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Original Research Article

Effect of serum cystatin C and chromogranin A on left ventricular mass index in patients with chronic heart failure

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Abstract

Purpose: *To investigate the expression of serum cystatin C (CystC) and chromogranin A (CgA) in chronic heart failure (CHF) patients, and their correlation with left ventricular mass index (LVMI).*
Methods: *CHF patients (135) in the study hospital were randomly selected, and assigned to different groups on the basis of heart function grade (grades II to IV). Grades II, III and IV had 45 patients each. In addition, 45 people with normal physical examination results were assigned to the control group. In all patients, N-terminal natriuretic peptide (NT-proBNP), CysC and CgA were measured. In addition, left ventricular end-diastolic diameter (LVEDD), left ventricular end-diastolic volume (LVEDV), and left ventricular ejection fraction (LVEF) were measured using transthoracic echocardiography, and the results were used to calculate LVMI values.*
Results: *There were significantly higher levels of CystC and CgA in CHF patients than in control patients ($p < 0.05$). In grade IV patients, CystC and CgA levels were higher than the corresponding levels in patients with cardiac function grades II and III, while their levels in grade III patients were higher than in grade II patients ($p < 0.05$). The results of correlation analysis indicated that serum CgA was positively correlated with serum CystC. Serum CgA and CystC levels in CHF patients were negatively correlated with LVEF, but positively correlated with NT-proBNP and LVMI levels.*
Conclusion: *Serum CgA and CysC are correlated with cardiac function grade and ventricular remodeling in CHF patients. Thus, to some extent, these two indices can be used to measure the degree of ventricular remodeling in CHF individuals.*

Keywords: *Chromogranin A (CgA), Heart failure, Cystatin C (CysC), Left ventricular mass index*

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INTRODUCTION

It has been established that CHF is caused by abnormal structure or function of the heart, leading to a decrease in cardiac output and low perfusion of peripheral tissues and organs [1–3]. The pathology of CHF is complicated, the death rate is high and the prognosis is poor in most cases. With developments in social economy, chronic heart failure now occurs in young individuals [4,5]. Recent studies have shown that ventricular remodeling is the basic mechanism

involved in cardiac malfunction. Some scholars have reported that blood level of chromogranin A (CgA) in CHF patients is significantly increased after myocardial infarction, in addition to a correlation between CgA level and mortalities in VCHF patients [6,7].

Moreover, a large number of studies have shown that increased levels of cystatin C (CystC) are associated with left ventricular concentric hypertrophy and increased left ventricular volume in CHF individuals. Incidents of left ventricular hypertrophy and diastolic dysfunction are elevated in response to increases in blood level of CystC. Studies have shown that the blood CgA concentrations in CHF patients increase significantly with severity of cardiac malfunction [8].

This study was carried out to investigate the expressions of serum CystC and CgA in CHF patients, and their correlation with ventricular remodeling.

METHODS

Clinical data

Patients with CHF (135) from January 2015 to December 2017 in our hospital were randomly selected and grouped according to heart function grade (grades II to IV). There were 45 cases in grade IV group, and 45 cases each in grades III and II. All patients were diagnosed with CHF, and they met the NYHA diagnostic and cardiac function classification standards. In addition, 45 normal subjects were selected as control group.

This study received approval from the Ethical Committee of Dongfang Hospital, Beijing University of Traditional Chinese Medicine, China (approval no. 201879), and was implemented in line with Helsinki declaration of 1964 as amended in 1996 [9].

Exclusion criteria

The following categories of patients were excluded from the study: (1) subjects with severe liver and kidney disease, malignant tumor, immune system disease, connective tissue disease, acute infection, anemia, pregnancy and stroke; (2) subjects with stress-related mental disorders, paranoid mental disorders, bipolar affective disorders, split affective disorders, schizophrenia and other severe mental disorders; (3) cases of CHF due to causes other than coronary heart disease and hypertension; and (4) subjects who did not want to be enrolled in the project.

Assessment of clinical parameters

The body surface area of the selected patients was estimated on admission, and each patient provided information on the history of the disease. In the early morning of the next day after admission, overnight fasting venous blood was used for assaying NT-proBNP, liver and kidney function, lipid profiles and blood glucose. These indices were determined using fully automatic biochemical analyzer (Roche). Serum CystC and CgA were determined by ELISA in strict accordance with the instructions of the kit manufacturer. Values of LVEDV, LVEDD) and LVEF were measured using IE33 Color Ultrasound Diagnostic instrument (Philips). The results obtained were used to calculate LVMI.

Statistical analysis

Numeric data are presented as mean ± standard deviation (SD). Multiple groups were compared with single factor ANOVA, while comparison between two groups were effected using LSD-*t* test.. Count data are presented as percentage (%), and were compared using Chi-square test. Data analyses were carried out using SPSS statistical software (version 18.0, IBM, USA). Values of $p < 0.05$ were assumed to be statistically significant.

RESULTS

General patient biodata

As shown in Table 2, the CHF patients did not differ significantly from normal control group with respect to age, sex and BMI ($p > 0.05$).

Table 1: General patient profile (n = 45)

Group	Age (years)	Male/female	BMI (kg/m^2)
Grade NYHA Ⅱ group	62.18 ± 7.29	24 /21	24.05 ± 2.65
Grade NYHA Ⅲ group	63.91 ± 8.01	22 /23	23.65 ± 1.37
Grade NYHA Ⅳ group	62.48 ± 8.46	26 /19	24.36 ± 2.01
Control group	63.05 ± 9.26	25 /20	24.51 ± 1.98
F/χ^2	0.380	0.783	1.543
p	0.768	0.854	0.205

NT-proBNP, CystC and CgA levels

Table 2 shows that there were significant upregulations in CystC, CgA and NT-proBNP in CHF cases, relative to control cases ($p < 0.05$). In addition, NT-proBNP, CystC and CgA in cardiac function grade Ⅳ were higher than in patients with cardiac function grades Ⅱ and Ⅲ ($p < 0.05$). They were also higher in cardiac function grade Ⅲ patients than in cardiac function grade Ⅱ cases ($p < 0.05$).

Cardiac function indices

The CHF patients had higher LVEF, LVEDD and LVMI values than control group patients, their LVEF level decreased, when compared with that of the control group ($p < 0.05$) (Table 3). With aggravation of cardiac function, LVMI, LVEDD increased gradually, while LVEF decreased. There were significant differences between groups ($p < 0.05$).

Correlation between CystC and CgA, and cardiac function indices

Serum CgA and CystC levels were negatively correlated with LVEF in CHF patients (r = -0.78, -0.73, $p < 0.05$). However, there was positive correlation between serum CgA/CystC, and NT-proBNP/LVMI (r = 0.81, 0.89, 0.76, 0. 85, $p < 0.05$).

DISCUSSION

Recent investigations revealed that ventricular remodeling is the basic mechanism involved in heart failure. The pathological changes in ventricular remodeling include extracellular matrix remodeling and myocardial remodeling [10,11]. A recent study revealed that the content of chromogranin A (CgA) was elevated in CHF patients after myocardial infarction, with correlation between CgA level and mortality. In addition, several workers have reported that elevated CystC is related to left ventricular concentric hypertrophy and increased left ventricular volume in CHF patients. Therefore, CgA and CystC may be used to assess the severity of chronic heart failure [12,13].

The expressions of serum CystC and CgA in CHF patients, and their correlation with LVMI, were investigated in this study so as to generate data for application in the treatment and prevention of CHF. Chromogranin A (CgA) is a very important endogenous cathepsin inhibitor which provides a dynamic equilibrium by regulating the production and degradation of extracellular vascular matrix [14]. An important mechanism involved in the development of ventricular remodeling in CHF patients is the imbalance in the ratio of cathepsin and endogenous protease inhibitors in extracellular matrix of cardiomyocytes [15].

When increased synthesis occurs, collagen accumulates around the myocardial vessels and in the intercellular substance. When excessive degradation occurs, the original physiological collagen scaffold will be destroyed, and the composition and structure extracellular matrix will also be changed.

Table 2: NT-proBNP, CysC and CgA levels in patients (mean ± SD, N = 45)

Group	CgA (ng /ml)	CysC (μg /L)	NT-proBNP (pg/ml)
Grade NYHA group	136.28±12.66$^{*\#\triangle}$	819.44±17.28$^{*\#\triangle}$	6482.41±471.26$^{*\#\triangle}$
Grade NYHA Ⅲ group	226.49±15.82$^{*\#}$	1027.3±41.46$^{*\#}$	7082.77±428.48$^{*\#}$
Grade NYHA Ⅳ group	311.24±22.71*	1164.4±43.28*	7894.28±455.62*
Control group	72.88±4.72	702.52±13.60	1538.64±182.74
F	2061.46	1890.41	2286.77
P	＜0.001	＜0.001	＜0.01

$^{*}p < 0.05$, relative to control; $^{\#}p < 0.05$, relative to NYHA Ⅳ; $^{\triangle}p < 0.05$, relative to NYHA Ⅲ

Table 3: LVEF, LVEDD and LVMI levels (mean ± SD, N = 45)

Group	LVEF (%)	LVMI	LVEDD/mm
Grade NYHA Ⅱ group	41.38±9.67$^{*\#\triangle}$	131.42±12.44$^{*\#\triangle}$	53.91±7.24$^{\#\triangle}$
Grade NYHA Ⅲ group	41.66±7.82$^{*\#}$	142.37±14.81$^{\#}$	57.52±8.92$^{*\#}$
Grade NYHA Ⅳ group	36.50±6.39*	158.87±15.05*	62.03±8.28*
Control group	54.11±5.37	106.29±12.36	50.02±6.36
F	44.17	116.35	19.63
P	＜0.001	＜0.001	＜0.001

$^{*}P < 0.05$, relative to control; $^{\#}p < 0.05$, relative to NYHA Ⅳ; $^{\triangle}p < 0.05$, relative to NYHA Ⅲ

The patient eventually develops heart failure due to myocardial fibrosis and ventricular remodeling. It has been found that an increased level of serum CystC leads to increased diastolic dysfunction and left ventricular hypertrophy.

In this study, the levels of CystC and CgA were markedly higher in CHF patients than in control patients. The levels of CystC and CgA in patients with cardiac function grade Ⅳ were higher than those in patients with cardiac function grades Ⅱ and Ⅲ, and also higher in cardiac function grade Ⅲ than in cardiac function grade Ⅱ cases. The level of LVEF in cases with elevated CgA and CystC was significantly reduced, with significant elevation in LVEDD, LVMI and NT-proBNP, relative to control. This is consistent with the results of similar studies [16-22]. These findings indicate that, to some extent, CystC and CgA may serve as indices of extent of ventricular remodeling in CHF patients, as well as their prognosis. In addition, the results of correlation analysis indicated positive correlation between serum CgA and serum CystC. Correlation analysis revealed negative correlation between CgA and CystC levels in serum and LVEF, and positive correlation of LVMI with NT-proBNP in CHF patients. There were positive correlations between serum CystC level and levels of LVEDD, LVMI, NT-proBNP and CgA in CHF. The levels of CgA and CystC increased with decrease in cardiac function and increase in myocardial weight and heart enlargement. These results suggest that serum CgA and CystC levels in CHF patients can be used for evaluating the severity of heart failure, at least to some extent.

CONCLUSION

Serum CgA and CystC levels are correlated with cardiac function grade and ventricular remodeling in CHF patients. Thus, to some extent, these two indices can serve as criteria for assessing the severity of ventricular remodeling in CHF patients.

DECLARATIONS

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Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the author(s) named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors, all authors read and approved the manuscript for publication. Liu Yan conceived and designed the study, Xue Xiaoxuan, Liu Yan collected and analyzed the data, Xue Xiaoxuan wrote the manuscript.

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