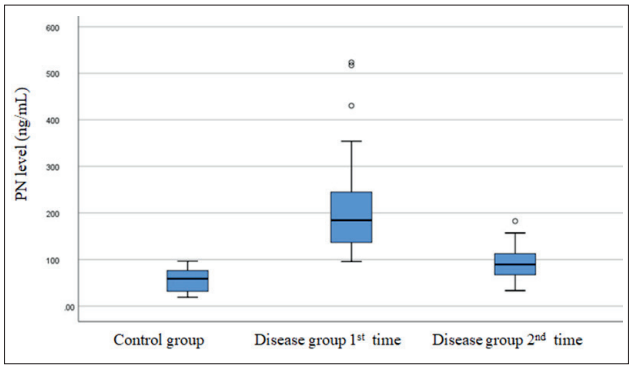

Figure 1. Serum PN level in control group (n = 52), disease group 1st time (n = 52) disease group 2nd time (n = 52).

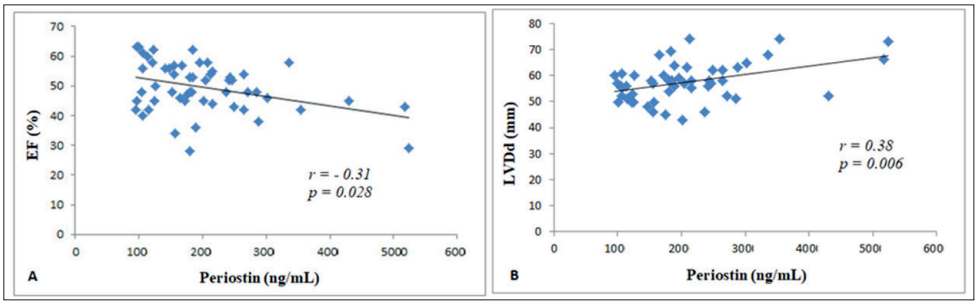

Figure 2. The relationship between serum PN and EF (A) and LEVDd (B) 3 months after AMI (n = 52).

3. MATERIAL AND METHODS

3.1. Study population

We prospectively enrolled 52 patients of acute myocardial infarction from the two hospitals in Vietnam between October 2020 and July 2022. The controls were 52 patients without coronary lesions confirmed by clinical examination and electroencephalogram (ECG). Patients in the controls were the same age as the study group.

Patients who met two of the following criteria were included: (1) Elevation of cardiac troponins in peripheral blood (Troponin T and/or Troponin I); (2) Presence on EEG of new ST elevation at the J point in at least 2 contiguous leads of 0.2

Parameters		PN	
		rs	p
Pro-BNP	1st time	0.25	0.077
	2nd time	0.40	0.004
Parameters on 1st echocardiogram	EF	0.05	0.712
	LAD	- 0.22	0.110
	LEVDs	- 0.13	0.357
	LEVDd	- 0.08	0.571
Parameters on 2nd echocardiogram	EF	- 0.31	0.028
	LAD	- 0.19	0.172
	LEVDs	0.26	0.066
	LEVDd	0.38	0.006

Table 4. Correlation between echocardiographic parameters, pro-BNP and 1st serum PN.. LAD: Left Atrium Diameter; LEVDs: Left Ventricular End Sysstolic Diameter

Factors	OR (95% confidence interval)	p
Pro-BNP 2nd time	0.01 (- 0.03 – 0.05)	0.552
EF 2nd time (%)	- 31.73 (- 59.86 - - 3.59)	0.028
LEVDd 2nd time (mm)	51.54 (17.97 – 85.11)	0.003

Table 5. Multivariate regression analysis.

Parameters	Higher PN	Lower PN	p
Male gender (n (%))	13 (50.00)	14 (53.85)	0.781
SBP increased (n (%))	18 (69.23)	17 (65.38)	0.768

Table 6. Characteristics of categorical variables in non ST elevation AMI patients in 2 groups of PN for the first time.

mV in males or 0.15 mV in females in leads V2–V3 and/or of 0.1 mV in other contiguous chest leads or the limb leads; New or presumably new left-bundle branch block; (3) Clinical manifestation of ischemic type chest pain.

We excluded patients with moderate to severe valvular heart disease, dilated cardiomyopathy, concomitant inflammatory or malignant disease, hypertrophic or idiopathic cardiomyopathy, myelofibrosis, pulmonary fibrosis, scleroderma, atopic dermatitis, malignancies, or blood creatinine levels > 356.6 μmol/L (4 mg/dL).

3.2. Determination of serum PN

The first PN serum sample was taken on days 5-7 of AMI, and other blood parameters were taken during the patient's hospital stay. These first PN parameters will be used to compare and find correlations in this article. Serum samples for the 2nd PN and 2nd pro-BNP were taken three months after the patient had AMI. The second test of serum PN aims to monitor the change in PN concentration over time.

Serum periostin levels were quantified by enzyme-linked immunosorbent assay technique using the My BioSource Human Periostin kit according to the manufacturer's instructions. This technique uses a human-specific anti-periostin antibody attached to a well. First, 100 μl of diluent serum samples and periostin standards of different concentrations were added to the well and incubated for 90 min at room temperature. Then, the wells were washed with wash buffer, and 100 μl of biotin-bound human anti-periostin antibody was added and incubated for 60 min at 37°C. After washing off unbound biotin-bound antibodies, 100 μl of HRP-conjugated streptavidin was added to the well and incubated for 45 min at 37°C. Next, the wells were washed again, and 100 μl of TMB substrate solution was added to each well and incubated for 30 min at 37°C. The reaction was stopped with 100 μl of stopping solution. The color intensity of the response was measured at 450 nm.

Parameters	Higher PN	Lower PN	p
Age (year)	72.08±15.48	69.96±13.94	0.607
BMI (kg/m2)	22.79 ±3.36	22.16±3.18	0.492
Killip	1.81±0.85	1.62±0.80	0.406
Troponin Ths (ng/L)	2782.56±3369.85	2531.69±3171.33	0.827
Glucose (mmol/L)	8.42±2.99	8.33±5.38	0.937
Ure (mmol/L)	7.14±3.17	7.47±4.35	0.757
Creatinin (μmol/L)	110.57±59.99	99.96±58.76	0.522
ChoTP (mmol/L)	5.71±1.44	5.15±1.25	0.141
HDL-c (mmol/L)	1.15±0.35	1.20±0.57	0.731
Triglycerid (mmol/L)	2.56±2.25	2.07±1.18	0.328
WBC (103/μL)	11.80±3.72	12.30±5.73	0.713
Hb (g/dL)	12.34±2.23	12.28±2.19	0.925

Table 7. Characteristics of continuous variables in non ST-elevation AMI patients in 2 groups of PN for the first time.

3.3. Echocardiography

The first echocardiography was performed during the patient's hospital stay; the second echocardiography was done three months after AMI.

3.4. Statistical analysis

The statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) software (IBM SPSS Statistics 20.0, IBM Corp., Armonk, NY, USA). The measurement data were expressed as mean±SD, and the categorical data were expressed as percentages. Comparisons between 2 measurement groups were performed with Student's t-test, and comparisons among three or more groups were analyzed by one-way ANOVA. A Chi-square test was used to compare the difference between categorical variables. Spearman correlation was used to perform the relationship between serum PN level and other parameters. A p value of <0.01 or <0.05 was considered significant.

4. RESULTS

Among 52 AMI patients, males accounted for 51.92%, and females were 48.08%. The mean age of AMI patients was 71.02±14.63 years (males 67.33±15.15 years, females 75.00±13.20 years). The concentration of PN in the AMI group when taking serum for the first time on days 5-7 of the disease was 205.73±95.81 ng/mL (in males 200.45±79.18 ng/mL, in females 211.44±112.47 ng/mL). The concentra-tion of serum PN at three months post-AMI collection was 91.52±33.18 ng/mL.

The mean serum PN concentration of the control group was 57.21±24.57 ng/mL, which was 52.45±25.78 ng/ mL (18.68 94.55 ng/mL) in males and 62.34±22.58 ng/ mL (188.89 965.12 ng/mL) in females.

Gender, SBP, smoking, diabetes were not correlated with PN concentrations (Table 1). The concentrations of serum PN in different risk groups in the TIMI, GRACE scales were not different (Table 2).

The median value of PN in the control group was 58.79 ng/mL, while and in the group of patients, the median value of the first sampled PN was 184.18 ng/mL, the second time was 89.24 (Figure 1).

These continuous variables were not correlated with PN concentrations (all p > 0.05) (Table 3). Second-time ProBNP

and two echocardiographic parameters three months after AMI as EF and LEVDs were correlated with serum PN level 1st time (with p of 0.004; 0.028 and 0.006), respectively (Table 4). After multivariable regression analysis, we recorded that two parameters collected for the second time three months after AMI (EF and LEVDd) were correlated with PN (Table 5). Gender, increased SBP did not significantly differ between the two groups of higher and lower PN concentrations ($p > 0.05$) (Table 6). The presented continuous variables did not have a significant difference between the two groups of higher and lower PN concentrations ($p > 0.05$) (Table 7). Serum PN concentration is positively correlated with LEVDd (Figure 2A) and negatively correlated with EF (Figure 2B).

5. DISCUSSION

This study aimed to evaluate the possibility of using serum PN level as a biomarker to predict cardiac function three months after AMI. The study examined the change of PN concentration over time after MI as well as explored the relationship between serum PN concentration and cardiac function, clinical and laboratory characteristics, TIMI, GRACE scores.

The mean age of the group of patients was 71.02±14.63 years old, slightly higher than that of the research of Ling (63.30± 12.78 years) (12). The concentration of serum PN was highest in the group of patients when the first serum was drawn. Three months after AMI, serum PN concentration decreased strongly but was still higher than the control group. This is consistent with the process of changing PN levels in the blood after MI that He, Taniyama, and Walker mentioned (13-15).

The rate of gender difference between men and women in our study is just a little (51.92% and 48.18%). This result is much different from the study of Cheng, where men account for a much higher percentage than women (76.7% and 23.3%) (2). The difference can be explained by this ratio depending on the time of study.

Serum PN levels were found to not correlate with categorical variables, including age, sex, the elevation of systolic blood pressure at admission, TIMI, and GRACE scores. The concentration of PN in this study was also not correlated with continuous variables, including age, BMI, Killip, troponin Ths, glucose, urea, creatinine, ChoTP, HDL-c, triglyceride, white blood cell, and Hb.

Serum PN concentration correlated with parameters of the second echocardiography re-evaluated three months after AMI, including EF and LEVDd. Specifically, PN was negatively correlated with EF ($r = - 0.31$, $p = 0.028$). This result is similar to the study of Cheng and the correlation level is not too different: - 0.31 compared to - 0.50 of Cheng et al (2) In a study by Ling, the group of subjects with ST-elevation myocardial infarction also had similar conclusions about the negative correlation between PN and EF after six months of AMI with $p = -0.472$ (12). This shows that patients with lower EF have higher PN levels, meaning that patients with higher PN levels have more impaired cardiac function. Sanada et al found that periostin levels were significantly correlated with the severity of AMI (16). Imoto et al demonstrated that periostin stimulates nitric oxide production in right ventricular fibroblasts. This may induce systolic dysfunction by inhibiting the activity of myocardial calcium channels due to pulmonary arterial hypertension (17).

In addition, serum PN levels were positively correlated with LEVDd ($r = 0.38$, $p = 0.006$). The study of Ling also recorded the correlation between PN and LEVDd with a similar result ($r = 0.46$, $p = 0.004$) (12). This means that the higher the concentration of PN, the greater the LEVDd 3 months after MI, indicating more thickening of the left ventricular wall due to excessive remodeling after AMI. An advantage of periostin is that it can be detected and quantified in peripheral blood samples, making it easy to perform (18). Therefore, PN may be a potential biomarker of cardiac remodeling in patients with heart failure (19).

6. CONCLUSION

In AMI patients, serum PN levels increased significantly at day 5-7 of the disease and had a strong decrease after three months. Serum PN level was correlated with two parameters in echocardiography at three months after AMI: PN was negatively correlated with EF, and positively correlated with LEVDd. Higher serum PN levels are associated with poorer left ventricular function and a worse short-term prognosis. Therefore, serum PN concentrations collected 5-7 days after MI can be used to predict cardiac function three months after AMI.

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- **Conflict of interest:** None declared.
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