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RESEARCH ARTICLE

Catestatin is useful in detecting patients with stage B heart failure

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Abstract

Screening patients with stage B heart failure(HF) may be one strategy for reducing human morbidity. To describe catestatin levels in different stages of HF and evaluate the diagnostic utility of catestatin for detecting stage B HF, we included 300 patients. Catestatin, BNP testing and echocardiogram were performed. Our studies showed catestatin decreased gradually from stage A to C. There was significant difference between stage A and B. Cutoff value for detecting stage B HF was 19.73 ng/ml for catestatin with 90% sensitivity and 50.9% specificity. These results may have implications in the new method to detect patients with stage B HF.

Keywords: Catestatin, B-type brain natriuretic peptide (BNP), heart failure, biomarkers

Introduction

Heart failure (HF) is a progressive and lethal disease affecting almost 4 million persons in China (GU et al. 2003; Hunt et al. 2009). It can lead to significant morbidity and poor quality of life and disproportionately affects minority communities (Yancy 2004). To reduce the morbidity of HF, it is important to detect its early stages and ensure appropriate treatment during these stages (Wang et al. 2003). This view has been supported by the HF model proposed by American Heart Association (AHA) and the American College of Cardiology (Hunt et al. 2005; Ammar et al. 2006). In this model, HF is classified into different stages to illustrate the progression of heart disease: Stage A—the presence of HF risk factors with no functional or structural heart disorder; Stage B—a structural heart disorder but no symptoms; Stage C—symptomatic HF in the context of an underlying structural heart problem; and Stage D—end-stage HF. Screening patients with stage B heart failure may be one strategy for reducing both human and economic costs associated with HF. We may be able to stop the further development of HF by identifying patients during the early stages (stage A and B) and providing medications such as angiotensin-converting enzyme inhibitor (ACEI), which works to reduce the progression of left ventricular (LV) dysfunction hence the risk of symptomatic HF (Goldberg & Jessup 2006). However to detect early-stage HF is not without difficulty, as the patients normally show no symptoms. What we usually use to detect LV dysfunction and identify stage B HF is echocardiography (ECHO). However, it is expensive and associated with long wait times.

Because a continuous increase in sympathetic activity is an important factor in the development and progression of HF, research has focused on finding the biomarkers of such activity for early screening. Catestatin, a chromogranin A (Chga)-derived peptide, affects the cardiovascular system by inhibiting the release of catecholamines such as norepinephrine (NE) (Mahata 1997; Mahata 2000; Mahapatra 2008; Mahata et al. 2010). It can adjust cardiac function by increasing parasympathetic activity, inhibiting sympathetic activity, reducing cardiac output and diminishing the inotropic effects of isoproterenol and endothelin (Rao et al. 2007). However, little is known about changes of plasma catestatin levels at different stages of HF and whether catestatin level can be used for detecting stage B HF. If plasma catestatin cutoff

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Abbreviations

HF, heart failure;
BNP, B-type brain natriuretic peptide;
LV, left ventricular;
ACEI, angiotensin-converting enzyme inhibitor;
ECHO, echocardiography;
Chga, chromogranin A;
NE, norepinephrine;
LVEF, left ventricular ejection fraction

concentrations, set at a high sensitivity, were associated with a clinically useful specificity, this biomarker could be used as a screening test to select patients for further assessment by echocardiography. The purposes of this study were to describe catestatin levels in different stages of heart failure and evaluate the diagnostic utility of catestatin and B-type brain natriuretic peptide (BNP) measurements for the detection of stage B HF.

Materials and methods

Patient recruitment

This single-center trial, performed from July 2007 to September 2009 at the Peking University Third Hospital, Beijing, was approved by the Peking University Third Hospital ethics committee in accordance with the Declaration of Helsinki, and informed consent was obtained from the study participants. Patients with acute myocardial infarction during the preceding 12 weeks, severe HF (without response to treatment), prosthetic valves, pericardial disease, pulmonary embolism, acute stroke or actual transient or temporary stroke, congenital heart disease, autoimmune disease, hematological disorders, tumors and renal failure (serum creatinine level >176 μmol/l) were excluded. All patients with symptomatic HF were receiving treatment with diuretics and/or vasodilators.

All patients have hypertension according to the 2007 European Society of Hypertension (ESH)/European Society of Cardiology (ESC) hypertension guidelines (Mancia et al. 2007).

Stage A ($n=108$) included stable angina pectoris patients ($n=45$) diagnosed according to ESH/ESC 2006 guidelines (Fox et al. 2006).

Stage B ($n=76$) included patients with old myocardial infarction (OMI, $n=54$), left ventricular hypertrophy (LVH, $n=22$) and systolic dysfunction. OMI patients complied with the universal definition of myocardial infarction (Thygesen et al. 2007). LVH was confirmed with echocardiographic assessment criteria (left ventricular mass index, LVMI: male ≥ 125g/m^2, female ≥ 110 g/m^2) (Whitworth 2003).

Stage C ($n=116$) recruited previously symptomatic and currently asymptomatic CHF patients according to the ACC/AHA guideline (Hunt et al. 2005).

Echocardiography

Each patient underwent echocardiography lying in the left decubitus position at the time of study entry using a GE-VingMed echocardiographic machine (Vivid 7) with a 3.3-MHz multiphase array probe. In accordance with the guidelines of the American Society of Echocardiography (Schiller et al. 1989), the echocardiographic techniques were performed and different cardiac dimensions and volumes were calculated. A modified biplane version of Simpson's method with apical two- and four-chamber views was used to get left ventricular ejection fraction (LVEF). The cardiologists who conducted the studies are with proven experience. LVMI was calculated according to the Devereux equation (Devereux et al. 1986).

Measurement of catestatin and BNP levels

Blood was collected by venipuncture in Vacuette polyethylene terephthalate glycol EDTA tubes (Greiner Bio-One) on the day of the echocardiography evaluation. Samples were centrifuged at 3500*g* for 10 min at 4°C immediately after collection. Plasma catestatin and BNP levels were assayed by use of a Molecular Devices Emax analyzer with the catestatin and BNP assay (ELISA kit, Phoenix Pharmaceutical Inc., Burlingame, CA). The minimal detection limits for catestatin and NE were 0.06 ng/ml and 10 pg/ml, respectively.

Data analysis

Data were expressed as mean ± standard deviation (SD) or as a percentage. The Kolmogorov–Smirnov test was used to test for normal distribution of continuous variables. Variables with two groups were compared with the Student's t-test. One-way ANOVA was used for comparing data for more than two groups; Spearman coefficient of rank correlation was used to assess the relationship between catestatin and BNP concentrations. To determine the diagnostic accuracy of plasma catestatin and BNP for detecting B heart failure we analyzed the ROC curves and calculated AUCs for both analytes. Cutoff concentrations for catestatin and BNP were determined at the 90% sensitivity criterion derived directly from the ROC curves. A logistic regression model was used to assess the association between catestatin levels and stage B heart failure. All analyses involved use of SPSS 17.0 (SPSS Inc., Chicago, IL). A p value < 0.05 (two-tailed) was considered statistically significant.

Results

Characteristics of patients

Patient characteristics are summarized in Table 1. Stage C patients more likely have a higher average age, heart rate, diuretic usage and a lower creatinine clearance than the other two groups. Risk factor profiles and most baseline

Table 1. Baseline clinical characteristics in different stages of heart failure ($n=300$).

Demographic and clinical features	Different stages of heart failure			p
	Stage A ($n=108$)	Stage B ($n=76$)	Stage C ($n=116$)	
Male sex, n (%)	68 (63)	40 (52.6)	56 (48.3)	0.081
Mean age, years	62.30 ± 10.94	68.58 ± 8.63	71.55 ± 9.60[a]	<0.001
Mean body mass index, kg/m^2	26.89 ± 3.98	27.09 ± 5.02	25.92 ± 2.92	0.076
Systemic arterial hypertension, n (%)	108 (100)	76 (100)	116 (100)	NA
Mean blood pressure, mmHg				
Systolic	139.63 ± 23.80	138.68 ± 19.45	137.41 ± 19.50	0.734
Diastolic	80.00 ± 18.34	77.89 ± 11.23	76.21 ± 7.88	0.105
Mean heart rate, beats/min	75.11 ± 12.95	65.95 ± 10.76[b]	74.79 ± 16.21	<0.001
Diabetes mellitus, n (%)	32 (29.6)	32 (42.1)	36 (31)	0.169
Smoking, n (%)	43 (39.8)	26 (34.2)	36 (31)	0.385
Coronary artery disease, n (%)	45 (41.7)	54 (71.1)	84 (72.4)	0.054
Medication, n (%)				
Angiotensin-converting enzyme inhibitors	40 (37)	20 (26.3)	40 (34.5)	0.300
Angiotensin-receptor blockers	32 (29.6)	29 (38.2)	44 (37.9)	0.345
Calcium antagonists	32 (29.6)	29 (38.2)	47 (40.5)	0.216
Beta-blockers	84 (77.8)	60 (78.9)	100 (86.2)	0.225
Diuretics	8 (7.4)	11 (14.5)	46 (39.7)[a]	<0.001
Echocardiographic data				
Mean LV ejection fraction, %	70.11 ± 4.45	54.95 ± 9.82[c]	43.40 ± 9.89[c]	<0.001
Systolic dysfunction, n (%)	0 (0)	26 (34.2)	79 (68.1)	NA
LV hypertrophy, n (%)	0 (0)	22 (28.9)	8 (6.9)	NA
Biochemical markers				
Mean eGFR, mL min^{-1} (1.73 m^2)$^{-1}$	71.23 ± 24.18	69.20 ± 12.29	61.16 ± 9.42[d]	<0.001
Mean plasma catestatin, ng/ml	21.29 ± 7.10	14.61 ± 4.69[b]	13.42 ± 4.90	<0.001
Mean plasma BNP, pg/ml	39.16 ± 26.06	58.56 ± 37.50	233.49 ± 153.74[a]	<0.001

[a]Stage C patients had a higher average age, diuretic usage and BNP than the other groups.
[b]Stage B patients were more likely to have lower heart rate and catestatin level than stage A patients.
[c]The LV ejection fractions of stage B and C patients were lower than those of stage A patients.
[d]A lower creatinine clearance was found in stage C. NA, not applicable; LV, left ventricular; eGFR, estimated glomerular filtration rate.

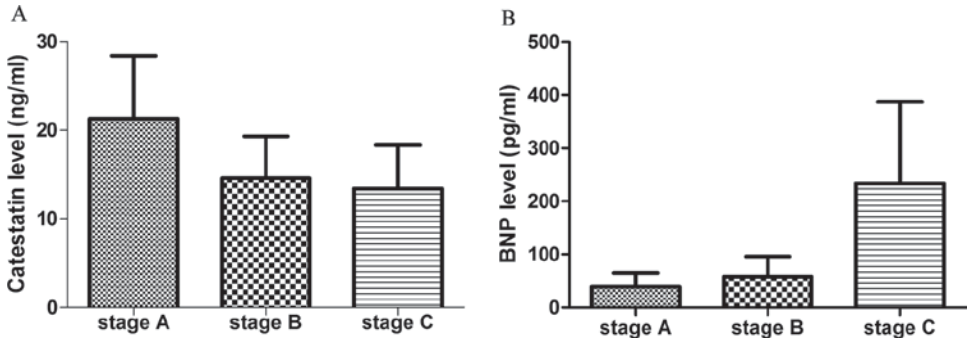

Figure 1. Mean catestatin (A) and B-type brain natriuretic peptide (BNP) (B) levels for different stages of heart failure. Bar indicates ± SD. (A) Patients diagnosed with stage B heart failure had significantly lower catestatin than those with stage A heart failure ($p<0.05$). (B) Patients diagnosed with stage C heart failure had significantly higher BNP than those with stage B and stage A heart failure ($p<0.001$).

clinical parameters such as sex, BMI, blood pressure and concomitant illness were comparable between these groups.

Plasma catestatin and BNP levels

As shown in Table 1 and Figure 1, plasma catestatin decreased gradually from stage A (21.29 ± 7.10 ng/ml), stage B (14.61 ± 4.69 ng/ml) to stage C (13.42 ± 4.90 ng/ml).There was significant difference between stage A and B ($p<0.05$). Plasma BNP increased from stage A (39.16 ± 26.06 pg/ml), stage B (58.56 ± 37.50 pg/ml) to stage C (233.49 ± 153.74 pg/ml) (Table 1 and Figure 1). There was no significant difference between stage A and B ($p>0.05$). Catestatin level was not correlated with BNP level ($r=0.107$, $p=0.150$).

Predictive values of catestatin and BNP in detecting stage B heart failure

In distinguishing between stage B HF and stage A HF, the AUCs were 0.809 (SE = 0.033, 95% confidence interval 0.744–0.873) for catestatin and 0.684 (SE = 0.039, 95% confidence interval 0.607–0.760) for BNP (Figure 2).

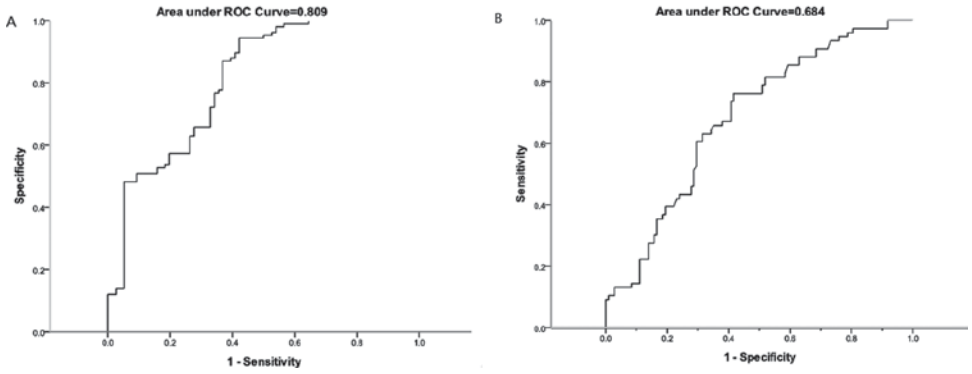

Figure 2. Receiver operating characteristic curves for the ability of catestatin (A) and B-type brain natriuretic peptide (BNP) (B) to detect stage B heart failure.

Table 2. Results of logistic regression analyzing the capability of catestatin and BNP to detect stage B heart failure independently of possible confounding variables.

Independent variables	Odds ratio	*p*
Multivariate logistic regression model including catestatin		
Male sex (vs. female sex)	1.68	0.195
Body mass index (+5 kg/m^2)	1.37	0.242
Blood pressure (+20 mmHg)		
Systolic	0.152	0.090
Diastolic	3.00	0.244
Smoking (vs. not)	0.03	0.867
Diabetes Mellitus (vs. not)	2.40	0.122
Plasma catestatin concentration (+10 ng/ml)	0.14	0.000
Multivariate logistic regression model including BNP		
Male sex (vs. female sex)	3.15	0.502
Body mass index (+5 kg/m^2)	2.30	0.129
Blood pressure (+20 mmHg)		
Systolic	2.09	0.057
Diastolic	1.19	0.276
Smoking (vs. not)	1.13	0.288
Diabetes Mellitus (vs. not)	2.34	0.064
Plasma BNP concentration (+100 pg/ml)	2.32	0.003

The cutoff values with a 90% sensitivity for detecting stage B HF were 19.73 ng/ml for catestatin (specificity, 50.9%) and 23.5 pg/ml for BNP (specificity, 31.5%). The positive and negative predictive values were 56.2% and 87.3% for catestatin, 47.9% and 81.0% for BNP.

Logistic regression analyzing the capability of catestatin and BNP to detect stage B HF independently of possible confounding variables

As shown in Table 2, catestatin and BNP concentrations were predictors of stage B HF independent of possible confounding variables. In the first multivariate model, catestatin was an independent and significant predictor ($p = 0.000$) of stage B HF with an odds ratio of 0.14 for an increment of 10 ng/ml. The second statistical model revealed that BNP was also independently related to stage B HF ($p = 0.003$), displaying an odds ratio of 2.32 for an increment of 100 pg/ml. All other variables included failed to reach statistical significance.

Discussion

Patients at stage A have risk factors such as hypertension, coronary artery disease, diabetes, obesity, metabolic syndrome, heredofamilial dilated cardiomyopathy or history of exposure to cardiotoxins such as doxorubicine or alcohol. Patients at stage B demonstrate structural abnormalities or left ventricular dysfunction but have no symptoms of HF (Hunt et al. 2005). Because patients at this stage are usually identified incidentally, this stage has not been well investigated. Moreover, because such patients have no symptoms of HF, only large-scale epidemiological surveys have been able to evaluate the incidence and prevalence of asymptomatic LV disease. Patients at stage B HF would benefit greatly from active intervention and regular follow-up. We found that plasma catestatin level was significantly lower for those at stage B than those at stage A, which suggests that catestatin can help to distinguish patients at high risk before they demonstrate any symptoms. Therefore, a decrease in catestatin level might reflect an early stage of the pathophysiological process of HF; It could detect asymptomatic patients at early stages of HF.

Catestatin is a Chga-derived peptide that participates in the integrated control of cardiovascular function. Previous studies suggested that this peptide can decrease cardiac output by reducing catecholamine secretion (Rao et al. 2007). We aimed to discribe the level of catestatin in different stages of HF, evaluate the diagnostic value of catestatin for detecting stage B HF and compare the diagnostic value of catestatin and BNP. Plasma catestatin level was significantly lower in patients at stage B and C HF than in those at stage A. The decrease may relate to the activation of the sympathetic system with HF. In the presence of a hemodynamic factor that causes a primary change in myocardial contractive force or ventricle overload, the heart has to rely on many compensatory mechanisms to maintain its pump function, a critical one being the activation of the neurohumoral mechanism. In such a mechanism, noradrenalin, the neurotransmitter released by the adrenergic nerve to argument the myocardial contractility, plays a key role. These compensatory mechanisms are launched early in HF. The substudy of the studies of left ventricular dysfunction (SOLVD)

also confirmed the increase of plasma NE in high-risk asymptomatic patients (Francis et al. 1990). Thus, the sympathetic nerve system is clearly activated by change in cardiac structure. The level of plasma catestatin therefore decreases in the early stages of HF because of the early activation of the sympathetic nerve system which plays a role in adjustment. This result was also confirmed by Gaede & Pilowsky (2010).

An increase in BNP secretion reflects an increase in ventricular load and dilation; therefore, an assessment of BNP level could be used to distinguish and monitor patients presenting with HF (Maisel 2002; Wu & Smith 2004). We found BNP level in patients at stage B increased slightly and increased significantly in patients at stage C as that in patients at stage A. In distinguishing between stage B HF and stage A HF, the AUCs were 0.809 for catestatin and 0.684 for BNP. The cutoff values with 90% sensitivity for detecting stage B HF were 19.73 ng/ml for catestatin (specificity, 50.9%) and 23.5 pg/ml for BNP (specificity, 31.5%). Because of higher specificity of the catestatin test, it is more useful to detect stage B HF than BNP. Therefore, asymptomatic patients with high risk factors could obtain regular follow-up visits and timely medical intervention from the catestatin measurement. These findings about BNP are similar to those of Mueller et al. (2005). BNP level in patients at stage C was higher than that in patients at stages A and B, which suggests that although assessment of BNP level has few advantages in detecting early HF, it can be used to distinguish symptomatic HF from those asymptomatic HF. Combination of BNP and catestatin may help in evaluating all stages of heart failure.

We found no correlation between levels of catestatin and BNP. In the normal state, when the carotid sinus, which mediates sympathetic activity, releases impulses to the central nerve system, sympathetic activity is inhibited and vasopressin is released. With chronic HF, because of the decrease in cardiac output and blood pressure, the reduced number of impulses has less effect on inhibiting the autonomic nervous system, so sympathetic activity is activated and neurosecretory hormone is released. The increase in sympathetic activity can lead to an increase in cardiac output, total peripheral resistance and redistribution of blood flow in organs to help retain sodium and water and perfusion of important organs. In general, these neurohumoral responses can be viewed as compensatory mechanisms for the short term. However, with prolonged activation of the hormonal systems, ventricular remodeling and intraventricular pressure increase. With increased intraventricular pressure, more BNP is secreted and induces natriuresis and diuresis, which is contrary to the role of NE (Suzuki et al. 2001; de Denus et al. 2004; Villars et al. 2004). Secreted at different phases, catestatin and BNP produce antagonistic effects at different stages of HF. Therefore, there was no correlation between levels of catestatin and BNP.

Most of the patients in our study were receiving oral antihypertensive medication and drugs such as diuretics, angiotensin-converting enzyme inhibitors; adrenergic agonists can modify the circulating concentrations of natriuretic peptides (Cowie et al. 2003; Pfister and Schneider 2004; Silver et al. 2004). A recent study demonstrated that BNP concentrations in treated hypertensive patients did not significantly differ from those in an age-matched control population (Wieczorek et al. 2002). However, no studies have investigated the influence of drug therapy on catestatin concentration.

To the best of our knowledge, this is the first study to demonstrate plasma catestatin level at different stages of HF. Our study has several limitations. It was a single-center study of a relatively small sample of patients. Therefore, our results may not accurately represent those of the general population of patients with HF. Furthermore, the assays used in our study may have influenced the optimal cutoff concentrations and probably the diagnostic accuracy; some recent reports have suggested that the diagnosis based on measurement of natriuretic peptides may be method dependent (Prontera et al. 2003; Clerico and Emdin 2004; Clerico et al. 2005). As well, we did not investigate patients with acute myocardial infarction during the preceding 12 weeks because of the difficulties in deciding the time of collecting blood samples, because myocardial infarction may influence the concentration of catestatin (Wang et al. 2011).

In conclusion, plasma catestatin level decreases with progression of HF. Because alteration of catestatin level precedes that of BNP and catestatin has a higher specificity than BNP at a selected cutoff value, it could be a more useful method to detect stage B HF. Catestatin might be proposed for widespread use in clinical practice. Further investigation is needed to determine the particular underlying mechanism.

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Declaration of interest

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