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Role of plasma neuropeptide Y in acute myocardial infarction: a case-control study

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Abstract

Background As neuropeptide Y is associated with endothelial dysfunction, this study explored the relationship between neuropeptide Y and acute myocardial infarction.

Methods We included 128 acute myocardial infarction cases and 62 controls. Using the SYNTAX scoring system, the acute myocardial infarction group was sub-grouped into "SYNTAX ≤ 22," "SYNTAX = 23–32," and "SYNTAX ≥ 33." Plasma neuropeptide Y, endothelin, endothelial nitric oxide synthase, and thromboxane A2 levels were measured.

Results The acute myocardial infarction group had higher plasma neuropeptide Y, endothelin, and thromboxane A2 levels than controls ([58.76 ± 17.63 vs. 37.48 ± 11.36 ng/ml, $P = 0.000$], [36.16 ± 10.04 vs. 27.80 ± 7.18 pg/ml, $P = 0.000$], and [27.69 ± 6.91 vs. 24.32 ± 7.28 pg/ml, $P = 0.002$], respectively). The acute myocardial infarction group also had lower plasma endothelial nitric oxide synthase levels than controls (3.00 ± 0.94 vs. 4.05 ± 1.44 ng/ml, $P = 0.000$). Additionally, the receiver operating characteristic curve analysis showed that a neuropeptide Y value of 49.94 ng/ml could help diagnose acute myocardial infarction (sensitivity: 70.9%; specificity: 91.9%). The SYNTAX scores, smoking, plasma endothelin, thromboxane A2, and neuropeptide Y levels were positively correlated, whereas plasma endothelial nitric oxide synthase and neuropeptide Y levels were negatively correlated. Lastly, plasma neuropeptide Y levels were different among subgroups ($P < 0.05$); patients with higher SYNTAX scores had higher neuropeptide Y levels.

Conclusions The levels of plasma NPY may be accociated with the AMI process.

Highlights

- NPY may be involved in the occurrence and progression of AMI.
- NPY is closely related to endothelial dysfunction.
- NPY can be used to diagnose AMI and indicate the severity of coronary artery disease.

Keywords Acute myocardial infarction, Endothelial function, Neuropeptide Y

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Background

In recent decades, cardiovascular disease has become the leading cause of death worldwide, and acute myocardial infarction (AMI) is the main cause of cardiac death. While the diagnosis and treatment of heart disease have become major challenges in global healthcare [1], high-sensitivity detection of cardiac troponin levels significantly improves the diagnostic rate for AMI [2]. Traditional treatments for AMI including antiplatelet, thrombus prevention, lipid-lowering medications, coronary intervention, and surgical treatment, have reduced the rate of sudden cardiac death [3]. However, owing to the metabolic characteristics of myocardial zymograms and the shortcomings of coronary enhanced computed tomography and coronary angiography examinations, diagnoses of atypical AMI are often clinically missed [4]. For the diagnosis and treatment of AMI, technologies that improve its prevention and treatment are urgently needed.

Recent research has shown that the neuropeptide Y (NPY) system is closely associated with risk factors for coronary heart disease [5]. As nicotine present in tobacco is the main cause of endothelial function $^{\text{disruption}}$ [6], multiple animal studies have shown that smoking affects plasma NPY levels [7]. The NPY family includes the peptide NPY, a pancreatic peptide, and peptide YY, each of which is composed of 36 amino acids. NPY plays an important role in appetite, anxiety, angiogenesis, and vasoconstriction, and is distributed in both the central and peripheral nervous systems, especially in the hypothalamus. As an appetite-promoting peptide, NPY can lead to obesity [8], promoting food intake and fat storage and thereby increasing the blood lipid concentration and synthesis of oxidized lipoprotein. This peptide also induces insulin resistance. Various pathological and physiological processes in coronary heart disease such as vascular regeneration, vasoconstriction, inflammatory response, and platelet aggregation are also affected by peptide Y, which is believed to be associated with endothelial dysfunction [9]. Endothelial products including endothelial nitric oxide synthase (eNOS), endothelin (ET), and thromboxane A2 (TXA2) affect the contraction and dilation of human blood vessels [10]. As AMI is difficult to properly diagnose, this study aimed to explore the relationship between NPY and AMI by answering the following questions: are plasma NPY concentrations related to the levels of endothelial hormones, and is there a correlation between the occurrence and progression of AMI and NPY?

Methods

The aim of this case-control study was to investigate the relationship between NPY and AMI.

Study population

Patients were enrolled at the Second Affiliated Hospital of Fujian Medical University between February 2019 and February 2021 after receiving approval from the Regional Ethics Council. All patients provided informed consent. All data are registered in ResMan in the form of "Case Record Form " (http://www.medresman.org.cn/login.aspx). The experimental group consisted of 128 patients with AMI who were hospitalized in the cardiovascular department. The control group consisted of 62 patients who met the inclusion at the physical examination center. The sample size of this study was estimated using "http://www.gpower.hhu.de/."

The following criteria were required for inclusion: (1) patients with a diagnosis of AMI (including acute ST-segment elevation myocardial infarction [STEMI] and acute non-ST-segment elevation myocardial infarction [NSTEMI]); (2) all patients with AMI who underwent coronary angiography that indicated coronary artery occlusion; (3) patients in the control group who had to complete tests such as cardiac ultrasound, electrocardiogram, and high-sensitivity troponin to rule out AMI; and (4) complete patient information, including basic information, medical history, and examination reports. The exclusion criteria were as follows: (1) patients in the control group who had a history of coronary heart disease; (2) patients who had a medical history of cerebrovascular disease, chronic infection, chronic obstructive pulmonary disease, malignant arrhythmia, diabetes, hypertension, and malignant tumors; and (3) patients with incomplete information. All patients with AMI underwent coronary angiography and complete revascularization and were administered standard drug treatment.

AMI adjudication, coronary angiogram interpretation, and coronary vessel assessment

Myocardial infarction was determined by a panel of two cardiologists using the Fourth Universal Definition and was further divided into the categories of STEMI and NSTEMI [11].

A cardiologist blinded to the patient characteristics evaluated the coronary angiography images, and two cardiologists with at least 10 years of experience in interventional surgery reviewed the interpretation of the imaging results and the severity of coronary artery disease. Differences between the two readers were resolved by consensus.

The anatomical complexity of coronary artery disease was graded according to the SYNTAX score, with higher scores indicating more complex coronary artery disease. SYNTAX scores were defined according to tertiles, with scores of 22 or lower defined as low, 23–32 as intermediate, and 33 or higher as high. The mechanisms and imaging manifestations of AMI are shown in Fig. 1.

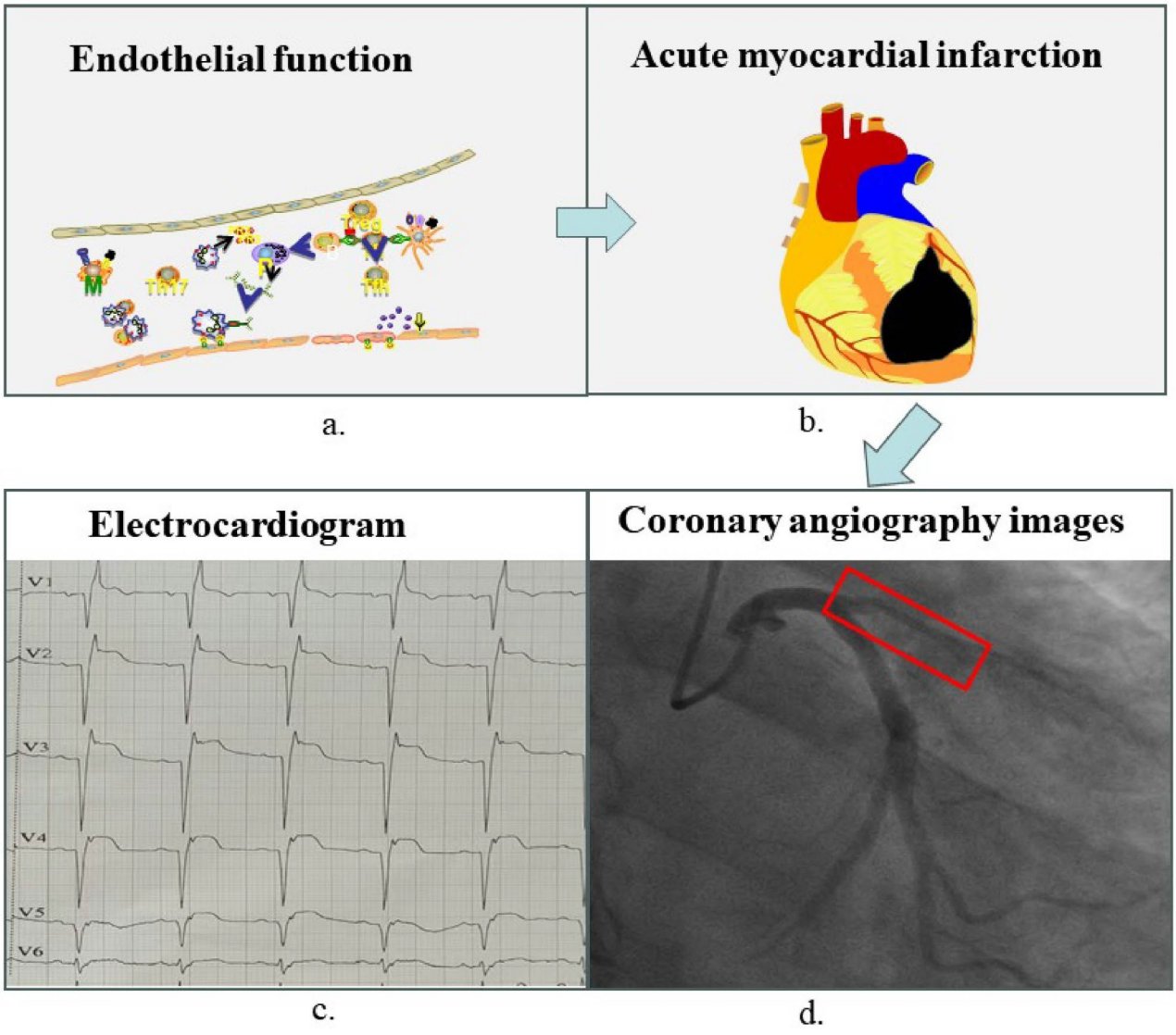

Fig. 1 Schematic diagram of acute myocardial infarction. **(A)** Schematic diagram of endothelial dysfunction. **(B)** Schematic diagram of acute myocardial infarction. **(C)** Electrocardiogram showing the acute manifestation of left anterior descending coronary artery occlusion. **(D)** Coronary angiography image showing occlusion of the left anterior descending branch of the coronary artery

Measurement of NPY, ET, eNOS, and TXA2 levels

Peripheral venous blood samples were collected from all patients. After centrifugation, the plasma samples were frozen at -80 ℃ until use. Plasma levels of NPY, ET, eNOS, and TXA2 were then measured using an enzyme-linked immunosorbent assay according to the manufacturer's instructions (Life Sciences, Wuhan, China).

Statistical methods

Continuous variables are defined as mean±standard deviation; categorical variables are defined as percentages. The homogeneity of variance was tested using Levene's test, continuous variables were compared using Student's t-test, and categorical variables were compared using the chi-square test. Correlations between variables that followed a positive distribution were compared using Pearson's linear correlation analysis. All statistical tests were two-tailed, and a P-value less than 0.05 was considered statistically significant. We further determined the critical optimal NPY concentration for predicting AMI using a receiver operating characteristic (ROC) curve. Statistical analyses were conducted using the Statistical Package for the Social Sciences for Windows (version 26, IBM Corp., Armonk, NY, USA) and GraphPad Prism (version 8.3.0).

Results

Patient characteristics

In total, 190 patients were included in this study: 128 in the AMI group and 62 in the control group. The AMI

group was further divided into three subgroups based on SYNTAX scores. The detailed grouping of this study is shown in Fig. 2, with the baseline and clinical characteristics of the study groups displayed in Table 1. The two patient groups had similar characteristics regarding age, sex ratio, blood glucose level, and average blood pressure. However, a significant difference was observed between the two groups in terms of smoking history.

NPY, ET, eNOS, and TXA2 levels in the study groups

Plasma levels of NPY in patients with AMI were significantly higher than those in the control group (58.76±17.63 vs. 37.48±11.36 ng/ml, P=0.000) (Fig. 2A). Additionally, plasma levels of ET in patients with AMI were significantly higher than those in the control group (36.16±10.04 vs. 27.80±7.18 pg/ml, P=0.000) (Fig. 2B). Plasma TXA2 levels in patients with AMI were significantly higher than those in the control group (27.69±6.91 vs. 24.32±7.28 pg/ml, P=0.002) (Fig. 2D); in contrast, eNOS levels were significantly lower in patients with AMI (3.00±0.94 vs. 4.05±1.44 ng/ml, P=0.000) (Fig. 2C). To better explain the relationship between NPY and ET levels and myocardial infarction, we compared the NPY and ET levels for different types of myocardial infarction. As shown in Table 2, although there was no statistical difference in endothelial function and NPY levels between the STEMI and NSTEMI groups, we can see that NPY levels (74.91±14.92 vs. 61.91±13.80 ng/ml, P=0.081) and ET (38.74±10.80 vs. 35.27±9.75 pg/ml, P=0.076) tend to be higher in the NSTEMI group than in the STEMI group.

NPY concentration for predicting AMI

The ROC analysis results showed that the critical value of the NPY concentration for diagnosing AMI was 49.94 ng/ml, with a sensitivity of 70.9% and specificity of 91.9% (Fig. 3).

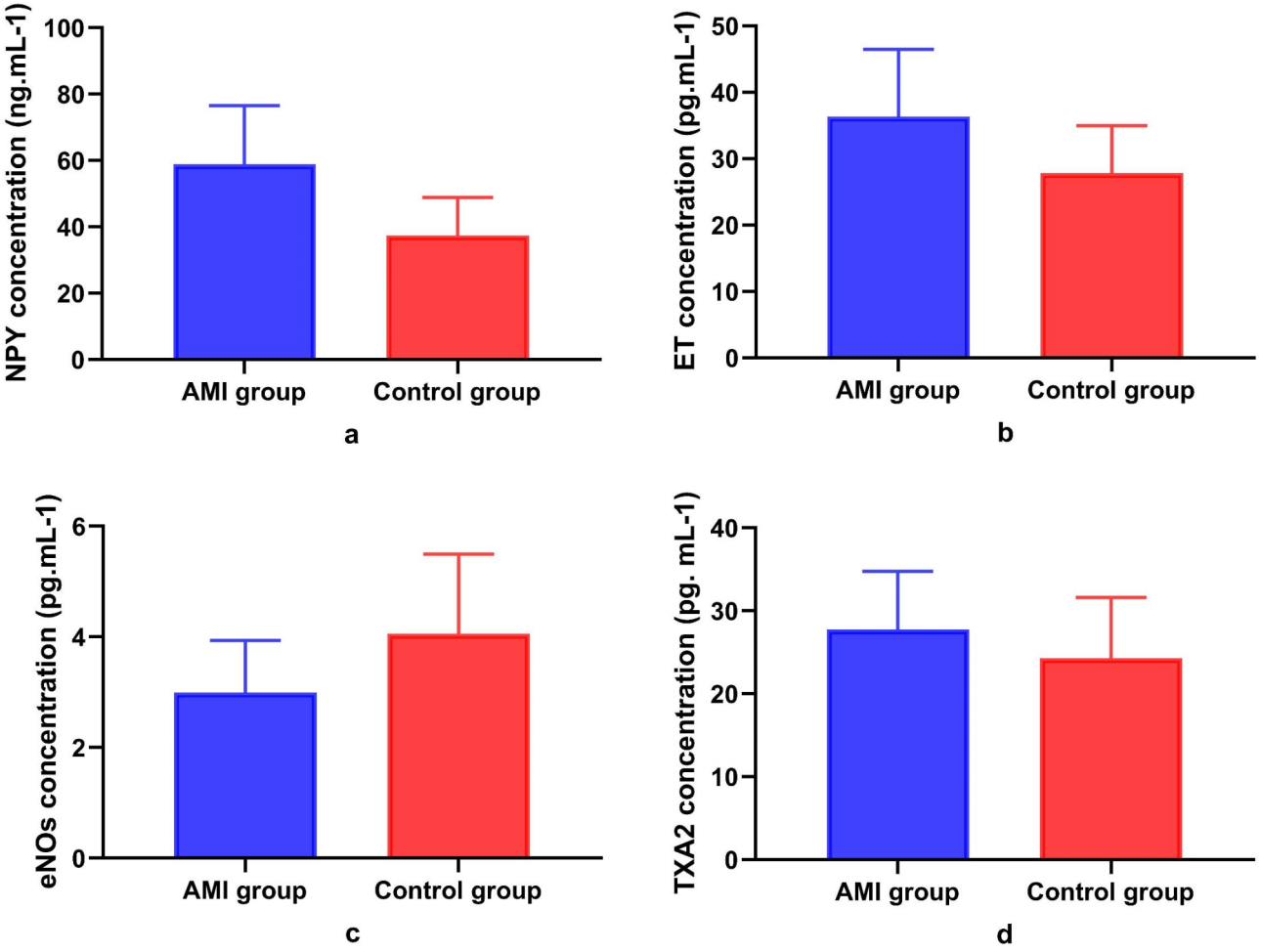

Fig. 2 Comparison of neuropeptide Y levels and endothelial function between the AMI and control groups. **(A)** Differential expression of NPY levels in two groups (P<0.05). **(B)** Differential expression of ET levels in the two groups (P<0.05). **(C)** Differential expression of eNOS in the two groups (P<0.05). **(D)** Differential expression of TXA2 in the two groups (P<0.05). AMI, acute myocardial infarction; ET, endothelin; eNOS, endothelial nitric oxide synthase; NPY, neuropeptide Y; TXA2, thromboxane A2

Table 1 Clinical characteristics of the two groups of participants

Index	AMI group($n=128$)	Control group($n=62$)	*P*
Demographics			
Smoking	71(55.5%)	20(32.3%)	0.009
Men	87(68.0%)	40(64.5%)	0.636
Age	54.34 ± 8.39	51.77 ± 8.50	0.05
BMI, kg/m^2	25.60 ± 1.24	24.58 ± 1.16	0.18
Clinical features			
mBP/mmHg	96.74 ± 13.86	90.94 ± 13.76	0.07
FPG/mmol.L^{-1}	6.03 ± 1.71	5.35 ± 0.89	0.04
HbA1c/%	6.22 ± 1.13	5.99 ± 0.68	0.086
Cre/umol.L^{-1}	81.68 ± 19.08	72.62 ± 18.72	0.184
TC/mmol.L^{-1}	4.91 ± 0.91	4.75 ± 1.26	0.05
TG/mmol.L^{-1}	1.70 ± 1.18	1.34 ± 1.49	0.100
LDLC/mmol.L^{-1}	3.09 ± 0.75	2.81 ± 1.00	0.043
Clinical presentation			
NSTEMI	60(46.9%)		
STEMI	68(53.1%)		
SYNTAX score			
≤ 22	46(35.9%)		
23 = 32	46(35.9%)		
≥ 33	36(28.1%)		
Culprit vessel			
Left anterior descending artery	77(60.2%)		
Left circumflex artery	10(7.8%)		
Right coronary artery	41(32.0%)		
Medication history (before sampling)			
Antiplatelet	58(45.3%)	16(25.8%)	
Beta-blocker	54(42.2%)	24(38.7%)	
Statin drugs	60(46.9%)	21(33.9%)	

BMI, body mass index; mBP, mean blood pressure; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; Cre, creatinine; TC, total cholesterol; TG, triglyceride; LDLC, low-density lipoprotein cholesterol

Table 2 Comparison of endothelial function and NPY levels between STEMI group and NSTEMI group

Index	STEMI	NSTEMI	*P*
n	64	62	
NPY/ng.mL^{-1}	61.91 ± 13.80	74.91 ± 14.92	0.081
ET/pg.mL^{-1}	35.27 ± 9.75	38.74 ± 10.80	0.076
eNOS/ng.mL^{-1}	3.02 ± 1.04	2.93 ± 0.83	0.638
TXA2/pg.mL^{-1}	27.50 ± 7.35	28.46 ± 6.17	0.476

Correlation analysis

Bivariate correlation analyses were conducted between NPY, cardiovascular risk factors, and endothelial function-related indicators. The results showed a positive correlation between smoking, ET concentration, TXA2 concentration, SYNTAX score, and NPY concentration and a negative correlation between the eNOS concentration and NPY levels (Table 3).

Subgroup analysis

Bivariate correlation analysis revealed a positive correlation between NPY concentrations and SYNTAX scores. Therefore, to further explore the correlation between NPY and coronary artery disease, the AMI group was divided into three groups based on SYNTAX scores, namely, "SYNTAX ≤ 22," "SYNTAX = 23–32," and "SYNTAX ≥ 33." The subgroup analysis demonstrated that the higher the SYNTAX score, the higher the NPY concentration. Thus, to some extent, the concentration of NPY indicated the presence of coronary artery lesions (Fig. 4).

Discussion

We found AMI group had higher plasma NYP, plasma ET and TXA2 levels and lower plasma eNOS levels than controls. The SYNTAX scores, smoking, plasma ET and TXA2 were positively correlated with NPY levels, whereas plasma eNOS were negatively correlated with NPY levels. Moreover, ROC curve analysis showed that the sensitivity and specificity of plasma NPY levels for predicting AMI were 70.9% and 91.9%, respectively.

Vascular endothelial cells secret eNOS and prostacyclin [12]for vasodilation, and secret ET and TXA2 [13] to promote platelet aggregation. Endothelial dysfunction may result in platelet aggregation, lipid deposition, and vascular plaque formation [14]. When the vascular plaque rupture and thrombus formation, the oxygen supply to the myocardial cells becomes disrupted, causing acute myocardial infarction [15]. Endothelial dysfunction is the critical pathological process of AMI. In the present study, the plasma ET and TXA2 concentrations were significantly higher, while the serum eNOS concentration was significantly lower in the AMI group than controls.Our findings further demonstrate a close correlation between endothelial dysfunction and AMI. At the same time, NPY was reported to associated with endothelial dysfunction. Nicotine, which induces endothelial dysfunction and atherosclerosis, can promotes NPY expression [16]. NPY levels were reported to positively correlated with ET and TXA2 levels [17]. And the concentrations of TXA2 and NPY in the blood were significantly enhanced after endothelial cell injury [18], . Herring et al. found that patients with STEMI after revascularization therapy had higher circulating NPY levels, and a positive correlation between NPY levels and infarct size compared to those with normal coronary angiography [19]. NPY promotes neovascularization by activating Y1R, Y2R, and Y5R, which are expressed in endothelial cells. Excessive neovascularization of atherosclerotic plaques accelerates plaque growth and increases the risk of plaque rupture and bleeding [20]. The present study found the level of NPY was increased with the level of plasma ET, TXA2, SYNTAX scores and smoking, and decreased with the level of eNOS in AMI group, which is consistent with

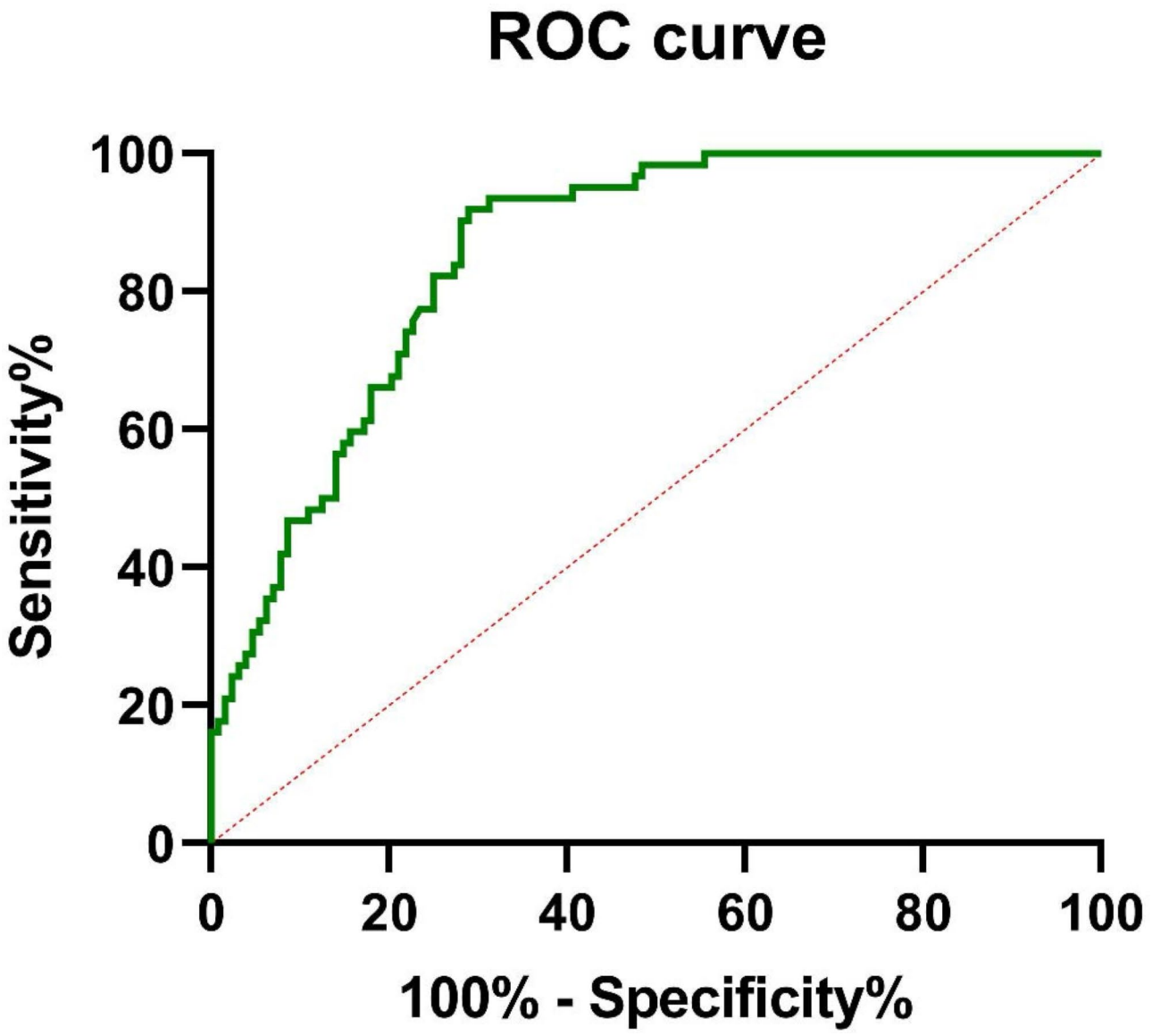

Fig. 3 Receiver operating characteristic curve analysis of neuropeptide Y levels for predicting acute myocardial infarction

Table 3 Bivariate correlation analysis results. NPY, neuropeptide Y; ET, endothelin; eNOS, endothelial NOS; TXA2, thromboxane A2

Variable	Bivariate correlation analysis	
	r	*P*
Smoking	0.19	0.009
ET	0.46	0.000
eNOS	-0.26	0.000
TXA2	0.242	0.001
SYNTAX score	0.82	0.000

previous research. It indicates that NPY may be accociated with the AMI process.And the possible pathological mechanism may involved in endothelial dysfunction. Our ROC analysis of the NPY concentration for diagnosing AMI was 49.94 ng/ml, with a sensitivity of 70.9% and specificity of 91.9%. It imply that the level of NPY may predict the the occurrence of AMI with more confidence.

The SYNTAX scores is a grading system that evaluates the complexity and prognosis of patients undergoing percutaneous coronary intervention (PCI). Higher SYNTAX score could predict major cardiac outcomes [21]. Our findings implies that the level of plasma NPY may also related to the major cardiac outcomes following PCI in patients. To clarfy the the diffenrence of NPY level in STEMI and NSTEMI patients, we also compared NPY and ET levels between STEMI and NSTEMI AMI patients. We found that the NPY and ET level of NSTEMI patients tends to be higher in STEMI patients. However, the final results proved to be no significant difference in NPY levels between the two types of AMI.

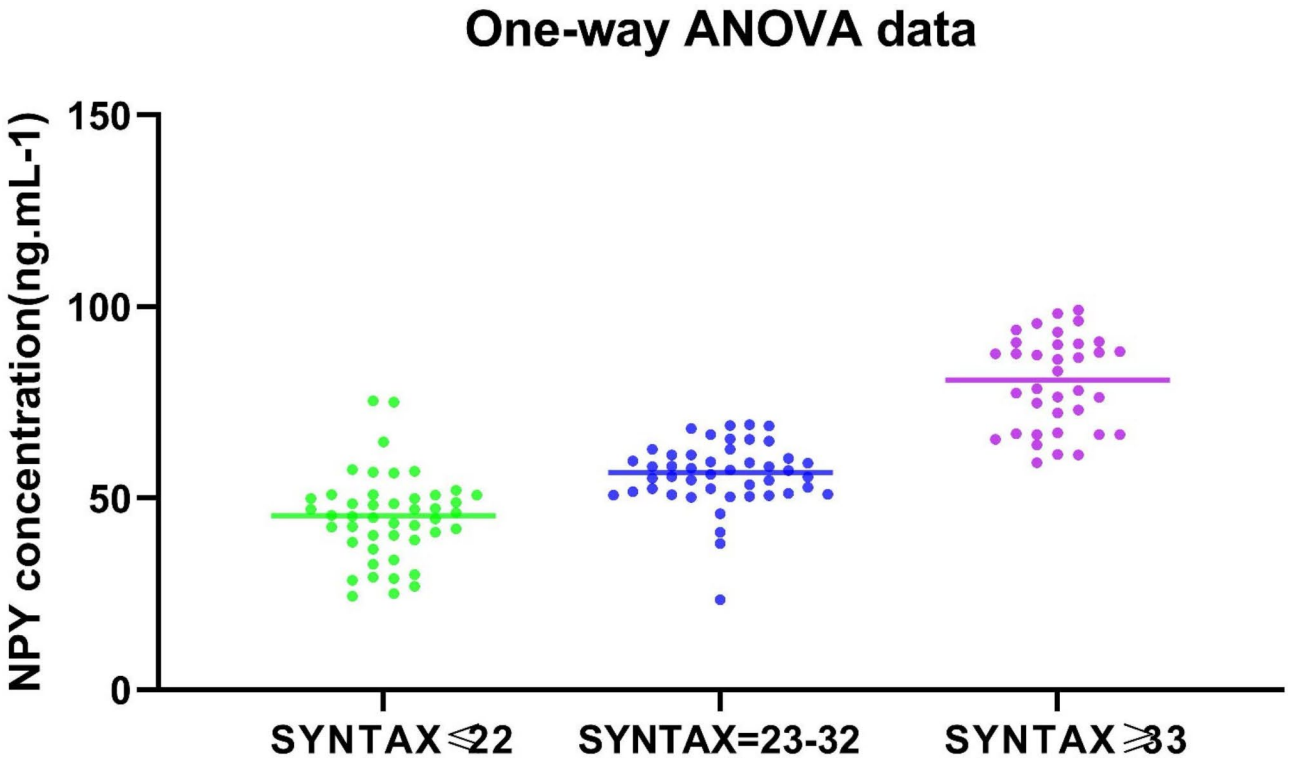

Fig. 4 Differential expression of neuropeptide Y in different grades of coronary artery scoring. There is a significant difference in NPY levels among the three groups ($P < 0.05$). NPY, neuropeptide Y

In previous studies, it was reported that NPY was significantly enhanced in PCI patients and animals with STEMI. And the incidence of ventricular tachycardia / ventricular fibrillation was increased at the same time [22, 23].Our results may be limited. It may due to the small sample size of the study. And we did not stratify the cardiovascular event rate, specific lesion severity, thrombus properties, etc. of the two types of AMI patients in the study. It should be carefully investigated in our future research.

Limitations of the study

The diversity of NPY determines its functional complexity. And the conclusions of this study cannot apply to all types of AMI. Additionally, the sample size of the study was relatively small, which result in the conclusions is limited. Thus, future studies which have increased sample size and multiple centers are need. Currently, research on NPY is primarily limited to animal experiments, and more human studies are required to confirm its function and effects.

Conclusions

The levels of plasma NPY may be accociated with the AMI process. The possible pathological mechanism may involve in endothelial dysfunction. Further randomized controlled studies are needed.

Abbreviations

AMI	Acute myocardial infarction
CRF	Case report form
eNOS	endothelial Nitric oxide synthase
ET	Endothelin
NPY	Neuropeptide Y
NSTEMI	Non-ST-segment elevation myocardial infarction
ROC	Receiver operating characteristic
STEMI	ST-segment elevation myocardial infarction
TXA2	Thromboxane A2

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12872-024-04373-1.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Supplementary Material 6

Author contributions

Yanli Zheng: Conceptualization, Data curation, Writing – original draft, Methodology, Supervision, Validation, Funding acquisition, Project administration, Formal analysis. Yueting Li: Conceptualization, Data curation, Writing – original draft, Methodology, Supervision, Validation. Meimei Li: Project administration, Data curation. Jingru Du: Writing – review & editing, Software. Wanda Wang: Project administration, Data curation. Yaoguo Wang: Project administration, Data curation. Yin-lian Cai: Project administration, Data

curation. Huili Lin: Conceptualization, Project administration, Investigation, Writing – review & editing.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study received approval from the Regional Ethics Council. All patients provided informed consent.

Competing interests
The authors declare no competing interests.

Clinical trial number
Not applicable.

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