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The predictive value of plasma catestatin for all-cause and cardiac deaths in chronic heart failure patients

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ABSTRACT

Catestatin (CST) is a proteolytic fragment of Chromogranin A with a broad spectrum of activities in the cardiovascular system. The level of plasma CST increases in chronic heart failure patients, but its potential relationship to patient prognosis is unknown. In this study, we measured plasma CST levels in 202 chronic heart failure patients and followed them for a median of 52.5 months. The plasma CST level was higher in patients with all-cause death and cardiac death than in survivors. According to univariate COX regression, higher plasma CST levels predicted increased risk of all-cause and cardiac death. After adjustment for other confounding factors, plasma CST was an independent risk factor for both outcomes, and the hazard ratios (HRs) were 1.84 (95% CI: 1.02–3.32, p = 0.042) and 2.41 (95% CI: 1.26–4.62, p = 0.008) for all-cause death and cardiac death, respectively. The new risk-predictive model considering CST was superior to the previous model for both outcomes by ANOVA and likelihood ratio tests (p = 0.040 and p = 0.008, respectively). Concurrent increases in plasma BNP (B-type natriuretic peptide) and CST levels predicted the highest risk for both all-cause and cardiac deaths [HR = 5.18 (95% CI: 1.94–13.87, p = 0.001) and HR = 9.19 (95% CI: 2.75–30.78, p < 0.001), respectively]. Large-scale studies are needed to further assess the value of plasma CST in predicting heart failure prognosis.

1. Introduction

Although much progress has been made in recent decades, heart failure remains a global health problem, with increasing morbidity and high mortality. The integration of biomarkers in the evaluation of heart failure facilitates diagnosis, risk stratification and treatment titration. Successful examples of these biomarkers include BNP (B-type natriuretic peptide) and NT-proBNP (N-terminal prohormone B-type natriuretic peptide). Recently, a lot of work has focused on factors involved in the pathophysiology of heart failure, including the novel candidates soluble suppression of tumorigenicity 2 (sST2), galectin-3 and high-sensitivity cardiac troponins (hscTn), which have been suggested to perform well in risk stratification and guiding therapy [10,34]. Given the complex pathophysiology of heart failure, additional potential biomarkers might have roles in the comprehensive understanding of its pathogenesis.

The sympathetic nervous system (SNS) has been well-recognized to play a fundamental role in the pathophysiology of heart failure by initially acting as a compensatory mechanism; however, it eventually facilitates adverse ventricular remodeling. Beta-blockers provide protective effects and improve patient survival by inhibiting over-stimulation of the SNS. Accordingly, they are fundamental to the management of heart failure. Recently, catestatin (CST), a proteolytic fragment of Chromogranin A, has been shown to inhibit the release of catecholamine at the ends of sympathetic nerves and chromaffin cells through a negative-feedback mechanism [26]. CST is co-stored and co-released with Chrogranin A and catecholamine at the end of sympathetic nerves and in chromaffin cells, where it then acts specifically at the nicotinic cholinergic receptor to potently inhibit nicotine-evoked catecholamine secretion [26]. In later work, CST was identified as a multifunctional peptide that can enhance the migration and proliferation of skin keratinocytes to promote cutaneous wound closure [17]. CST also has antimicrobial activity [1,2,7] and induces the chemotaxis of monocytes [12] and mast cells as well as stimulates mast cell cytokine production [3,20].

In the cardiovascular system, CST has vasodilative [13] and anti-hypertensive effects [25]. It protects the heart from

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ischemia/reperfusion injury [4,22,30] and modulates the autonomic nervous system [11,14,15]. In recent studies in acute myocardial infarction patients, plasma CST was found to predict adverse cardiac events both during hospitalization and after discharge [24,29,36]. In our previous study, we found that plasma CST levels increased in heart failure patients, and the level of plasma CST correlated with New York Heart Association (NYHA) functional class [23]. Whether plasma CST has roles in predicting the prognosis of heart failure patients is unknown.

This study aims to investigate the probable prognostic role of baseline plasma CST levels for all-cause and cardiac mortality in a cohort of chronic heart failure patients and to further examine whether plasma CST can provide some incremental information to established predictors in a modified model.

2. Methods

2.1. Study population

A cohort of 228 patients diagnosed with chronic heart failure was successively recruited between July 2010 and November 2011 at the cardiology department of Peking University First Hospital. Chronic heart failure was diagnosed according to the modified Framingham criteria [19]. Patients with concurrent acute coronary syndrome, end-stage renal disease, serious infection, pheochromocytoma, autoimmune disease, confirmed or suspected malignant diseases or recent surgeries were excluded. Twenty-six patients were excluded because of incomplete baseline information or unavailability for follow-up. Thus, 202 patients were followed up. This study was approved by the Ethics Committee of Peking University First Hospital and complied with the Declaration of Helsinki. All patients signed written informed consent.

2.2. Study protocol

Baseline characteristics and blood samples were obtained at admission or the first visit, and CST and biochemical tests were completed as previously described [23]. Briefly, blood samples were centrifuged and aliquoted at 4 °C and stored at −80 °C until CST was measured using a human catestatin enzyme immunoassay kit (Phoenix Pharmaceuticals, Inc., EK-053-27). The minimum detectable concentration of the kit is 0.07 ng/mL. The kit has no cross-reactivity with chromogranin A (343–355), human vasostatin I/II or chromogranin A (374–388). BNP, hemoglobin levels and biochemical parameters were determined in the clinical laboratories of Peking University First Hospital. BNP was tested by the chemiluminescent immunoassay method (UniCel DxI 800, Beckman Coulter Inc. Fullerton, CA) with a reference range of less than 100 pg/mL. Chronic renal dysfunction was defined as an estimated glomerular filtration rate(eGFR, estimated according to the Modification of Diet in Renal Disease (MDRD) formula [21]) lower than 60 mL/min/1.73 m^2. Anemia was defined as hemoglobin (Hb) less than 120 g/L (for male) or 110 g/L (for female). Hypoproteinemia was defined as serum albumin (Alb) lower than 40 g/L.

Follow-up visits were conducted through on-site visits or telephone conversation every 3 months. Major adverse events (all-cause and cardiac deaths) and medications were recorded. Medicines for heart failure were used according to recommended guidelines. Experienced doctors confirmed the causes of death according to medical records or death certificates provided by direct relatives. Cardiac death included death resulting from an acute myocardial infarction (MI), sudden cardiac death, death due to heart failure (HF) and death due to other cardiovascular causes.

2.3. Statistical analyses

The normal distribution of continuous variables was tested using the Kolmogorov-Smirnov test. To describe normal-distributive variables, the mean ± standard deviation (SD) was used. To describe non-normal-distributive variables, the median and the interquartile range (IQR) were used. An independent sample *t*-test or the Mann-Whitney *U* test was used to compare differences between two groups of continuous variables, whereas the χ^2 test or Fisher's exact test was used for categorical variables. Pulmonary artery systolic pressure (PASP) was recorded as a continuous variable with 10 mmHg as one unit from the minimum. BNP was analyzed as a categorical variable according to the median value. CST was analyzed as both a continuous variable and a categorical variable. Participants lost during the follow-up period were analyzed as censored cases. A univariate COX regression and a Kaplan-Meier analysis were performed for the survival analysis of individual variables. Variables with confirmed prognostic implications or statistical significance according to univariate COX regression analysis were chosen as covariates, and multivariate COX regression was conducted. ANOVA and likelihood ratio tests were performed using R software to compare differences among the models. Two-tailed *p*-values < 0.05 were considered statistically significant. The analysis was conducted with SPSS 16.0 software for Windows (SPSS Inc., Chicago, IL, USA) and R 3.2.4.

3. Results

3.1. Baseline characteristics

A total of 202 patients were included, among whom 10 were lost during follow-up. The median patient age was 72.0 (57.8–78.0) years, and 60 patients (29.7%) were female. Coronary heart disease (CHD) was the primary cause of heart failure. More than half (56.9%) of the patients were diagnosed as having heart failure with reduced ejection fraction. The majority (55.9%) of these patients were classified as NYHA functional class III–IV at baseline. Detailed patient characteristics are shown in Table 1.

3.2. Increased plasma CST predicts a higher risk of all-cause and cardiac death

3.2.1. Plasma CST increased in patients with all-cause or cardiac death

Patients were followed for a median of 52.5 (23.6–59.5) months. A total of 59 patients died, and 49 deaths were identified as cardiac deaths. Patients with all-cause or cardiac death had higher plasma CST levels relative to survivors [1.06 (0.66–1.82) ng/mL vs. 0.75 (0.58–1.12) ng/mL, p = 0.005, 1.18 (0.69–1.83) ng/mL vs. 0.75 (0.58–1.12) ng/mL, p = 0.002]. Detailed comparisons between groups are shown in Table 2.

3.2.2. Increased plasma CST predicts higher risk of all-cause and cardiac death

In the univariate COX regression analysis, patients with higher plasma CST levels had an increased risk of all-cause and cardiac death. The hazard ratios (HRs) were 1.81 (95% CI, 1.39–2.36, p < 0.001) and 1.89 (95% CI, 1.43–2.50, p < 0.001), respectively. In the multivariate COX regression, after adjustment for covariates including age, gender, BNP, NYHA function class, LVEF, renal dysfunction, anemia, hypoproteinemia, pulmonary artery systolic pressure and medications, CST remained as an independent risk factor for cardiac death (HR = 1.52, 95% CI: 1.02–2.25, p = 0.039). For all-cause death, CST levels were marginally significant (HR = 1.43, 95% CI: 1.00–2.05, p = 0.051) (Table 3).