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Original Article

The clinical significance of changes in cTnT, CRP and NT-proBNP levels in patients with heart failure

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Abstract: Objective: This study was designed to explore the clinical significance of changes in troponin T (cTnT), C-reactive protein (CRP) and amino-terminal pro-brain natriuretic peptide (NT-proBNP) levels in patients with heart failure (HF). Methods: A total of 193 patients with HF admitted to our hospital from October 2013 to June 2019 were enrolled as the study subjects (group A). Another 191 healthy controls were included as group B. Both groups were compared in terms of cTnT, CRP, NT-proBNP levels and left ventricular ejection fraction (LVEF), and the correlations between LVEF and cTnT, CRP, NT-proBNP were analyzed. The differences in cTnT, CRP, NT-proBNP were compared among patients with different cardiac function, different causes of HF, and between patients with and without cardiac events. Results: cTnT, CRP, and NT-proBNP levels in group A were higher than those in group B (P<0.05). LVEF in group A was lower than that in group B (P<0.05). Negative correlations were found between CRP, cTnT, NT-proBNP and LVEF (P<0.05). As cardiac function improved, cTnT, CRP, NT-proBNP levels also increased, with significant differences between groups (P<0.05). cTnT, CRP, and NT-proBNP levels exhibited no significant difference between the ischemic and non-ischemic HF groups (P>0.05). Patients with cardiac events showed higher levels of cTnT, CRP, and NT-proBNP than those without cardiac events (P<0.05). Conclusion: cTnT, CRP and NT-proBNP levels were elevated in patients with HF, which were negatively correlated with LVEF, and their levels increased with the improvement of cardiac function, independent of the cause of HF. The combination of these three indices is of great significance in the diagnosis and prognosis of HF.

Keywords: Heart failure, troponin T, C-reactive protein, amino-terminal brain natriuretic peptide precursor, clinical significance

Introduction

Heart failure (HF) is the final stage of severe heart diseases, and it is caused by diastolic or (or) contractile dysfunction of the heart, which makes it difficult to drain sufficient amount of venous cardiac blood back to the heart, thus causing the venous system to stagnate blood and the arterial system to suffer from hypoperfusion, eventually leading to cardiac dysfunction syndrome, characterized by vena cava stasis and pulmonary stasis [1, 2]. Most clinical cardiovascular diseases eventually lead to HF. Inflammation, hemodynamic overload, cardiomyopathy, and myocardial infarction can damage the myocardium, leading to changes in its function, structure, ultimately ventricular filling or (and) hypopumping [3]. Secondly, inappropriate activities and negative emotions, effects of drugs, severe arrhythmias, and infections are also predisposing factors for HF [4].

Cardiac ultrasound is a clinical method for the diagnosis of HF, which can determine the function and structure of the heart, left ventricular ejection fraction, pericardial disease, *etc*. [5]. With the continuous deepening of clinical research, the pathophysiological mechanism of HF has been explored. Some biological markers have been found to be effective for the diagnosis and prognosis of HF [5]. Troponin T (cTnT) is the most sensitive index to determine the sensitivity of cardiomyocyte necrosis, and its level is positively correlated with the degree of cardiomyocyte necrosis [6]. C-reactive protein (CRP) is one of the common non-specific inflammatory

response factors, and it is also an acute phase protein secreted and synthesized by the liver [7]. CRP levels were strongly associated with disease severity and the number of cardiomyocyte necrosis in patients with acute coronary syndromes [8]. During HF, elevated levels of inflammatory factors not only originate in the myocardium, but can also be stimulated by circulating macrophages, monocytes, and leukocytes [9]. HF is a key prerequisite for the production of inflammatory factors, and the inflammatory response can also exacerbate tissue and organ damage. Amino-terminal pro-brain natriuretic peptide (NT-proBNP) is a polypeptide secreted in response to ventricular volume overload or traction force and has a long half-life, the level of which can effectively reflect the degree of myocardial damage [10, 11].

Previous clinical studies mainly focused on the changes of cTnT, CRP and NT-probNP levels in patients with HF before and after treatment, while in order to improve the accuracy of HF diagnosis, this study focused on the clinical significance of the changes in cTnT, CRP and NT-proBNP levels in HF patients, and compared the differences in the levels of cTnT, CRP and NT-proBNP in HF patients with different cardiac function classification and causes of HF, with and without cardiac events, which is innovative and feasible.

Materials and methods

Baseline data

A total of 193 patients with HF admitted to our hospital from October 2013 to June 2019 were enrolled as the study subjects (group A). Another 191 patients who received health checkups in our hospital during the same period were enrolled as group B. The inclusion criteria of group A: patients who met the diagnostic criteria of HF by the Cardiovascular Branch of the Chinese Medical Association; and patients who signed informed consent. This study was approved by the medical ethics committee. Exclusion criteria: patients with acute cerebrovascular disease; presence of connective tissue disease; presence of severe infectious disease; endocrine insufficiency; severe hepatic and renal insufficiency; chronic obstructive pulmonary disease, aortic dissection, acute pericarditis, acute myocarditis, acute coronary syndrome.

Methods

Determination of cTnT, CRP and NT-proBNP levels: 10 ml of early morning fasting cubital venous blood was drawn, followed by anticoagulation and centrifugation for 15 min (3500 r/min). After the serum was separated, the samples were stored in a refrigerator at -20°C. CRP level was measured by immunoturbidimetric method using a fully automatic immunofluorescence turbidimetric analyzer. The kit provider is Jinan Ainova Co., Ltd.; cTnT was measured by fully automatic immunoassay (Roche Biotech). NT-proBNP was determined by the automatic immunoluminescence chemical analyzer (Abbott AXSYM plus).

LVEF measurement: Cardiac ultrasound examination was performed using GE Vivid 7 color Doppler ultrasound imaging device. Before the test, patient laid motionless for 5 min. The synchronized ECG monitoring electrodes were correctly connected to determine each cardiac cycle. The apex and parasternal views were visualized using two-dimensional ultrasound in combination with M-ultrasound cardiogram examination. After the collection of image, the patient was instructed to breathe deeply, and then hold the breath. The image was frozen and saved to calculate LVEF.

Outcomes measurement

(1) The differences in the levels of cTnT, CRP, and NT-proBNP were compared between groups A and B.

(2) The differences in left ventricular ejection fraction (LVEF) and the correlation between cTnT, CRP, NT-proBNP levels and LVEF were analyzed.

(3) Cardiac function was assessed according to NYHA classification [12]. Class I - No symptoms and no limitation in ordinary physical activity, *e.g.* shortness of breath when walking, climbing stairs *etc*. Class II - Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity. Class III - Marked limitation in activity due to symptoms, even during less-than-ordinary activity, *e.g.* walking short distances (20-100 m). Comfortable only at rest. Class IV - Severe limitations. Symptoms can occur even at rest. Mostly bedbound patients. No NYHA class listed or unable to determine.

Table 1. Comparison of baseline data [n (%)]/($\bar{x}$ ± sd)

Baseline data		Group A (n=193)	Group B (n=191)	t/X^2	*P*
Gender	Male	99 (51.30)	101 (52.88)	0.097	0.756
	Female	94 (48.70)	90 (47.12)		
Age (years)		59.86±3.18	60.02±3.16	0.495	0.621
NYHA class					
Class I		50 (25.91)	--	--	--
Class II		55 (28.50)	--	--	--
Class III		45 (23.32)	--	--	--
Class IV		43 (22.28)	--	--	--
Causes of heart failure			--	--	--
Ischemic heart failure		72 (37.51)	--	--	--
Non-ischemic heart failure		121 (62.69)	--	--	
Underlying cardiovascular diseases					
Cardiomyopathy		45 (23.32)	--	--	--
Valvular heart disease		38 (19.69)	--	--	--
Hypertension		41 (21.24)	--	--	--
Coronary heart disease		69 (35.75)	--	--	--

Note: - indicates none.

(4) Comparison of differences in cTnT, CRP, and NT-proBNP levels in patients with HF caused by different etiologies: (i) Ischemic HF: the presence of a previous history of definite non-elevation or elevation myocardial infarction, unstable or stable angina; the presence of myocardial infarction, *e.g.*, a more than threefold increase in troponin; the presence of bilateral lower extremity edema, rales, pink frothy sputum, cyanosis, orthopnea, wheezing and chest tightness; LVEF <47% and left ventricular hypertrophy; plasma natriuretic peptide (BNP) >400 pg/ml. (ii) Non-ischemic HF: previous history of organic heart disease such as hypertrophic cardiomyopathy, dilated heart disease and valvular heart disease; no clear history of myocardial infarction; left ventricular diastolic dysfunction on cardiac ultrasound; LVEF <47% or normal; BNP >400 pg/ml; signs and symptoms such as bilateral lower extremity edema, rales in both lungs, coughing up pink frothy sputum, cyanosis, orthopnea, shortness of breath and chest tightness [13].

(5) Both groups were followed up for 2-16 months, including regular outpatient visits and telephone follow-up. The differences in cTnT, CRP, and NT-proBNP levels between patients with and without cardiac events were compared. The cardiac events included hospitalization for worsening cardiac function, and death from HF.

Statistical analysis

SPSS22.0 was used to analyze the data. Measurement data expressed as the mean ± standard deviation and conformed to the normal distribution were compared by *t* test. While the Mann-Whitney U test was performed for the data that did not conform to the normal distribution. Count data expressed as [n (%)] were compared by X^2 test. Pearson's correlation analysis was performed between cTnT, CRP, NT-proBNP levels and LVEF. $P<0.05$ suggested the presence of statistically significant diference.

Results

Comparison of general information

Group A included 99 males and 94 females, with the average age of 59.86±3.18 years, while group B included 101 males and 90 females, with the average age of 60.02±3.16 years. There was no significant difference in gender, age, NYHA classification, causes of HF, between the two groups ($P>0.05$) (**Table 1**).

Comparison of cTnT, CRP, and NT-proBNP levels

The cTnT, CRP, and NT-proBNP levels in group A were 17.52±0.28 mg/L, 0.53±0.19 ng/ml, and 2418.96±12.36 pg/ml, respectively, which were higher than those in group B ($P<0.05$) (**Figure 1**).

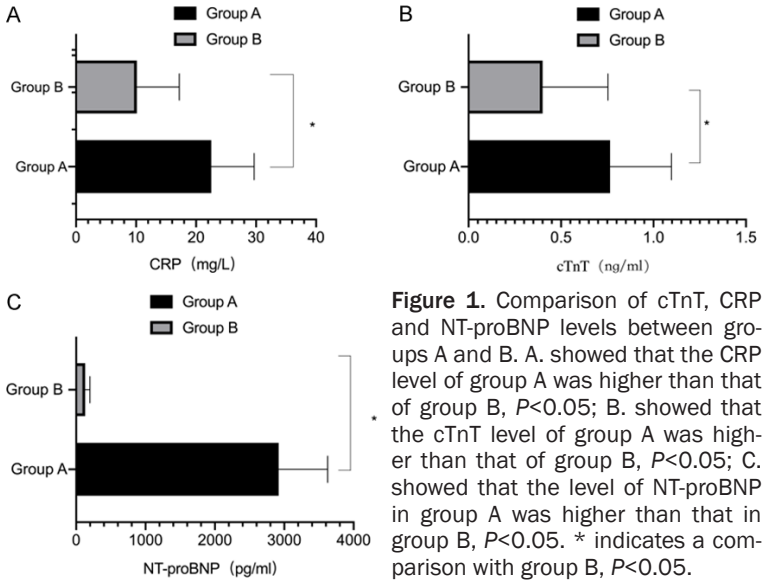

Figure 1. Comparison of cTnT, CRP and NT-proBNP levels between groups A and B. A. showed that the CRP level of group A was higher than that of group B, $P<0.05$; B. showed that the cTnT level of group A was higher than that of group B, $P<0.05$; C. showed that the level of NT-proBNP in group A was higher than that in group B, $P<0.05$. * indicates a comparison with group B, $P<0.05$.

Table 2. Comparison of LVEF ($\bar{x}$ ± sd, %)

Group	LVEF
Group A (n=193)	45.12±5.28*
Group B (n=191)	56.96±3.16
t	26.628
P	0.000

Note: *indicates comparison with group B. $P<0.05$.

Table 3. Correlation analysis between each index and LVEF

Index	CRP	cTnT	NT-proBNP
r	-0.359	-0.536	-0.815
P	0.002	0.019	0.003

Comparison of LVEF

The LVEF of patients in group A was 45.12± 5.28%, which was lower than that in group B ($P<0.05$) (**Table 2**).

Correlation between the indicators and LVEF

Pearson's correlation analysis showed that there was a negative correlation between CRP, cTnT, NT-proBNP and LVEF (r=-0.359, -0.536, -0.815, $P<0.05$) (**Table 3**).

Comparison of indices in patients with different cardiac function

The levels of cTnT, CRP, and NT-proBNP in patients with Class II, III, and IV HF were higher than those in patients with Class I HF. As cardiac function improved, cTnT, CRP, and NT-proBNP levels also increased, with significant differences between groups ($P<0.05$) (**Figure 2**).

Comparison of indices in patients with different etiologies of HF

There was no significant difference in cTnT, CRP, and NT-proBNP levels between the ischemic HF group and the non-ischemic HF group ($P>0.05$) (**Figure 3**).

Comparison of indices between patients with and without a cardiac event

All patients in group A were followed up for 2-16 months, and none of the patients were lost. A total of 19 patients had a cardiac event, while 174 patients had no cardiac events. Patients with cardiac events had higher levels of cTnT, CRP, and NT-proBNP than those without cardiac events ($P<0.05$) (**Figure 4**).

Discussion

The occurrence and development of HF are affected by many mechanisms and factors. Once the disease starts, it develops progressively. Patients in the late stage of HF have low quality of life and high mortality rate. In order to improve the quality of life and the prognosis of patients, it is necessary to make a clear diagnosis and actively take intervention measures in the early stage [14, 15]. Evidence has shown that ventricular myocardial remodeling is the most fundamental mechanism for the occurrence and development of HF, in which changes in ventricular myocyte membrane permeability occur and a series of biomolecules are released [16]. At present, specific biomarkers of ventricular muscle are commonly used in clinical practice to assess ventricular injury [17]. Based on the presence of damage to ventricular myocytes during the development of HF, these biomarkers may be widely used in the diagnosis and prognosis of HF.

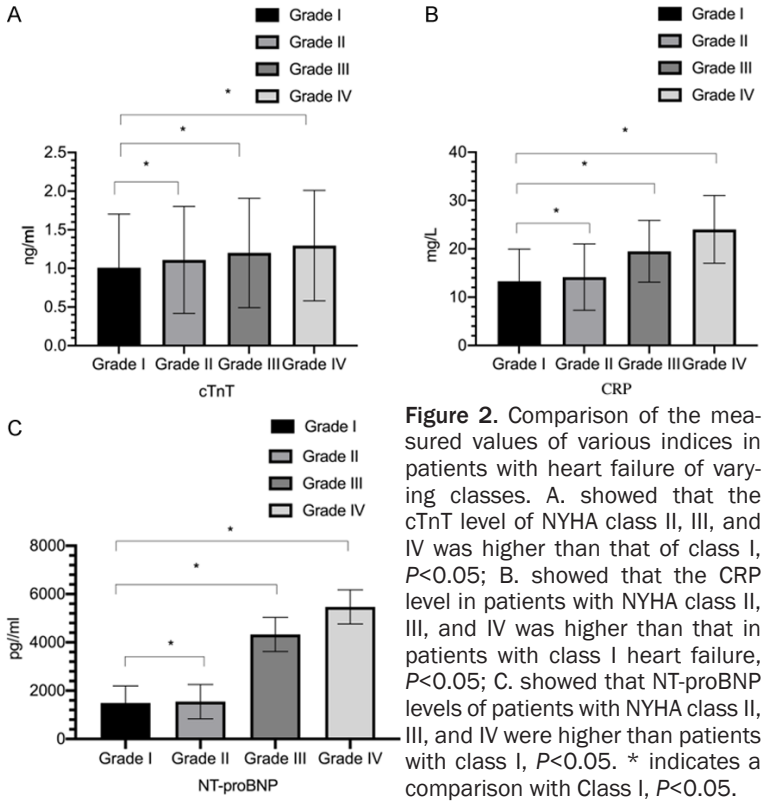

Figure 2. Comparison of the measured values of various indices in patients with heart failure of varying classes. A. showed that the cTnT level of NYHA class II, III, and IV was higher than that of class I, $P<0.05$; B. showed that the CRP level in patients with NYHA class II, III, and IV was higher than that in patients with class I heart failure, $P<0.05$; C. showed that NT-proBNP levels of patients with NYHA class II, III, and IV were higher than patients with class I, $P<0.05$. * indicates a comparison with Class I, $P<0.05$.

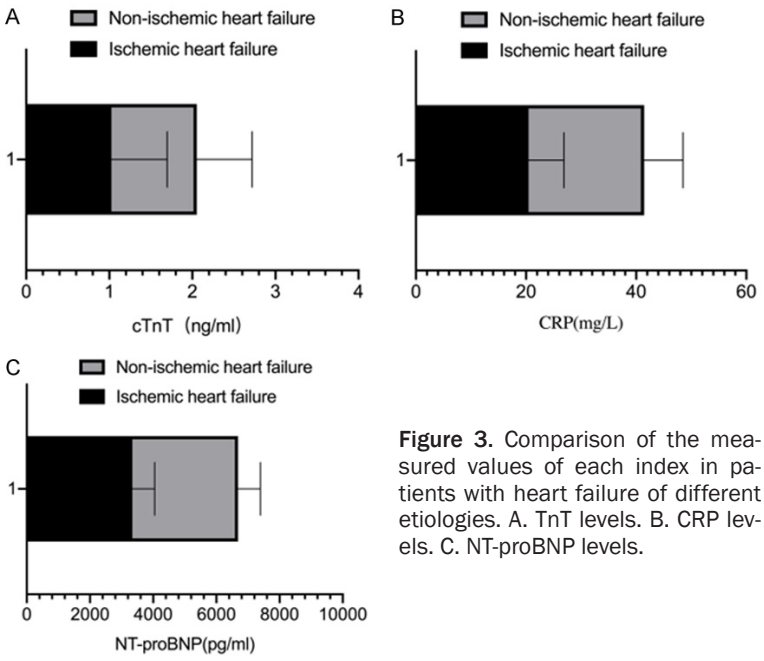

Figure 3. Comparison of the measured values of each index in patients with heart failure of different etiologies. A. TnT levels. B. CRP levels. C. NT-proBNP levels.

CRP induces monocytes to release cytokines, activates the fibrinolytic and coagulation systems, and is therefore considered an independent risk factor for cardiovascular events [18, 19]. CRP levels are significantly elevated in the presence of deep vein thrombosis, myocardial infarction, organic infection, and trauma, and are positively correlated with the severity of inflammation. When CRP is highly produced, it can significantly damage the vascular endothelium, causing hypoxic and ischemic myocardium, activating the coagulation system and reducing cardiac function. Alonso-Martinez et al. [20] found that the higher NYHA class of HF indicated the higher CRP level. Elevated CRP level was closely correlated with mortality and hospital admission rate. CRP can be used as an independent indicator to determine the severity of HF. cTnT is one of the troponin subtypes and is normally present in the bound state in cardiomyocytes. Under normal circumstances, the level of cTnT in the peripheral circulating blood is extremely low. When cardiomyocytes are damaged, the cell membrane is disrupted and a large amount of cTnT is released into the peripheral circulating blood, increasing the level of cTnT. Due to the high specificity and sensitivity of cTnT, it is now used as the gold standard for determining myocardial necrosis [21, 22]. cTnT has also developed into a key method for rapid bedside test. It has been clinically shown that serum cTnT levels are significantly elevated in some patients with HF in the absence of significant myocardial ischemia. A study showed that the poorer cardiac function indicated the higher cTnT levels and incidence of long-term major adverse cardiac events [23]. NT-proBNP, an important member of the natriuretic peptide family, is a neurosecretory factor. When the ventricular volume load increases, ventricular myocytes syn-

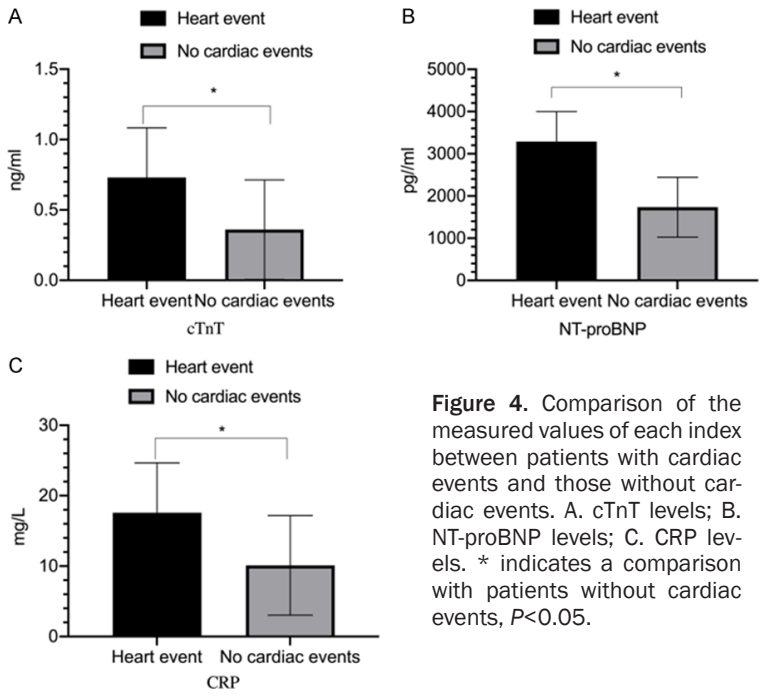

Figure 4. Comparison of the measured values of each index between patients with cardiac events and those without cardiac events. A. cTnT levels; B. NT-proBNP levels; C. CRP levels. * indicates a comparison with patients without cardiac events, $P<0.05$.

thesize pre-brain natriuretic peptide progenitor (preProBNP), which is then proteolytically sheared to become ProBNP. When ProBNP is released into the blood circulation, it is cleaved to brain natriuretic peptide (biologically active) and NT-proBNP (not biologically active). The level of NT-proBNP can reflect the degree of ventricular myocyte injury in real time, and has good stability and long half-life. The detection method for NT-proBNP is highly uniform, and has been widely used in clinical practice [24]. The results of this study showed that the levels of cTnT, CRP, and NT-proBNP in group A were higher than those in group B, and the measured value of LVEF in group A was lower than that in group B. There was a negative correlation between CRP, cTnT, NT-proBNP and LVEF, suggesting that the levels of cTnT, CRP, and NT-proBNP in patients were relatively high. Measuring cTnT, CRP, and NT-proBNP levels is helpful for the diagnosis of HF, and patients with HF have ventricular remodeling. cTnT, CRP, and NT-proBNP levels could be helpful to judge the severity of ventricular dysfunction in patients with HF. NYHA class is an index used clinically to determine the severity of HF. The results showed that as cardiac function class improved, cTnT, CRP, and NT-proBNP levels also increased, suggesting that monitoring of cTnT, CRP, and NT-proBNP levels was beneficial for determining the severity of HF. Acute myocardial infarction is one of the ischemic cardiovascular diseases with a high clinical incidence, and with the improvement of interventional technology, the response rate to treatment for myocardial infarction has also increased significantly. In some patients with myocardial infarction, pump function is reduced to varying degrees after treatment, thus increasing the incidence of ischemic HF [25]. The present study showed that there was no significant difference in cTnT, CRP, and NT-proBNP levels between the ischemic and non-ischemic HF groups, suggesting that there was no correlation between cTnT, CRP, NT-proBNP levels and the cause of HF. Both groups were followed up, and the results showed that patients with cardiac events had higher levels of cTnT, CRP, and NT-proBNP than those without cardiac events, suggesting that cTnT, CRP, and NT-proBNP levels had some predictive value for the prognosis of patients with HF.

In summary, cTnT, CRP and NT-proBNP levels were elevated in patients with HF, all indices were negatively correlated with LVEF, and their levels increased with cardiac function class, independent of the cause of HF. The combination of these three indicators is of great significance in the diagnosis and prognosis of HF.

These are also limitations. Although this study concluded that cTnT, CRP and NT-proBNP were valuable in the diagnosis of HF, more biological markers should be actively explored in order to further improve the accuracy of diagnosis.

Disclosure of conflict of interest

None.

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