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Usefulness of catestatin to predict malignant arrhythmia in patients with acute myocardial infarction

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ABSTRACT

Catestatin (CST) displays potent vasodilatory effect and acts on lowering blood pressure in vivo. The clinical utility of CST in patients with acute myocardial infarction (AMI) has not been clearly delineated. The aim of this study was to investigate the predictive value of CST for the development of in-hospital malignant arrhythmia and other adverse cardiac events in patients with AMI. A total of 125 consecutive patients diagnosed with AMI were included. The clinical characteristics and previous history of the patients were collected. Malignant arrhythmia and other major adverse cardiac events (MACE) such as postinfarction angina pectoris or reinfarction and death were recorded during hospitalization. The levels of plasma CST, norepinephrine (NE) and amino-terminal pro-brain sodium peptides (NT-proBNP) were determined by sandwich ELISA. A multiple logistic regression model was used to predict the influence factors of malignant arrhythmia and other MACE during hospitalization of AMI patients. The results showed that the levels of plasma cystatin-C (CysC), high sensitivity C-reactive protein (hs-CRP), NE and NT-proBNP increased in a CST concentration dependent manner. The incidence of malignant arrhythmia significantly increased as the elevation of CST level ($P < 0.05$). Age, CST and NT-proBNP were independent predictors for the MACE occurred during hospitalization. Increased blood glucose ($\geq$6.1 mmol/L) and CST were independent predictors for the complicated malignant arrhythmia of AMI patients. These data demonstrated that CST can be used as a new biological marker for prediction of malignant arrhythmia in patients with AMI.

1. Introduction

Acute myocardial infarction (AMI) is the worst acute syndrome of coronary heart diseases (CHD) with high morbidity and mortality [22], and it has become a serious threat to human health. Myocardial infarction (MI) complicated by adverse cardiac events such as heart failure (HF) and malignant arrhythmia is associated with a poor prognosis [5,18]. Therefore, early assessment of patients with MI has a very important clinical value. Activation of sympathetic nervous system is a critical pathophysiological mechanism when AMI complicated by adverse cardiac events.

Catestatin (CST, human sequence: SSMKL SFRAR AYGFR GPGPQ L) [21] is a 21-amino acid residue, cationic and hydrophobic peptide which is generated endogenously by proteolytic cleavage of its precursor chromogranin A (CHGA), a major protein costored and coreleased with a group of acidic secretory proteins catecholamines, acetylcholine, ATP and calcium from the storage vesicles in adrenal chromaffin cells and adrenergic neurons [10,12,23]. The gene sequence of CST is highly conservative in mammals [10]. CST can inhibit catecholamine release from chromaffin cells and noradrenergic neurons [14] and desensitization of catecholamine release induced by nicotine [13]. It has been found to exert effects on cardiovascular system. For example, CST displays potent vasodilatory effect in vivo whose actions is mediated, at least in part, by triggering histamine release via stimulation of mast cells and action at H1 receptors [10]. CST also acts on lowering blood pressure in rodents and humans by inhibiting catecholamine release from the sympathoadrenal system directly and by stimulating histamine release from mast cells indirectly [3,11].

Recent studies showed a correlation between plasma catestatin level and ventricular remodeling in patients with AMI [16]. We have previously demonstrated that the plasma CST level was an

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independent predictor for the development of in-hospital HF in patients with ST-segment elevation myocardial infarction [7]. Liu et al. [8] reported an significantly elevated plasma CST level in patients with moderate to severe HF, and HF patients with ischemic etiology had significantly higher plasma CST levels than patients with non-ischemic heart disease. Plasma CST level was positively correlated with that of norepinephrine (NE) and was elevated in parallel with that of NE in the different myocardial ischemia states [9]. However, it is not yet clear whether CST could be served as a biological marker for occurrence of malignant arrhythmia in AMI inpatients. Therefore, the aim of this study was to investigate the predictive value of CST for the development of in-hospital malignant arrhythmia and other adverse cardiac events in patients with AMI.

2. Methods

2.1. Subjects

A total of 125 consecutive patients diagnosed as AMI (ST elevation myocardial infarction, STEMI) in the Second Hospital of Shanxi Medical University (53 cases) and Taiyuan City Centre Hospital (72 cases) (China), between November 2010 and June 2011, were included. The criteria for inclusion was the levels (elevated or reduced after elevation) of cardiac biomarkers (especially troponin) exceeding the upper limit of 99% reference value (for troponin, reference value: <0.05 ng/mL, fluorescence immunoassay) more than once and at least one of the following proof of myocardial ischemia: (1) Clinical symptoms of myocardial ischemia, (2) emerging myocardial ischemia in electrocardiogram (ECG), (3) pathological Q-wave in ECG and (4) emerging myocardial viability deprivation or regional wall movement abnormalities observed by imaging methods. The study excluded patients with cardiomyopathy, renal diseases, atrophic gastritis, acute cerebrovascular diseases, neuroendocrine diseases, severe infections, thyroid dysfunction, immunologic diseases, malignant tumor or treated with antacid within 3 months. Local medical ethics committees approved the study, and all patients provided written informed consent.

2.2. Study protocol

Antecubital venous blood samples were drawn just on the enrollment of the patients. It was 4.12 ± 2.76 h since the onset of AMI. The blood samples were anticoagulated with ethylenediaminetetraacetic acid (EDTA), then centrifuged at $700 \times g$ for 20 min at 4 °C to pellet the cells. The plasma was then removed and stored at −80 °C before analysis. The tests of the biochemical indexes were completed in the same central lab or clinical lab. The levels of plasma CST, NE and amino-terminal pro-brain natriuretic peptide (NT-proBNP) were determined by sandwich ELISA, using the respective dual antibody kits (R&D Systems, MN) according to the manufacturer's instructions. The gender, age, body mass index (BMI), smoking history and previous history of the patients were recorded. The previous history included past histories of hypertension, diabetes, angina cordis, myocardial infarction, heart failure, and apoplexia according to patients' statement or past medical records. Resting blood pressure (BP) and heart rate (HR) were measured at the same time when the patients were admitted to the hospital. Echocardiography was performed within 72 h of the hospitalization and the left ventricle ejection fraction (LVEF) was determined using biplane modified Simpson's measurements. The course of treatment including early reperfusion therapy and medication was also recorded. Early reperfusion therapy referred to thrombolytic therapy and/or percutaneous coronary intervention (PCI) and/or coronary artery bypass grafting (CABG) within 24 h of the hospitalization. Medication referred to the use of aspirin and/or clopidogrel and/or beta-receptor blockers and/or angiotensin-converting enzyme inhibitors (ACEI)/angiotensin receptor antagonist (ARB) statins and/or diuretic.

The incidence of malignant arrhythmia and other major adverse cardiac events (MACE) such as postinfarction angina pectoris or reinfarction and death were recorded during hospitalization. Malignant arrhythmia was defined as emerging atrial fibrillation or flutter, ventricular tachycardia, ventricular fibrillation and advanced A-V block with unstable hemodynamic except for reperfusion arrhythmia. Postinfarction angina pectoris or reinfarction referred to emerging angina pectoris or reinfarction between 48 h and 2 w after acute myocardial infarction. Biochemical indicators including fasting plasma glucose (FBG), triglyceride (TG), total cholesterol (TC), low density lipoprotein (LDL), high density lipoprotein (HDL), high sensitivity C-reactive protein (hs-CRP), leukocyte count, haematoglobin, urea, creatinine, blood uric acid (BUA), cystatin-C (CysC), homocysteine (HCY), troponin I (TnI), creatine kinase-MB (CK-MB) and fibrinogen (FIB) were determined.

The patients were divided into four groups according to the quartile of CST concentration. The clinical characteristics, course of treatment and the incidence of MACE were compared in each group. AMI patients were also divided into different groups according to whether complicated by malignant arrhythmia. The levels of plasma CST, NE and NT-proBNP were compared in these groups.

2.3. Statistical analyses

SPSS 13.0 software was used for statistical analysis. Data were subjected to the Shapiro–Wilks test to determine distribution. If normally distributed, they are presented as mean ± SD and two independent groups were compared by *t*-test. Three or more groups were compared by one-way ANOVA, and post hoc multiple comparisons (Bonferroni's multiple comparison test) were also conducted. Data distributed non-normally are presented as median with first and third quartile and analyzed by the Kruskal–Wallis test. Categorical variables are presented as rate and constituent ratio, and analyzed by chi-square test, or the Fisher's exact test if the subjects count in any contingency table cell was expected to be less than 5. Multiple comparisons between multiple sample rates are analyzed by partitions of chi-square method. A multiple logistic regression model was used to predict the influence factors of MACE during hospitalization of AMI patients. Differences with a *P*-value <0.05 were considered statistically significant. Particularly, a *P*-value <0.0071 were considered statistically significant in multiple comparisons between rates of four groups by partitions of chi-square method.

3. Results

3.1. Clinical characteristics

The composition of gender, smoking history, hypertension history, myocardial infarction history, CK-MB peak, TnI peak, BP, HR, blood glucose, blood fat and early reperfusion were no statistical differences in each group divided by CST concentration ($P > 0.05$, Table 1). However, the composition of age, diabetes history, angina cordis history, BMI, leukocyte count and diuretic treatment were significantly different in each group ($P < 0.05$). The levels of plasma CysC, hs-CRP, NE and NT-proBNP increased in a CST concentration dependent manner. The LVEF determined by echocardiography within 72 h of the hospitalization was negatively correlated with CST concentration (Table 1).