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Research on the correlation of urine calcium integrin binding protein-1 and pro-BNP with ischemic heart failure

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Abstract. – OBJECTIVE: To investigate the correlation between the levels of urine calcium integrin binding protein-1 (CIB1) and serum precursor N-terminal brain natriuretic peptide (pro-BNP) and ischemic heart failure.

PATIENTS AND METHODS: 30 patients diagnosed as acute ischemic heart failure for the first time in our hospital from January to August 2016 were continuously selected as the observation group 1, 30 patients with chronic stable ischemic heart failure as the observation group 2, and 30 healthy volunteers as the control group. Urine CIB1 level was detected via enzyme linked immunosorbent assay (ELISA) and serum pro-BNP level was detected via radioimmunoassay. The linear correlation between the CIB1 and pro-BNP levels in observation group 1 was observed, and the diagnostic value of CIB1 and pro-BNP levels for chronic stable ischemic heart failure were analyzed using the receiver operating characteristic (ROC) curve.

RESULTS: CIB1 and pro-BNP levels in the observation group 1 were significantly higher than those in the observation group 2. These levels were significantly lower in the control group ($p < 0.05$). In the observation group 1, CIB1 and pro-BNP levels were positively correlated ($p < 0.05$). The diagnostic accuracy of CIB1 for chronic stable ischemic heart failure in the observation group 2 (area under the curve, AUC) was 0.854, the sensitivity was 86.6% and the specificity was 82.5%, respectively. The diagnostic accuracy of pro-BNP was 0.823, the sensitivity was 83.5% and the specificity was 85.9%, respectively.

CONCLUSIONS: There is a significant correlation between the urine CIB1 and serum pro-BNP levels in patients with acute ischemic heart failure. In patients with chronic stable ischemic heart failure, the diagnostic value of urine CIB1 outperforms that of serum pro-BNP, which still needs further study.

Key Words:
Calcium Integrin Binding Protein-1, pro-BNP, Ischemic heart failure, Receiver operating characteristic curve.

Introduction

Acute and chronic stable ischemic heart failure has become the terminal phase of various organic heart diseases. It is also the major cause of death and organ dysfunction in liver, lung, and kidney[1,2]. As the significant extension of people's life expectancy and intensive intervention in various chronic diseases, the morbidity rate of heart failure has been gradually increased. According to statistics, the prevalence of heart failure is 0.5 to 1.5 per ten thousand people in China, with 3-5 million new cases and annual mortality of 8 to 20%. The total medical expenses due to heart failure are about 1 to 1.8 billion yuan per year[3]. Heart failure is an irreversible pathological process characterized by chronic onset and development. Intervention treatment exerts the best effect on high-risk and early-stage patients[4]. Therefore, developing biomarkers with high sensitivity and specificity is an important clinical method for an early detection of heart failure. The secretion of serum precursor N-terminal brain natriuretic peptide (pro-BNP) is throughout the whole process of heart failure. In the early stage, it increases the cardiac output, decreases the ventricular volume load and slows the ventricular remodeling[5]. In the advanced stage, it accelerates the progression of heart failure[6]. However, the level of pro-BNP cannot predict high-risk and early-stage heart failure without symptoms[7]. Recent studies have shown that the expression of serum and urine calcium integrin binding protein-1 (CIB1) may be correlated with the onset of earlier-stage heart failure[8]. CIB1, a member of soluble cell adhesion molecule family, takes part in calcium ion metabolism and influences the contraction and motion of smooth muscle cells and endothelial cells[9]. In this work, the correlation of the levels of urine CIB1 and serum pro-BNP with ischemic heart failure was investigated via the clinical test.

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Patients and Methods

Patients

30 patients diagnosed as acute ischemic heart failure for the firs time in our hospital from January to August 2016 were continuously selected as the observation group 1, 30 patients with chronic stable ischemic heart failure as the observation group 2, and 30 healthy volunteers as the control group. This investigation was approved by the Ethics Committee of Daqing Oilfield General Hospital. Written informed consent was obtained from all participants before the study.

Inclusion criteria: (1) Patients with organic heart disease history in conformity with the diagnostic criteria of acute and chronic heart failure of US and EU in 2015; (2) patients with initial heart failure without taking any anti-heart-failure medication, such as diuretics, β-receptor inhibitor or angiotensin-converting enzyme inhibitors (ACEI) in the past 1 month after enrollment in this research; (3) patients with well-documented clinical data. All patients were informed of the purpose of the study and gave written informed consents.

Exclusion criteria: (1) Patients with serious diseases, such as hepatic failure, respiratory failure, renal insufficiency, severe high blood pressure, diabetes mellitus or any other diseases affecting the metabolism of CIB1 and pro-BNP; (2) pregnant patients or those who suffered from infection or tumor.

There were 17 males and 13 females in the observation group 1 aged 48-75 years old (average age = 66.3 ± 12.4 years old). According to Killip grade, 12 patients were at stage I, 13 patients were at stage II and 5 patients were at stage III. The left ventricular end-diastolic diameter (LVEDd) was 49-55 mm (mean = 51.6 ± 2.4 mm). There were 16 males and 14 females in the observation group 2 aged 51-77 years (mean = 65.4 ± 13.7 years old). According to New York Heart Association (NYHA) grade, 10 patients were at stage I, 8 patients were at stage II, 8 patients were at stage III and 4 patients were at stage IV. The LVEDd was 45-52 mm (mean = 48.9 ± 2.3 mm). There were 15 males and 15 females in the control group aged 45-76 years old (mean = 65.8 ± 15.5 years old). LVEDd was 45-50 mm (mean= 47.8 ± 2.5 mm). No differences in gender and age among these groups were observed ($p > 0.05$). The LVEDd in the observation group 1 was higher than that in the observation group 2 and that in the control group was the lowest ($p < 0.05$).

Methods

The level of urine CIB1 was detected via ELISA and the serum level of pro-BNP was detected via radioimmunoassay. Reagents of CIB1 were purchased from Beyotime Biotechnology (Nanjing, Jiangsu, China) and the microplate reader (Bio-Rad, Hercules, CA, USA) was purchased from Bio-Rad (Hercules, CA, USA).

Measurement of pro-BNP: Blood samples were collected and mixed with aprotinin (500 IU/mL) in the anticoagulant tube. The mixed solution was centrifuged at 2000 rpm for 10 min, and then the serum was separated and stored at -70°C. Reagents were purchased from Sigma-Aldrich (St. Louis, MO, USA). All experiments strictly followed the manufacturer's instructions.

Statistics Analysis

Statistical Product and Service Solutions (SPSS) 20.0 (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. Measurement data were presented as mean ± standard deviation. ANOVA was used to compare the differences among groups, while pair-wise comparison was performed with LSD *t*-test. Count data were presented as case or percentage (%) and the difference was assessed by the chi-square test. Linear correlation was used to analyze CIB1 and pro-BNP levels. The area under receiver operating characteristic (ROC) curve was used to assess the CIB1 and pro-BNP levels to diagnose chronic ischemia heart failure. $p < 0.05$ suggested that the difference was statistically significant.

Results

Comparison Between CIB1 and pro-BNP Levels

Both CIB1 and pro-BNP levels in the observation group 1 were significantly higher than those in the observation group 2. These levels were the lowest in the control group ($p < 0.05$) (Table I).

Correlation Between CIB1 and pro-BNP Levels in Ischemic Heart Failure Patients

In the observation group, CIB1 level showed a positive correlation with pro-BNP level ($p < 0.05$) (Figures 1 and 2). No significant correlation between CIB1 and pro-BNP levels was detected in the observation group 2 ($p > 0.05$).

Table I. The comparison of the level of CIB1 and pro-BNP.

Group	CIB1 (μg/L)	pro-BNP (pg/ml)
Observation group 1	5.86 ± 2.37	1721.4 ± 1048.6
Observation group 2	3.24 ± 1.26	452.5 ± 102.3
Control group	0.89 ± 0.24	89.2 ± 35.7

Diagnostic Value of CIB1 and pro-BNP levels in Chronic Stable Ischemic Heart Failure

CIB1 and pro-BNP levels were used to classify patients into the chronic ischemic heart failure group or control group by ROC analysis. The diagnostic accuracy of CIB1 level was 0.854, the sensitivity was 86.6% and the specificity was 82.5% with the cutoff value of 2.16 μg/L. The accuracy of pro-BNP level was 0.823, the sensitivity was 83.5% and the specificity was 85.9% with the cutoff value of 215.6 pg/ml.

Discussion

Although acute and chronic ischemic heart failure are two different states of the same disease, their pathological mechanisms are completely different. For patients with acute ischemic heart failure for the first time, the compensatory mechanisms in the body, including Frank-Starling mechanism, neuroendocrine and sympathetic excitement mechanism, fail to prevent the damage to myocardial cells. The level of damage to myocardial cell is often severe, while the ventricular remodeling is not obvious. Patients often suffer from mechanical diastolic and systolic disorders and pump dysfunction[10]. Compared with acute heart failure, the progression of chronic heart failure is less aggressive and usually accompanied with persistent compensatory mechanism. In most cases, patients suffer from myocardial cell dysfunction, such as ischemia, hypoxic, calcium overload and abnormal energy metabolism under various myocardial compensatory adjustments[11]. The biomarkers for myocardial cell injury caused by different heart failure are not identical[12]. It has been shown that CIB1 protein conformation can alter via combining with Ca^{2+} and then target a variety of proteins, such as PKD2, AKT, ERK, and PIK3. CIB1 protein plays a significant role

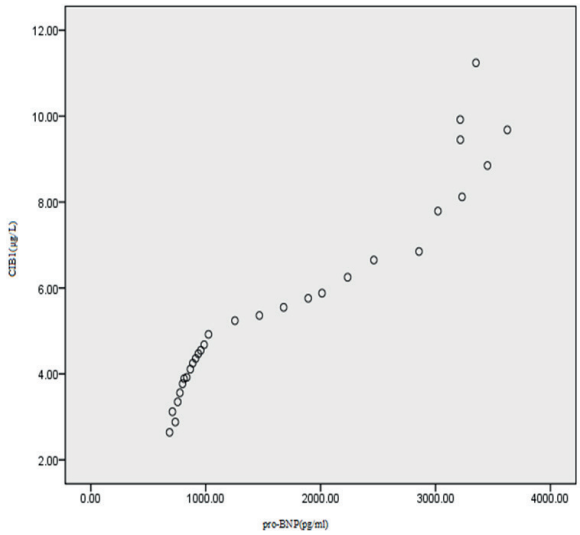

Figure 1. Correlation between the levels of CIB1 and pro-BNP in acute ischemic heart failure (the level of CIB1 has a positive correlation with the level of pro-BNP, r = 0.624, $p = 0.009$).

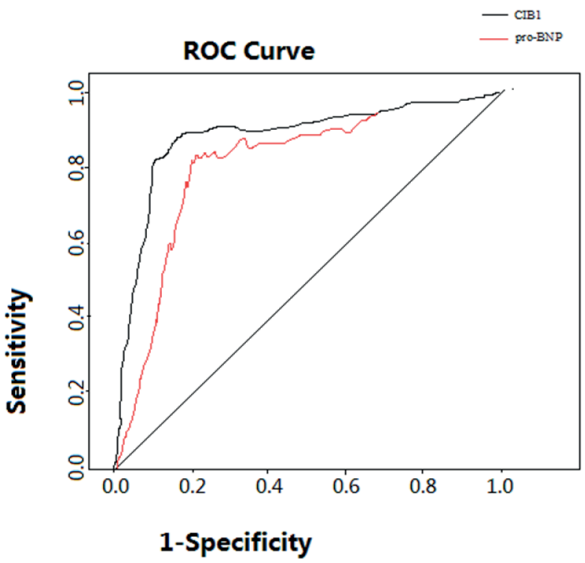

Figure 2. Correlation between the levels of CIB1 and pro-BNP in acute ischemic heart failure (the level of CIB1 has a positive correlation with the level of pro-BNP, r = 0.624, $p = 0.009$).

in regulating cell growth, differentiation, migration, coagulation, DNA damage repair response, apoptosis, cell cycle, embryonic development, and other physiological and pathological processes[13,14]. The abnormal expression of CIB1 is correlated with the development and progression of various tumors[15,16]. CIB1 is also a key factor in the etiology of cardiac diseases. CIB1, as a cell adhesion molecule, can mediate intercellular and cell-matrix adhesion. The CIB1 expression has been observed in endothelial cells, leukocytes, platelets, and smooth muscle cells. Its soluble form can be found in plasma and can be metabolized and excreted by kidney[17,18]. Both acute and chronic heart failure are closely related to the renal metabolism. In "heart kidney syndrome" theory, it is considered that a variety of myocardial metabolic products may be found in blood as well as urine[19]. Pro-BNP has already been widely used to evaluate the severity and prognosis of acute and chronic heart failure caused by various factors. In this study, CIB1 and pro-BNP levels in the observation group 1 were significantly higher than those in the observation group 2. Among all groups, the control group had the lowest levels of CIB1 and pro-BNP. The increased level of CIB1 can enhance apoptosis in myocardial cell, and lead to dysfunction of the nerve impulse conduction[20]. It can also increase metabolism in myocardial cell and create disorder in mechanical diastole and systole[21]. The abnormally high level of pro-BNP is also known as "Call for Help Before Death". CIB1 level showed a positive correlation with the pro-BNP level in the observation group 1. We did not find such a correlation in the observation group 2. These results suggested a greater difference between CIB1 and pro-BNP levels in acute heart failure state. According to the ROC analysis, we discovered that the diagnostic value of CIB1 for chronic stable ischemic heart failure outperformed that of serum pro-BNP. This can be used to evaluate the risk of heart failure in asymptomatic patients. Previous research[22] demonstrated that a variety of cell adhesion molecules, such as immunoglobulin superfamily, selectin family, integrin family, mucin-like family and calcium-dependent adhesion family, were related to myocardial ischemic lesions. Also, results obtained from previous investigations[23] revealed that CD54 (intercellular adhesion molecule 1, ICAM) could be used as a stable and reliable diagnostic indicator for congestive heart failure and it played a great role in assessing pathogenic condition and prognosis. It was shown that the mechanism of anti-heart failure of ACEI and ARB is also related to the effect of ICAM-1. Hence, the abnormal expression of adhesion molecules may be a potential biomarker for the onset and diagnosis of heart failure.

Conclusions

The levels of urine CIB1 and serum pro-BNP in patients with ischemic heart failure can be used to assess whether the heart failure is in acute or chronic state. Further studies in this field can improve the treatment and identify a better therapeutic target. The sample size in this work is small, so these results need to be further validated.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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