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Correlation between growth differentiation factor-15 and the severity of chronic heart failure in patients with coronary atherosclerosis

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Abstract. – OBJECTIVE: To explore the correlation of the growth differentiation factor-15 (GDF-15) with the severity of chronic heart failure (CHF) in patients with coronary atherosclerosis.

PATIENTS AND METHODS: 300 coronary atherosclerosis patients with CHF treated in our hospital from January 2019 to December 2019 and 300 healthy people (control group) were collected and retrospectively analyzed. The basic clinical information of the patients, such as age, gender, smoking/drinking history, waist-hip ratio, BMI and blood lipid were collected, and GDF-15, cystatin C and c-reactive protein (CRP) were determined. The severity of heart failure was classified.

RESULTS: No significant differences in clinical information were found such as age, gender, smoking/drinking history, waist-to-hip ratio, BMI and blood lipid. However, there were significant differences in GDF-15, cystatin C and CRP among patients with different severities of heart failure. The GDF-15 level was 582.6 ± 104.4 pg/ml in patients with grade IV heart failure and 408.4 ± 94.8 pg/ml in patients with grade I heart failure. There was a significance after GDF-15, cystatin C and CRP were adjusted ($p = 0.03$) and also after the clinical information and GDF-15 were adjusted ($p < 0.001$).

CONCLUSIONS: GDF-15 level is correlated with the CHF severity in patients with coronary atherosclerosis, indicating that it is a potential index to evaluate the CHF severity, providing clues to the biological mechanism and treatment of heart failure.

Key Words:
Coronary atherosclerosis, Chronic heart failure, Growth differentiation factor-15, Regression analysis.

Introduction

Chronic heart failure (CHF) is a kind of cardiovascular disease that seriously endangers human health. In recent years, the prevalence of CHF is steadily increasing with the population growth[1,2]. The etiology of CHF is complex, which is the final stage of the progression of various heart and blood vessel diseases and the main cause of death of cardiovascular diseases. Coronary atherosclerosis is one of the most common causes of CHF. The symptoms such as myocardial ischemia, hypoxia, increased cardiac preload and afterload, decreased cardiac compensatory capacity and ventricular remodeling caused by coronary atherosclerosis have an important impact on CHF progression[3]. With the improvement of medical level, although the overall survival (OS) of patients with cardiac diseases has been extended, the problems in CHF treatment have not been fundamentally solved. Therefore, in order to provide more directions for CHF treatment, it is necessary to study the exact molecular mechanism and pathogenesis of this disease.

Growth differentiation factor 15 (GDF-15), which is also called macrophage inhibition cytokine (MIC-1), is a member of the transforming growth factor (TGF-ß) superfamily. GDF-15 can be induced under conditions of stress and stress overload caused by oxidative stress, ischemia/reperfusion injury, inflammation and cardiac biomechanical stretching[4]. Relevant literature showed that GDF-15 is a new disease marker, which has a certain predictive role in cancer and atherosclerosis, including cardiovascular disease[5,6].

In this study, we retrospectively analyzed the expression of GDF-15 in coronary atherosclerosis patients with CHF and performed a regression analysis of the correlation between GDF-15 and disease progression.

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Patients and Methods

Patient Information

From January 2019 to December 2019, 300 coronary atherosclerosis patients with CHF definitely diagnosed in our hospital and 300 healthy people (control group) were collected and statistically analyzed. All subjects voluntarily participated in the study and signed the informed consent. The diagnostic process was strictly in accordance with the relevant diagnostic standards in Chinese Guidelines for the Diagnosis and Treatment of Heart Failure 2014. The inclusion criteria were as follows: 1. all patients met the above criteria; 2. the clinical data were complete; 3. the age was more than 60 years old. The exclusion criteria were as follows: 1. patients had CHF caused by rheumatic heart disease, primary dilated cardiomyopathy and other factors; 2. patients had previous mental disease, liver and kidney failure; 3. patients had incomplete examination data; 4. patients had malignant tumors. This study was approved by the Ethnic Committee of our hospital.

Heart failure was graded according to the criteria established by the New York Heart Association. Grade I: patients had heart disease, but their daily activities were not limited; normal activities would not cause fatigue, palpitation, dyspnea and angina pectoris. Grade II: patients had heart disease, and their activities were slightly limited after normal work and had no symptom after a short rest, but their daily activities might cause symptoms such as mild dyspnea, palpitation, angina pectoris and fatigue. Grade III: the daily activities of patients with heart disease w obviously limited, even an activity level less than normal daily activity level would cause a series of symptoms. Grade IV: patients with heart disease could not carry out any slight physical activity and could also have heart failure symptoms under the state of rest, which would be aggravated by slight physical activity.

Study Methods

In this study, the retrospective analysis method was used. After patients were included, the basic clinical data of the patients were collected, and GDF-15, cystatin C and CRP levels were measured.

Measurement of Various Indexes

GDF-15 measurement

The content of GDF-15 in human serum was measured by quantitative ELISA (R & D Systems, Minneapolis, MN, USA). The measurement range was 0-5000 pg/ml, and the measurement was strictly in accordance with the instructions of the kit.

Cystatin C measurement

Cystatin C was determined by cystatin C test kit of Dade Behring Inc. In this experiment, the polystyrene particles coated with specific anti-human cystatin C antibodies were reacted with cystatin C in the sample to form a solution of certain turbidity, and the solution emitted a certain intensity of scattered light under the illumination of the light source lamp, and the content of cystatin C in the sample was calculated by detecting the received scattered light signal. The operation steps should be in strict accordance with the manufacturer's instructions.

CRP measurement

CRP was measured by Nephstar specific protein analyzer. The experimental reagents were provided by Shenzhen Guosai Biotechnology Co., Ltd. (Shenzhen, China) and the operation steps were carried out according to the instructions. The normal reference range of hsCRP was less than 4 mg/L.

Statistical Analysis

The experimental data were described by mean ± SD or median and analyzed by Student's *t*-test using SPSS 12 software (SPSS Inc., Chicago, IL, USA). The correlation was assessed by regression analysis. $p < 0.05$ indicated a statistical difference.

Results

General Data of Patients

Based on the severity of CHF, the patients were assigned into four groups such as grade I-IV and compared with control group, respectively. Through comparison, it could be seen that there were no differences in the average age, number of people, gender, diabetes history, smoking/drinking history and BMI between grade I-IV patients and the healthy people (Table I), while TG, TC, HDL-C, LDL-C indexes in the grade III-IV patients showed an increasing trend, with a significant difference in comparison with those in the healthy people and grade I-II patients.

GDF-15, Cystatin C and CRP Levels in Patients

It could be seen from Table II that GDF-15, Cystatin C and CRP levels in patients with CHF

Table I. Basic information of patients.

Group	I	II	III	IV	Control
Age (mean±SD)	59.65±10.5	62.36±9.5	60.36±10.2	61.58±10.8	61.58±9.8
Number of people	39	99	87	75	300
Female (%)	46.10%	51.50%	51.50%	48.00%	54%
Diabetes mellitus history	34.60%	25.40%	17.60%	28.00%	26.00%
Smoking history (%)	23.2%	22.7%	31.6%	49.4%	39%
Drinking history (%)	37.6%	30.7%	40.5%	45.1%	34%
Waist-hip ratio	68.79±3.92	68.93±3.38	69.26±3.57	68.91±3.02	68.36±2.93
BMI	26.0 ± 4.8	26.2 ± 4.3	26.6 ± 4.3	25.2 ± 4.9	25.2 ± 4.9
TG	2.45 ± 1.72	2.53 ± 1.47	2.55 ± 1.82	2.73 ± 1.64	2.77 ± 1.64
TC	4.92±1.53	4.44 ± 1.62	4.86 ± 1.92	4.82± 1.87	4.82± 1.87
HDL-C	1.35±0.67	1.38±0.75	1.46±0.67	1.48±0.75	1.48±0.75
LDL-C	2.94±0.46	2.66±0.53	3.05±0.46	3.38±0.53	2.38±0.72

were significantly increased in comparison with those in the healthy people. GDF-15, Cystatin C and CRP levels in patients with grade III -IV were significantly higher than those in patients with grade I - II heart failure ($p < 0.05$). It could be seen that these three indexes were associated with the degree of inflammation in patients with CHF.

Regression Analysis of the Severity of CHF and Biomarkers

Table III showed the correlation analysis between the severities of CHF and various biomarkers. The *p* value of the unadjusted model was 0.84 without difference. After the patient data (including age, gender, smoking/drinking history, waist-to-hip ratio, BMI, blood lipid status), cystatin C and CRP were adjusted, and *p*-value was 0.12, which still had no difference. In the adjusted model 2, after two indexes of cystatin C and CRP were added, and the *p*-value was significant; after three indexes of GDF-15, cystatin C and CRP were added, *p*-value was extremely significant. The results revealed that GDF-15 had a great influence on the severity of CHF.

Discussion

GDF-15 is a member of TGF-ß superfamily and its level in human body is lower in most organs. When different organs such as heart, kidney, liver and lung are damaged, its expression will be increased[7-9]. GDF-15 can participate in the regulation of inflammatory pathway in the body, but also has several other biological functions such as repairing cell and regulating cellular apoptosis and growth. GDF-15 level is also abnormal in cardiovascular and tumor diseases[6,10]. A study on invasive *vs.* conservative treatment in unstable coronary Syndromes (ICTUS) has shown that GDF-15 is a potentially powerful prognostic marker for heart disease and cancer. GDF-15 is a potential long-term prognosis index for patients with non-ST-elevation acute coronary syndrome[11]. Recently, more researches focused on the correlation of GDF-15 with heart and blood vessel disease and showed that GDF-15 might be a reliable prognostic index for coronary diseases and heart failures, and it is a potential target for cardiac remodeling caused by primary hy-

Table II. GDF-15, Cystatin C and CRP concentrations in patients.

Index	I	II	III	IV	Control
GDF-15 (pg/mL)	408.4±94.8	428.5±104.6	489.5±124.5*#	582.6±104.4*#	388.4±92.5
Cystatin C (mg/L)	0.73±0.52	0.78±0.82*#	0.83±1.05*#	0.89±1.13*#	0.70±0.41
CRP (mg/L)	1.2±0.4	1.2±0.5	1.4±0.6*#	1.5±0.7*#	1.2±0.3

*: There was a significant difference compared with the patients with grade I heart failure #: There was a significant difference d with the patients with grade II heart failure.

Table III. Analysis of correlation between severity of CHF and various biomarkers.

Group	OR (95% CI)	*p*-value
Unadjusted mode l	1.02 (0.45-2.29)	0.84
Adjusted model 1	0.69 (0.63-3.35)	0.12
Adjusted model 2	1.18 (0.27-5.05)	0.03
Adjusted model 3	1.05 (0.33-3.39)	0.00
Adjusted model 4	1.05 (0.33-3.39)	0.00

Adjusted model 1: Analysis results after adjusting the clinical information of patients; Adjusted model 2: Analysis results after adjusting the clinical information, cystatin C and CRP; Adjusted model 3: Analysis results after adjusting the clinical information, GDF-15, cystatin C and CRP; Adjusted model 4: Analysis results after adjusting the clinical information and GDF-15.

pertension, hypertrophic cardiomyopathy and ischemic heart disease[12-14]. After noradrenaline stimulation, increased GDF-15 expression can neutralize noradrenaline induced cardiac hypertrophy. These results indicate that GDF-15 may also be a new therapeutic target for cardiac hypertrophy[15].

Conclusions

The results of our study for the first time reveal that the expression of GDF-15 is significantly elevated in coronary atherosclerosis patients and it is correlated with the severities of CHF, which is the novelty of our study, indicating that GDF-15 might be involved in the pathogenesis of coronary atherosclerosis and CHF, suggesting it might be a target for the treatment of CHF.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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