Original Article
Serum uric acid, NT-ProBNP and hs-CRP as biomarkers in chronic heart failure

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Abstract: Background/Aims: Heart failure (HF) is a common, debilitating disorder in which the heart is unable to pump an adequate blood supply to the tissues. Both Uric Acid (UA) and NT-proBNP was recently established as a prognostic marker for poor outcome in chronic HF. Inflammatory markers such as high-sensitivity C-reactive protein (hs-CRP) has also been suggested as cardiovascular risk biomarkers. This study aims to assess the serum levels of UA, NT-proBNP and hs-CRP in different clinical types chronic heart failure (CHF). Methods: 205 patients with chronic heart failure were divided into two groups according to left ventricular ejection fraction (LVEF): heart failure with ≤ reduced left ventricular ejection fraction (HFrEF group, LVEF ≤ 40%, n=110) and heart failure with preserved left ventricular ejection fraction (HFpEF group, LVEF ≥ 50%, n=95). Data of plasma UA, NT-proBNP, hs-CRP level and related echocardiography indexes were collected and compared in 205 patients with chronic heart failure and the normal control group (n=80). The correlation analysis were made between plasma UA, NT-proBNP, hs-CRP level and LVEF respectively in these two group. Results and conclusion: Patients with HFpEF had lower NT-proBNP and hs-CRP levels than those with HFrEF. We could observe a significant correlation between UA level and NT-proBNP (correlation coefficient r=0.728) and hs-CRP (correlation coefficient r=0.752), and a negative correlativity between UA level and LVEF (correlation coefficient r=-0.71) in the in HFrEF group. Therefore, our results revealed for the first time that combination of UA, NT-proBNP and hs-CRP is a useful biomarker for chronic heart failure.

Keywords: Uric acid, NT-ProBNP, hs-CRP, heart failure, LVEF

Introduction

Chronic heart failure (CHF) is still a leading cause of cardiovascular morbidity and mortality [1]. Moreover, the frequencies of novel cases of CHF arise progressively in china [2]. In the American Heart Association (AHA)/American College of Cardiology guidelines, HF is defined as “a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill or eject blood” [3]. Heart failure with reduced Ejection Fraction (HFrEF) and Heart failure with preserved Ejection Fraction (HFpEF) carry equal morbidity and mortality risks. HFrEF or HF secondary to systolic dysfunction is the result of disrupted pump function while HFpEF is secondary to increased filling pressures [4]. Epidemiological studies demonstrate that 50% of all heart failure patients suffer from heart failure with preserved ejection fraction (HFpEF), which-in contrast to heart failure with reduced ejection fraction (HFrEF)-cannot be adequately treated with current available therapeutical strategies [5]. In both HFrEF and HFpEF, there are similar signs and symptoms such as congestion, dyspnea at rest or on exertion, and poor perfusion. However as the underlying pathophysiology is markedly different, it is important to identify risk factors so that appropriate treatment strategies can be targeted, and in turn, readmission rates can be reduced, and quality of life measures can be improved [6].

Uric acid (UA) is produced in the terminal steps of purine nucleotide metabolism by xanthine oxidase

(XO) in a two-step process that also results in the formation of superoxide [7]. Up-regulation
of XO pathway activity may produce increases in serum (UA), oxidative stress, endothelial dysfunction, and left ventricular dysfunction [8], all of which have been linked to the pathogenesis of heart failure (HF) [9]. Plasma NT-proBNP (N-terminal pro-B-type natriuretic peptide) levels are often used as a biological marker of heart failure, brain type natriuretic peptide (BNP) and amino terminal pro-brain natriuretic peptide (NT-proBNP) are both derived from the same precursor proBNP. They are released from the cardiac ventricles in response to myocardial stretch [10]. NT-proBNP is significantly increased in case of left ventricular dysfunction and is recognized as strong predictors of morbidity and mortality in patients with heart failure [11, 12]. On the other hand, high sensitive C-reactive protein (hs-CRP) was positively associated with all-cause and cardiovascular mortality and are useful for estimating prognosis in persons with chronic stable heart failure [13]. Few studies have examined the examined the UA levels in different kinds of CHF, and few studies have explored the relationships between UA and NT-proBNP, or between UA and hs-CRP.

In this study, we have determined the plasma uric acid (UA), hs-CRP in different CHF patients, at the same time we investigated the relationship of these biomarkers with left ventricular ejection fraction (LVEF), to further evaluate the predictive value of these biomarkers in determining the severity, the treatment response and the prognosis of chronic heart failure.

Methods

Study population

Four hundred and thirty-five patients with CHF were admitted to Jining First People’s Hospital between February 2012 and August 2015. Each patient consented (written and informed) to have blood samples taken and outcomes surveyed. This study complied with the Declaration of Helsinki and was approved by the local ethics committee. The clinical diagnosis of CHF was made by the attending physician on the basis of the presence of symptoms and signs of CHF including moderate to severe dyspnoea (class III and IV according to the New York Heart Association), raised jugular venous pressure, and basal crepitations. Patients with chronic lung disease, myocardial infarction (within 12 weeks), or severe renal failure were excluded. All these patients were selected according to our inclusion and exclusion criteria.

After inclusion, participating patients underwent an echocardiography. A LVEF of ≤ 40% was considered as reduced ejection fraction. 435 patients with chronic heart failure were divided into two groups according to left ventricular ejection fraction (LVEF): heart failure with ≤ reduced left ventricular ejection fraction (HFrEF group, LVEF ≤ 40%, n=240) and heart failure with preserved left ventricular ejection fraction (HFpEF group, LVEF ≥ 50%, n=195) [14, 15].

NYHA classification

Heart function of all patients were categorized in three groups according to New York Heart Association (NYHA) Class IV, patients with NYHA I or II, patients with NYHA III and those with NYHA IV, respectively.

Echocardiography detection

All patients were administered with bedside echocardiography, using the SC-2000 Color Doppler ultrasound diagnostic apparatus (Siemens, Munich, Germany) before and after statin treatment at the left lateral position. The ultrasonic probe was adjusted to a frequency of 2.0-2.5 MHz, and a scanning speed of 50 mm/s. The apical four-chamber view, parasternal long axis view, and left ventricular long axis view were measured in order to know the left ventricular internal dimension, left ventricular end-diastolic dimension (LVEDD), left ventricular end-diastolic volume index (LVEDVI), left ventricular end-systolic volume index (LVESVI), the left ventricular ejection fraction \[LVEF = (LVEDVI-LVESVI)/LVEDVI \times 100\%]\, and the maximum flow rate of early diastolic and end-diastolic maximum flow rate ratio (E/A), with reference to the recommended checking points on echocardiography provided by the American Society of Echocardiography.

Biomarker determination

To measure the biological marker concentrations, blood samples were drawn in the morning (at 7-8 a.m.) into cooled silicone test tubes. Samples were processed according to the rec-
UA, NT-ProBNP and hs-CRP in CHF

Statistical analysis

Statistical analyzes were performed using IBM SPSS statistics software version 22. Data are presented as frequencies or mean ± SD as appropriate. Mono factor analysis of variance and linear correlation were used to analyze differences between groups.

Results

Study patient population

The characteristics of the patients participated in the study are depicted in Table 1. There is no statistical difference among control, HFpEF, HFrEF group of patients at gender, age, heart rate and Dyslipidemia (P>0.05). Compared with control group (122.0±0.8 mmHg) and HFrEF group (121.0±0.83 mmHg), the Hypertension in HFpEF group (144.9±1.21 mmHg) is higher, (significance at P<0.01). At the etiology, 32.75% of the HFrEF patients are coronary disease, 50.9% of the HFrEF patients are dilated cardiomyopathy. In the HFpEF group, 57.8% of the patients are Hypertensive heart disease, there is statistical significance between HFpEF and HFrEF in the etiology (P<0.05).

Patients’ heart function were evaluated by NYHA class, 73.5% of the patients in HFpEF group were assessed in NYHA II (Table 2); while 66.4% of the patients in HFrEF group were assessed in NYHA II. The NYHA heart function composition was significantly different between HFpEF and HFrEF in the etiology (P<0.05).

Compared with control (387.76±4.25 μmol/L) and HFpEF group (396.18±74.39 μmol/L), there was statistical difference in the serum UA level of HFrEF patients (456.95±70.91 μmol/L), (significance at P<0.01). As shown in Table 3, there was no statistical difference in UA bet-

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<th>Table 1. The characteristics of participants</th>
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<td>Variable</td>
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HFpEF: Heart failure with preserved Ejection Fraction; HFrEF: Heart failure with reduced Ejection Fraction; HR: heart rate; NVM: Noncompaction of ventricular myocardium; n.s.: Not significant.

<table>
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<th>Table 2. NYHA class of HFpEF and HFrEF patients</th>
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<td>NYHA class</td>
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NYHA: New York Heart Association; HFpEF: Heart failure with preserved Ejection HFrEF: Heart failure with reduced Ejection Fraction.
We determined the NT-proBNP level of the three groups (see Table 3). Concentration of NT-proBNP in HFrEF (4756.03±581.8 pg/ml) was significantly different with control group (136.9±67.0 pg/ml, significance at \( P < 0.01 \)) and HFpEF group (2807.4±249.3 pg/ml, significance at \( P < 0.01 \)), there was also significant difference in NT-proBNP between HFpEF and control group (significance at \( P < 0.01 \)).

As shown in Table 3, hs-CRP level in HFrEF group was (13.29±1.14 mg/L), which was significantly different with control group (1.17±0.08 mg/L, significance at \( P < 0.01 \)) and HFpEF group (2807.4±249.3 pg/ml, significance at \( P < 0.01 \)).

Left ventricular ejection fraction (LVEF) in HFrEF group was (39.61±3.03%), which was significantly lower (\( P < 0.01 \)) than that in HFpEF (61.80±3.76%) and control group (62.83±2.75%), there was no statistical difference in LVEF between the control group and HFpEF group (\( P > 0.05 \)).

Correlation analysis of UA level and NT-proBNP, hs-CRP, LVEF in HFpEF patients

We used pearson linear correlation analysis to identify the relationship between UA level and NT-proBNP, hs-CRP, LVEF in patients. As shown in Table 4, in HFrEF group, It is positive correlation between UA level and NT-proBNP (correlation coefficient \( r=0.728 \)) and hs-CRP (correlation coefficient \( r=0.752 \)), and There is a negative correlativity between UA level and LVEF (correlation coefficient \( r=-0.710 \)). The correlation analysis results were also presented by Figure 1 using the scatterplot. There were no correlation among these factors in HFpEF patients (Data not shown).

Discussion

Chronic heart failure (CHF) remains a leading cause of cardiovascular (CV) mortality and morbidity worldwide [16]. In most cases it presents as a slowly progressing condition termed chronic or congestive heart failure. Two types of heart failure are clinically distinguished based on assessment of systolic function: heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF). The distinction is relevant as effective disease-modifying therapies are available only for HFrEF, and In the last decades the incidence of newly HF in developed countries have been substantially declined especially for HF with reduced ejection fraction (HFrEF) [17]. While no clearly effective evidence-based treatments are available for HFpEF so far, there is marked increase in hospital admissions, CV and non-CV death rate predominance of HF with preserved ejection fraction (HFpEF) [18, 19].

In this study, we have demonstrated that HFpEF patients have exhibited elevated levels of Hypertension than HFrEF patients. We showed that plasma level of NT-proBNP and hs-CRP were powerful diagnosis factor in both HFpEF and HFrEF groups. We also showed that patients with HFrEF had lower NT-proBNP and hs-CRP levels than those with HFRE. Interestingly, we could observe a significant correlation between UA level and NT-proBNP (correlation coefficient \( r=0.728 \)) and hs-CRP (correlation coefficient \( r=0.752 \)).
UA, NT-ProBNP and hs-CRP in CHF

Figure 1. Correlation analysis of UA level and NT-proBNP, hs-CRP, LVEF in HFrEF patients. scatterplot showed there was positive correlation between UA level and NT-proBNP (correlation coefficient r=0.728) (A) and hs-CRP (correlation coefficient r=0.752) (B), and there was a negative correlativity between UA level and LVEF (correlation coefficient r=-0.71) (C).

HFpEF, defined as asymptomatic HF with normal to near normal LVEF, accounts for about one-half of patients hospitalized due to acute HF [5, 20, 21]. The pathophysiology includes LV diastolic dysfunction as well as multiple non-diastolic abnormalities such as systolic dysfunction, ventricular-vascular coupling, vascular dysfunction, chronotropic incompetence and impaired cardiovascular reserve [22, 23]. Anatomically, patients with HFpEF have a concentric remodelling with increased relative wall thickness and relatively preserved LV diameter, resulting in a high ratio of mass to volume, whereas patients with HFrEF have an enlarged LV cavity, but relatively normal LV wall thickness [22].

BNP is a cardiac neuropeptide that is most secreted from the ventricles reacting to an increase in wall tension [24]. Recent studies have
showed that the release of BNP from myocardium was largely determined by end-systolic wall stress, and that the effects of diastolic load were only weak [25]. Patients with HFrEF who have lower wall tension thus have lower natriuretic peptide levels than those with HFrEF [26]. During the past decades, studies have shown that the immune system, via its pro-inflammatory pathways, has been implicated in the development of adverse remodelling and ultimately HF [27]. In the present study, we explored the value of hs-CRP (an established inflammatory biomarker) for the diagnosis of CHF. Our finding showed that patients with HFrEF have a 1.7 fold higher NT-proBNP level than those with HFrEF. And HFrEF group have a 1.9 higher hs-CRP level than those with HFrEF. In combination with the result that 73.5% of the patients in HFrEF group were assessed in NYHA II (Table 2) and 66.4% of the patients in HFrEF group were assessed in NYHA IIigr, it was hypothesised that the plasma NT-proBNP and hs-CRP levels may have a vital role on heart function dependent on the type of HF, plasma NT-proBNP is also related to the severity of CHF and left ventricular function. Our finding can be helpful in diagnosis of HF type.

In HFrEF patients, there is a decrease in the cardiac output, tissue hypoxia and injury followed by venous congestion will eventually produce ischemia, hypoxia, tissue necrosis and inflammation factors which induced inflammatory response such as increase of cytokine and oxygen free radical [28]. Tissue ischemia in liver, kidney and other organs will induce the necrosis of cells. cells degeneration lead to an increase in the blood UA level. At the same time, inflammatory reaction associated with venous congestion is responsible for interstitial fibrosis and decline of eGFR by progressive HF [29]. This is the possible reason in our finding why there is a positive correlation between UA level and and hs-CRP.

Conclusions

We showed that plasma level of NT-proBNP and hs-CRP were powerful diagnosis factors in both HFrEF and HFrEF groups. Patients with HFrEF had lower NT-proBNP and hs-CRP levels than those with HFrEF. We could observe a significant correlation between UA level and NT-proBNP (correlation coefficient r=0.728) and hs-CRP (correlation coefficient r=0.752), and a negative correlativity between UA level and LVEF (correlation coefficient r=-0.71) in the in HFrEF group. The results of our study have revealed for the first time that combination of UA, NT-proBNP and hs-CRP is a useful biomarker for chronic heart failure.

Disclosure of conflict of interest

None.

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