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RESEARCH ARTICLE

Dramatic changes in catestatin are associated with hemodynamics in acute myocardial infarction

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Abstract

Acute myocardial infarction (AMI) is characterized by complex neuroendocrine activation. To investigate catestatin profiles, serial catestatin levels were determined by enzyme-linked immunosorbent assay in the first week after AMI in 50 patients. Catestatin levels reduced at admission and negatively correlated with heart rates; it increased significantly on the third day but remained decreased at 1 week and positively with blood pressure. In a subgroup of 20 patients admitted within 4 h after onset, circulating catestatin correlated inversely with norepinephrine. Catestatin might be involved in the course of AMI and act as a tool in monitoring the progression of AMI.

Keywords: Acute myocardial infarction; catestatin; hemodynamics; catecholamine

Introduction

Acute myocardial infarction (AMI) is associated with a complex pattern of neurohumoral activation in which catecholamines play an important role in both onset and course of AMI (Sigurdsson et al., 1993; Foy et al., 1995). Norepinephrine (NE) levels increase within the first hours of AMI and then remain increased for days or even weeks depending on infarct size and left ventricular function (Karlsberg et al., 1981; Petersen et al., 2003). Furthermore, catecholamines accelerate progression of myocardial cell damage and could produce necrosis even in the nonischemic heart (Waldenstrom et al., 1978; Bacaner et al., 2004).

Catestatin was originally discovered as a potent catecholamine release-inhibitory peptide, acting as an antagonist at the physiologic trigger for secretion (Mahata et al., 1997, 2000). This peptide is a 21-amino acid residue that is formed endogenously by proteolytic cleavage of its precursor chromogranin A (CHGA) (Taylor et al., 2000; Lee et al., 2003; Biswas et al., 2008, 2009), a major protein costored and coreleased with catecholamines from the storage vesicles in adrenal chromaffin cells and adrenergic neurons (Mahata et al., 1997, 2003). Accumulating evidence suggests that catestatin acts as a novel regulator of blood pressure (Mahapatra et al., 2005; Fung et al., 2010) and cardiac sympathetic activity (Rao et al., 2007; Gayen et al., 2009; Dev et al., 2010). Several investigators reported a close relationship between catestatin and circulating catecholamines: exogenous catestatin decreased the liberation of catecholamines stimulated by nicotine in animal model (Mahata et al., 2003); accordingly, a knockout mouse model by systemic deletion of CHGA gene (*chga*$^{-/-}$, lack of catestatin due to the absence of the parent molecule) had increased catecholamines levels (Mahapatra et al., 2005). However, the involvement of catestatin in the course of AMI (which involves excess sympathoadrenal activity) remains unclear. The relationship of catestatin and hemodynamics in patients with AMI is still lacking. The aims of the study were to investigate the clinical profile of plasma catestatin concentrations in the early stage of AMI and to determine the relationship between circulating catestatin and catecholamines.

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Methods

Study population

This study was approved by the ethics review boards of Peking University Health Center. Written informed consent was obtained from the study population. A total of 50 consecutive patients with first anterior AMI admitted to the Department of Cardiology, Peking University Third Hospital, from June 2008 to April 2009 were included. All patients received successful primary percutaneous coronary intervention (PCI) within 12 h from the AMI symptom onset. The ST-elevation myocardial infarction (STEMI) was diagnosed according to the American College of Cardiology/American Heart Association guideline in 2004. The study excluded patients with chronic obstructive pulmonary disease, significant kidney or hepatic diseases, tumor, and infectious disease. During the same study period, all 25 subjects who were admitted to the same hospital because of atypical chest pain but with normal coronary arteries confirmed by coronary angiography were included as controls. Resting blood pressure and heart rates (HRs) were measured at the same time when blood samplings were performed in triplicate in the supine position, using an oscillometric device (Philips IntelliVue MP20, Germany).

Blood sampling

At the acute phase of AMI, blood samples were obtained from an antecubital vein without stasis in all patients immediately after admission to the emergency room (ER), and in the morning of the third (D3) and seventh day (D7) after AMI ($n = 50$). In a subgroup including all of the patients admitted within 4 h after AMI onset ($n = 20$), additional blood samples were collected at 4–8 h, 8–12 h, 12–24 h, and 24–36 h from the onset of AMI. In the control subjects, blood samples were obtained from the antecubital vein in the morning of the same day when angiography was performed. The blood samples, anticoagulated with ethylenediaminetetraacetic acid (EDTA), were immediately centrifuged at 3000 rpm for 10 min at 4°C. An aliquot of the EDTA plasma was stored at –80°C till analysis. Repeated freeze-thaw cycles were avoided. The serum MB isoenzyme of creatine kinase (CK-MB) level was determined every 4 h during the first and second days of the admission and then once daily until the values returned to the normal range.

Assays

Plasma levels of catestatin were measured by enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instruction (ELISA kit, Phoenix Pharmaceutical Inc., Burlingame, CA). Plasma NE was also measured using ELISA to determine the sympathoadrenal activation degree (ELISA kit, Labor Diagnostika Nord GmbH & Co., Nordorn, Germany). The minimal detection limits for catestatin and NE were 0.06 ng/ml and 44 pg/ml, respectively. These assays were performed by an investigator blinded to the sources of the samples.

Echocardiography

Each patient underwent echocardiography lying in the left decubitus position during the first week after AMI using a GE-VingMedVechocardiographic machine (Vivid 7) with a 3.3-MHz multiphase array probe. Left ventricular ejection fraction (LVEF) was obtained using a modified biplane version of Simpson's method with apical two- and four-chamber views. These examinations were performed by experienced cardiologists.

Statistics

Baseline clinical parameters between the AMI and control group were compared using Student's unpaired *t*-tests or chi-squared tests. The catestatin levels in control subjects and patients with AMI in ER, D3, and D7 were logarithmically transformed before statistical analyses to normalize their distribution. Student's unpaired *t*-tests were used to compare the catestatin levels between the AMI and control group. One-way analysis of variance followed by *post hoc* analysis was used for comparing catestatin levels among patients with AMI in ER, D3, and D7. The catestatin or NE levels at the five time points during the first 36 h after AMI were evaluated by nonparametric tests. Spearman or Pearson correlation was used to identify the bivariate correlations. A logistic regression model was used to assess the association between catestatin levels and AMI, adjusting for confounders, such as age, gender, and atherosclerosis risk factors (diabetes mellitus, hypertension, hypercholesterolemia, and current smoking). Statistical significance was defined as $P < 0.05$. All analyses were performed with SPSS for Windows version 15.0 (SPSS, Chicago, IL).

Results

Baseline clinical characteristics

The clinical characteristics and laboratory findings of patients with AMI and the control subjects are summarized in Table 1. Totally, 50 patients with AMI (age, 62.2 ± 13.9 years; body mass index (BMI), 25.5 ± 3.5 kg/m^2) and 25 control subjects (age, 60.4 ± 10.4 years; BMI, 26.6 ± 5.1 kg/m^2) were included. Risk factor profiles and most baseline clinical parameters such as age, BMI, blood pressure, lipid profile, and concomitant illness were comparable between the two groups. Patients with AMI had faster HRs, higher high-sensitivity C-reactive protein and fasting glucose levels than the control subjects. There was no significant difference in receiving β-blocking drugs before admission between the two groups.

Time course of the plasma catestatin level (n = 50)

Compared with the control group (21.4 ± 6.4 ng/ml, $n = 25$), plasma catestatin concentrations were significantly decreased in ER (16.5 ± 5.4 ng/ml, $P < 0.01$), increased on the third day (30.7 ± 12.2 ng/ml, $P < 0.01$), but remained low at 1 week (13.8 ± 5.3 ng/ml, $P < 0.01$) after AMI (Figure 1). Catestatin levels were significantly different between the AMI group and control

subjects after adjusting for confounders at all time points (Table 2). Among the three time points (ER, D3, and D7), the highest concentrations of catestatin in patients with AMI were found on D3 ($F = 69.70$, $P < 0.01$), and the levels on D3 were higher than that obtained in ER ($P < 0.01$), whereas the concentrations on D7 were decreased than those measured on D3 ($P < 0.01$). There were no significant differences between the catestatin levels measured in ER and D7.

Relationship of catestatin with blood pressure and HRs (n = 50)

As shown in Figure 2A, there was a slight but significant correlation between the catestatin levels and HRs obtained on the ER in the patients with AMI, but no significant correlations on D3 ($r = 0.015$, $P = 0.92$) and D7 ($r = 0.064$, $P = 0.66$). The catestatin concentrations were positively correlated with blood pressure (both systolic blood pressure (SBP) and diastolic blood pressure (DBP), see Figure 2B and 2C) in the patients with AMI on D7. On other time points (ER and D3), catestatin levels did not correlate with either SBP (ER: $r = 0.007$, $P = 0.96$; D3: $r = 0.007$, $P = 0.96$) or DBP (ER: $r = -0.033$, $P = 0.82$; D3: $r = 0.076$, $P = 0.60$).

Correlation of changes in levels of catestatin and NE (n = 20)

In a subgroup including the patients with AMI who were admitted within 4 h of onset, although decreased at admission (within 4 h), plasma levels of catestatin increased markedly from admission to the following 36 h after AMI ($P < 0.01$, Figure 3A), whereas the NE levels decreased during the first 36 h after onset of AMI ($P < 0.01$, Figure 3B). Inverse correlation between plasma catestatin and NE levels was found during the first 36 h after AMI ($r = -0.302$, $P < 0.01$, Figure 3B).

Relationship of catestatin with peak CK-MB levels and LVEF (n = 50)

For all three time points (ER, D3, and D7), no correlations were demonstrated either between catestatin levels and peak CK-MB levels (ER: $r = -0.215$, $P = 0.14$; D3: $r = 0.077$, $P = 0.60$; D7: $r = -0.016$, $P = 0.91$) or between catestatin levels and LVEF (ER: $r = -0.063$, $P = 0.68$; D3: $r = -0.131$, $P = 0.39$; D7: $r = 0.177$, $P = 0.24$).

Table 1. Patient characteristics and laboratory findings at baseline ($n = 75$).

Variable	AMI $n = 50$	Controls $n = 25$	P
Age (years)	62.2 ± 13.9	60.4 ± 10.4	0.52
Male (%)	84	80	0.67
Body mass index (kg/m2)	25.5 ± 3.5	26.6 ± 5.1	0.43
Systolic blood pressure (mm Hg)	133.8 ± 18.0	129.0 ± 13.5	0.24
Diastolic blood pressure (mm Hg)	77.0 ± 13.3	75.2 ± 7.7	0.47
Heart rate (beats/min)	82.5 ± 12.0	70.5 ± 8.7	<0.01
Diabetes mellitus (%)	22.0	12.0	0.30
Hypertension (%)	62.0	76.0	0.30
Hypercholesterolemia (%)	56.0	52.0	0.81
Current smoking (%)	56.0	36.0	0.14
On β-blocker treatment (%)	6.0	8.0	0.74
Hs-CRP (mg/l)	19.95 ± 24.99	1.80 ± 2.28	<0.01
Creatinine (μmol/l)	97.0 ± 17.5	101.4 ± 25.4	0.38
Fasting glucose (mmol/l)	6.5 ± 2.3	5.1 ± 1.8	0.01
Total cholesterol (mmol/l)	4.82 ± 1.10	4.70 ± 1.05	0.67
LDL cholesterol (mmol/l)	3.19 ± 1.08	3.02 ± 1.00	0.52

Values represent mean ± SD or the percent of the patients and control subjects.
AMI, acute myocardial infarction; Hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein.

Discussion

The current study demonstrated the changes of plasma catestatin levels at certain time points during the first week in patients with first anterior AMI who underwent successful primary PCI within 12 h from onset: catestatin levels reduced at admission, increased significantly on the third day, but remained decreased at 1 week. Catestatin level was related to the hemodynamic indicators such as HRs and blood pressure. Moreover, lower catestatin concentrations were associated with a higher sympathoadrenal activity as determined by plasma NE levels in the first 36 h after symptom onset.

Catecholamines play an important role in a vicious circle that increases myocardial irritability and damage in AMI (Waldenstrom et al., 1978). CHGA is prohormone stored and released with catecholamines by exocytosis (Mahapatra et al., 2004); its fragment catestatin, formed *in vivo*, inhibits further catecholamine release (Mahata et al., 1997, 2000). Catestatin exhibits potent catecholamine release-inhibitory activity by acting on the neuronal nicotinic acetylcholine receptor (Mahata et al., 1997, 2000). In recent years, CHGA has been found to be

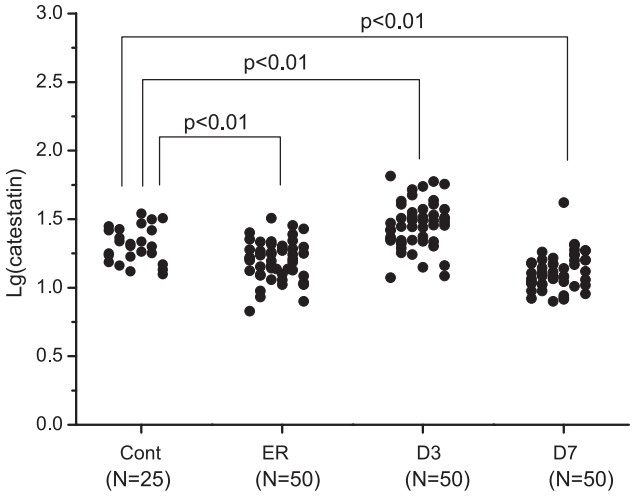

Figure 1. Plasma catestatin levels in the control subjects (Cont, $n = 25$) and patients with AMI ($n = 50$) during the first week after AMI. Data were log10 transformed. ER: in emergency room; D3: the third day after AMI; D7: the seventh day after AMI.

a sensitive marker of prognosis with a high predictive power of morbidity and mortality in acute coronary syndromes (ACS) (Jansson et al., 2009), especially for AMI (Estensen et al., 2006). The mechanism for the prediction effects of CHGA observed could probably contribute to the downstream product catestatin (Jansson et al., 2009). In this study, we found that catestatin levels changed dramatically during the first week after AMI. Because frequent sampling cannot be conducted on everyday during the first week of AMI as a result of operation difficulties, three time points (i.e., on admission to ER, third day, and seventh day) for blood samples were chosen according to the changes of catecholamine. It is well established that catecholamine levels in patients with AMI showed an early and rapid increase in the first 3 days, followed by a slow decrease to normal levels within 1 or 2 weeks in most patients (Karlsberg et al., 1981; Rouleau et al., 1991; Petersen et al., 2003). It is speculated that the decreased catestatin levels observed at admission may be the response to the increased catecholamines levels, which might inhibit catestatin release. In the current study, the highest concentrations of catestatin were found on the third day after AMI, and we found that NE values remained increased during the first 3 days (Rouleau et al., 1991). It is therefore indicated that the increased sympathoadrenal activities might promote negative feedback and increase the release of catestatin, which acts as a cardiac protective factor. As mentioned earlier, catecholamines in AMI regressed to normal levels within 1 or 2 weeks in most patients (Rouleau et al., 1991). Consistently, the catestatin concentrations decreased at 1 week; there is possibility that catestatin is to certain extent superior to catecholamines in predicting adverse events in chronic stage. Dramatic changes in catestatin in patients with anterior AMI might indicate its possible involvement in the progress of AMI.

Table 2. Plasma catestatin levels in patients with AMI during the first week in a logistic regression model ($n=50$).

Time points	OR	95%CI	P
ER	1.178	1.025–1.354	0.02*
D3	0.875	0.789–0.970	0.01*
D7	1.262	1.065–1.496	0.01*

*Adjusted for age, gender, diabetes mellitus, hypertension, hypercholesterolemia, and current smoking.
OR, odds ratio; CI, confidence interval; ER, emergency room.

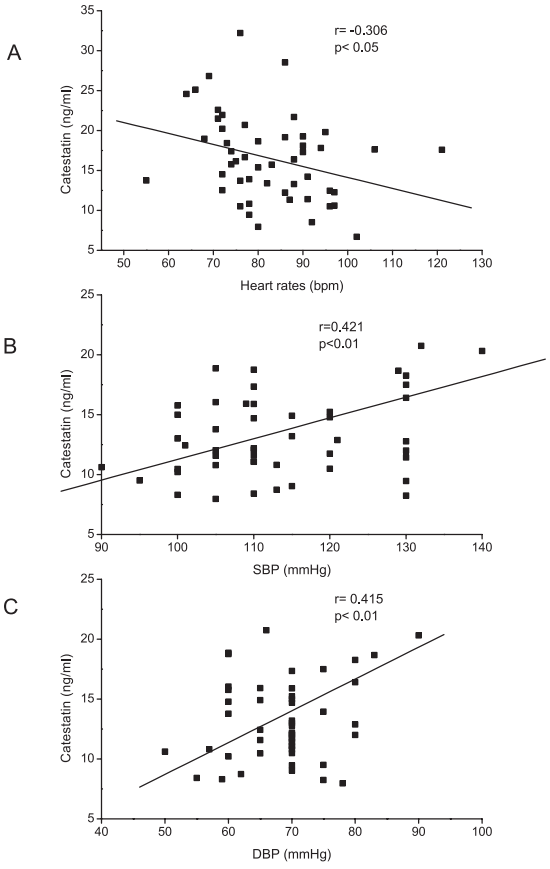

Figure 2. Correlation between catestatin levels and heart rates and blood pressure. (A) Negative correlation between plasma catestatin levels and heart rates in patients with AMI in ER ($n=50$). ER: in emergency room. (B) Positive correlation between plasma catestatin levels and systolic blood pressure in patients with AMI on D7 ($n=50$). (C) Positive correlation between plasma catestatin levels and diastolic blood pressure in patients with AMI on D7 ($n=50$). D7: the seventh day after AMI.

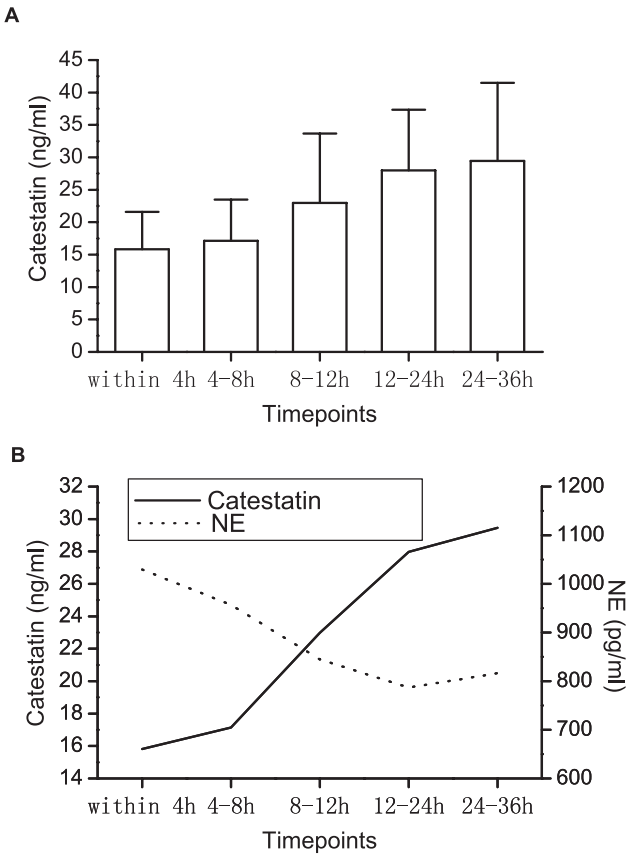

Figure 3. Catestatin and NE levels in the subgroup patients who were admitted early after AMI ($n=20$). (A) Catestatin levels increased from admission to the following 36 h in the subgroup patients ($P < 0.01$). Data are represented as mean ± SD. (B) Negative correlation between the plasma catestatin and NE in the subgroup patients during the first 36 h after AMI ($r=-0.302$, $P<0.01$). Lines represent the mean values.

Several investigators showed that catestatin can increase baroreceptor sensitivity and decrease cardiac sympathetic activity in animal experiments (Rao et al., 2007). As has been demonstrated in animal experiments, catestatin can increase HRs in a dose-dependent pattern (Angelone et al., 2008). We also found that catestatin levels were correlated inversely with HRs at admission, which is in accordance with the finding that catestatin can inhibit the release of catecholamines (Mahata et al., 1997, 2000). It is well known that increased epinephrine results in increased HRs in the early phase of AMI (Karlsberg et al., 1981; Cryer, 1992), and the effect could be attenuated by catestatin (Angelone et al., 2008). Consistently, baseline HR was higher in *chga*$^{-/-}$ mice compared with wild-type mice (Dev et al., 2010). Exogenous catestatin rescued increments in HR in *chga*$^{-/-}$ mice and diminished HR in response to immobilization stress (Gayen et al., 2009). In a large-scale prognostic study, increased CHGA on the first day of ACS predicted the higher mortality maybe related to the lower catestatin and faster HRs (Jansson et al., 2009). In addition, the current study showed that there was a moderately positive correlation between plasma catestatin and blood pressure (both SBP and DBP) in the patients with AMI on the seventh day after onset. However, catestatin replacement in *chga*$^{-/-}$ mice resulted in a substantial reduction of increased SBP toward the wild-type (*chga*$^{+/+}$ mice) level (Mahapatra et al., 2005). Because blood pressure was affected by complex and multiple factors in AMI, further studies are needed to determine the underlying mechanism. Acute ischemia and subsequent left ventricular dysfunction are both characterized by complex neuroendocrine and immune activation, and the activation will regress to homeostasis on late stage of AMI (Rouleau et al., 1991; Petersen et al., 2003). The fact that catestatin levels decreased again and correlated with blood pressure on the seventh day after onset indicates that catestatin maybe a new predictor to prognosis in addition to traditional biomarkers such as LVEF. Different correlation between catestatin and hemodynamic indicators observed in early and later stage of AMI suggests the possible involvement of catestatin in the course of AMI.

CHGA has been explored to be a sensitive marker of myocardial dysfunction (Ceconi et al., 2002). Compared with Gly364Ser variants, wild type and Pro370Leu variants increased infarct size in the ischemic-reperfused rat heart (Brar et al., 2010). However, in the current study, we failed to reveal obvious relationships between catestatin and peak CK-MB or LVEF. Whether there is a correlation between catestatin and infarct size of heart remains to be elucidated in a relatively larger sample size. Catestatin, as indicated in the current results, might provide additional information apart from traditional biomarkers such as peak CK-MB and LVEF.

Catestatin is demonstrated to be 16-fold more potent than the well-studied substance P (RPKPQQFFGLM) in inhibiting catecholamine release and the antagonistic action is noncompetitive (Mahata et al., 1997). In addition, it has been shown that bovine catestatin could effectively block catecholamine secretion stimulated by nicotine/acetylcholine from various types of catecholaminergic cells in *in vitro* study (Mahata et al., 1997, Mahapatra et al., 2006). Plasma catecholamine (both NE and epinephrine) levels in *chga*$^{-/-}$ mice were approximately twofold higher than those in *chga*$^{+/+}$ mice (Mahapatra et al., 2005). This observation is in accordance with a human study showing a lower plasma catestatin level and a twofold higher urinary epinephrine level in hypertensive individuals than normotensive controls (O'Connor et al., 2002). Because neurohumoral system changes markedly during the early phase of AMI (Karlsberg et al., 1981; Sigurdsson et al., 1993; Petersen et al., 2003), serial changes in catestatin concentrations during the first 36 h in a subgroup who were admitted within 4 h after AMI were investigated. Catestatin levels continued to increase in the first 36 h despite a decrease at admission. We also observed a significantly negative correlation between plasma catestatin concentrations and NE values during the first 36 h after AMI. As we know, cardiac non-neuronal cells can synthesize and release catecholamines (Pfeifer et al., 2004). At the same time, CHGA, the precursor of catestatin, was found in murine cardiac secretory granules (Biswas et al., 2010). Taking into consideration both previous and current findings, we assumed that catecholamines and catestatin, coexisting in the cardiac secretion granules, act as major cardiovascular regulators in stress.

To the best of our knowledge, this is the first study to demonstrate plasma catestatin level at certain time points during the first week in patients with first anterior AMI and its relationship with relevant factors. Some limitations in the current study still have to be acknowledged. Objective measures of hemodynamics (e.g. invasive hemodynamic monitoring) were not adopted in the analyses. Moreover, the study did not investigate CHGA or other humoral factors that might relate to the blood pressure or NE. Current findings of catestatin in this relatively modest number of patients need to be verified in a larger scale study with more patients and more intensive time points during AMI.

In conclusion, plasma catestatin changed dramatically during the first week and was related to NE levels, blood pressure, and HRs in patients with AMI, suggesting an important role of catestatin in the progress of AMI. Catestatin might therefore be a useful tool in monitoring the progression of patients with AMI along with other biochemical markers. Further investigation is warranted to determine the predictive role of catestatin in AMI and the particular underlying mechanism.

Declaration of interest

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