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The clinical application value of the plasma copeptin level in the assessment of heart failure with reduced left ventricular ejection fraction

A cross-sectional study

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Abstract

This study aimed to evaluate the clinical applicability of the plasma copeptin level to assess heart failure with reduced left ventricular ejection fraction (HFrEF).

One hundred thirty-one patients with HFrEF, 127 patients with heart failure with preserved left ventricular ejection fraction (HFpEF), and 119 healthy candidates were involved. The basic data and examination results of patients were collected. The heart function of the patients with HFrEF and HFpEF were graded on the basis of the criteria of New York Heart Association (NYHA) classification. The plasma copeptin and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels were tested using enzyme-linked immunosorbent assays (ELISAs).

The copeptin and NT-proBNP levels were higher in the HFrEF group than in the HFpEF group. The copeptin and NT-proBNP values increased as the NYHA grade increased in the patients with HFrEF. However, for the patients with HFpEF, the copeptin levels did not change markedly as the NYHA grade increased. The copeptin levels were positively correlated with the NT-proBNP levels in the patients with HFrEF; however, there was no correlation between the copeptin and NT-proBNP values in the patients with HFpEF.

Copeptin is involved in the process of progression in patients with HFrEF and the copeptin values might be useful for HFrEF prediction and assessment in the clinic.

Abbreviations: AVP = arginine vasopressin, BMI = body mass index, CHF = chronic heart failure, Cre = creatinine, CT = computed tomography, E/A = the ratio of the early to late diastolic transmitral filling velocity, ECG = electrocardiogram, ELISA = enzyme linked immunosorbent assay, ESC = European Society of Cardiology, FBG = fasting blood glucose, HDL-C = high-density lipoprotein cholesterol, HF = heart failure, HFpEF = heart failure with preserved left ventricular ejection fraction, HFrEF = heart failure with reduced left ventricular ejection fraction, LDL-C = low-density lipoprotein cholesterol, LV = left ventricular, LVEF = left ventricular ejection fraction, NT-proBNP = N-terminal pro-B-type natriuretic peptide, NYHA = New York Heart Association, RAAS = renin angiotensin aldosterone system, SD = standard deviation, TC = total cholesterol, TG = triglyceride, UA = uric acid.

Keywords: copeptin, HFpEF, HFrEF, NT-proBNP

1. Introduction

Heart failure (HF) refers to a change in the structure and function of the myocardium resulting from myocardial damage or hemodynamic overload, ultimately leading to poor pumping and filling of heart.[1] Patients with HF are always accompanied with dyspnea, pulmonary congestion, and peripheral edema.[1]

Chronic heart failure (CHF) is a clinical syndrome caused by the fact that the heart cannot discharge enough blood to satisfy the body's metabolism under normal venous return and heart filling pressure.[2] Many factors can result in CHF, mainly including myocardial infarction, hypertension, diabetes, obesity, valvular heart disease, viral myocarditis, and metabolic syndrome.[1,3]

During CHF, the ventricular myocytes secrete large amounts of NT-proBNP and BNP.[4] Thus, serum NT-proBNP and BNP have become validated biomarkers for assessing HF.[5,6] Furthermore, HF affects the atrial tension and increases the level of arginine vasopressin (AVP).[7] HF can also activate the renin angiotensin aldosterone system (RAAS), the sympathetic nervous system, and the AVP system.[8] As a result, the serum levels of NT-proBNP, BNP, and AVP play an important role in CHF assessment. However, the properties of AVP limit its further application in the clinic. The half-life of AVP is short in serum and it is difficult to detect the AVP concentrations in vitro.[7] Copeptin is a homologous peptide to AVP.[9,10] It is more stable and easier to detect in serum.[9,11] During CHF, the level of copeptin also increases and is positively correlated with the AVP level.[9,12] Therefore, the serum copeptin level is becoming more and more popular for CHF prediction. For example, Neuhold et al[11] concluded that copeptin was superior to BNP in predicting death

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caused by CHF. Zhong et al[9] also found that there was a significant positive correlation between increased an copeptin level and the risk of mortality from HF.

CHF can be divided into HF with reduced left ventricular ejection fraction (HFrEF) and HF with preserved left ventricular ejection fraction (HFpEF). HFpEF is more common than HFrEF in the clinic; however, the mortality rates of HFrEF and HFpEF are approximately equal.[1] Thus, it is still essential to accurately diagnose HFrEF at an early stage. At present, computed tomography (CT), cardiac ultrasound, and clinical features are still the mainstream methods used to diagnose HFrEF. However, no sensitive or specific biochemical factors have been reported. Although copeptin has been proven to be effective for the diagnosis of CHF and acute myocardial infarction in some studies,[13–15] little is known about the effectiveness of copeptin to assess HFrEF. In this study, we aimed to evaluate the effect of copeptin in HFrEF diagnosis. In addition, the serum copeptin level in combination with serum NT-proBNP level was analyzed for HFrEF prediction.

2. Materials and methods

2.1. Patients and design

This study was conducted as an observational and prospective study performed at the Cardiology Department of our hospital and was approved by the Ethics Committee and Institutional Review Board of School Hospital of Beihua University, Jilin, China. All the patients provided written informed consent. From October 2016 to June 2018, 258 patients with CHF were included in this study, comprising 131 HFrEF patients and 127 HFpEF patients. In addition, 119 healthy volunteers who went for a medical examination were also included as control.

All the patients with CHF were diagnosed according to the criteria of European Society of Cardiology (ESC). All the involved HFrEF and HFpEF patients had not received pharmacological treatment with sacubitril/valsartan when they were first admitted to our hospital. The basic heart diseases of these patients were mainly hypertension, valvular disease, cardiomyopathy, coronary heart disease, and diabetes. Candidates in the normal control group were excluded if they had a history of cardiovascular diseases, and their biochemical examination results, electrocardiogram, chest X-ray plain film, and cardiac color ultrasound should be normal. The patients with CHF were divided into the HFrEF group and HFpEF group. For the patients in the HFrEF group, symptoms of CHF could be observed, the left ventricular ejection fraction (LVEF) $\geq 45\%$, the left ventricular (LV) end-diastolic volume index $< 97\,mL/m^2$, and the diastolic dysfunction of the left ventricle could be found. Herein, the diastolic dysfunction referred to hemodynamic or Doppler echocardiographic index of abnormal LV relaxation, filling, or diastolic stiffness, which happened at least one time. For patients in the HFpEF group, symptoms of CHF could be observed, LVEF $\leq 45\%$, and the left ventricular end diastolic volume was enlarged. The cardiac function of all the patients in both the HFrEF and HFpEF groups was graded on the basis of the New York Heart Association (NYHA) classification.

Patients with pulmonary heart disease, obvious pulmonary infections, endocrine diseases, tumors, liver diseases, abnormal liver function, angina or acute myocardial infarction within 3 months, chronic kidney insufficiency, rheumatic diseases, nervous system diseases, and a history of taking nonsteroidal anti-inflammatory drugs or glycocalyx hormones or antibiotics within half a month were excluded from this study.

2.2. Data collection and blood sampling

For patients in the HFrEF and HFpEF groups and candidates in the control group, their age, sex, body weight, and body mass index (BMI) were recorded. Then, each patient underwent initial clinical examination, such as physical examination and 12-lead electrocardiogram (ECG), and common laboratory tests, including fasting blood glucose (FBG), total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), creatinine (Cre), and uric acid (UA). In addition, all the patients underwent an echocardiography examination, and the LVEF and the ratio of the early to late diastolic transmitral filling velocity (E/A) were recorded.

For copeptin and NT-proBNP analyses, blood samples were collected from the elbow vein and centrifuged at 3000 r/min for 15 minutes to obtain the blood serum. The copeptin and NT-proBNP levels were tested and analyzed using copeptin and NT-proBNP enzyme-linked immunosorbent assay (ELISA) kits (Longton, Co. Ltd., Shanghai, P. R. China), respectively.

2.3. Statistical analyses

Data are presented as the mean ± standard deviation (SD) and were analyzed using GraphPad Prism 7.0 software (Graphpad Inc., San Diego, CA). Student *t* test was applied when comparing 2 groups and 1-way analysis of variance (ANOVA) was used when comparing more than 2 groups. Pearson correlation or Spearman rank correlation analysis was also used to analyze the correlation between 2 continuous values.

3. Results

The patients' characteristics and basic clinical examination results are summarized in Table 1. There were no statistical differences in the age, sex, body weight, and BMI among the 3 groups. The FBG levels were higher in HFrEF and HFpEF groups than in the control group. However, no statistical difference was found between the HFrEF and HFpEF groups for the FBG levels. For the common cholesterol parameters, including TC, TG, LDL-C, and HDL-C, substantial differences were found between the patients with CHF and the healthy candidates, but not between the HFrEF and HFpEF groups. Similar results were also found for the Cre and UA values among the 3 groups. The LVEF values were significantly lower in the HFrEF or HFpEF groups than in the control group. Furthermore, a higher LVEF value was found in the HFrEF group than in the HFpEF group. There were statistical differences in E/A values among these 3 groups. The E/A values were lower in the HFrEF or HFpEF group than in the control group.

The copeptin and NT-proBNP levels for all CHF patients were 14.22 ± 6.38 pmol/L and 1026.55 ± 311.38 ng/L, respectively (Fig. 1A, B). The copeptin and NT-proBNP levels for the healthy candidates in the control group were 5.29 ± 1.05 pmol/L and 345.15 ± 92.35 ng/L, respectively (Fig. 1A, B). Both the copeptin and NT-proBNP values were significantly higher in the patients with CHF than in the healthy candidates. The copeptin levels were 17.44 ± 7.05 and 12.37 ± 5.01 pmol/L in the HFrEF and HFpEF groups, respectively (Fig. 1C, D). The NT-proBNP levels were 1264.48 ± 209.33 and 994.26 ± 189.74 ng/L in the HFrEF

Table 1

Patients' characteristics and basic clinical examination results.

Characteristics	HFrEF (n = 131)	HFpEF (n = 127)	Control (n = 119)
Age, y	72.34 ± 12.11	69.52 ± 13.15	69.82 ± 14.27
Male	48% (48)	52% (50)	50% (44)
Body weight, kg	64.1 ± 9.7	65.6 ± 9.1	63.2 ± 10.3
BMI, kg/m^2	25.6 ± 3.9	26.9 ± 3.7	26.1 ± 3.1
FBG, (mmol/L	5.91 ± 1.05*	5.98 ± 1.04*	5.23 ± 1.11
TC, mmol/L	5.20 ± 0.82^0	5.11 ± 1.31‡	4.49 ± 1.21
TG, mmol/L	1.88 ± 0.69*	1.78 ± 0.78*	1.56 ± 0.92
LDL-C, mmol/L	3.21 ± 0.66‡	3.27 ± 0.98‡	2.38 ± 1.08
HDL-C, mmol/L	1.33 ± 0.32‡	1.39 ± 0.19†	1.18 ± 0.52
Cre, μmol/L	134.64 ± 31.82‡	133.41 ± 26.93‡	69.72 ± 15.42
UA, μmol/L	484.66 ± 135.76‡	469.41 ± 162.43‡	346.22 ± 66.17
LVEF (%)	52.43 ± 8.32‡	42.11 ± 5.18‡,¶	69.33 ± 4.57
E/A	0.77 ± 0.26‡	0.70 ± 0.56‡	1.82 ± 0.92

Compared with that in the control group, $^*P < .05$, $^†P < .01$, $^‡P < .001$. Compared with that in the HFrEF group, $^¶P < .001$. BMI = body mass index, Cre = creatinine, E/A = the ratio of the early to late diastolic transmitral filling velocity, FBG = fasting blood glucose, HDL-C = high-density lipoprotein cholesterol, HFpEF = heart failure with preserved left ventricular ejection fraction, HFrEF = heart failure with reduced left ventricular ejection fraction, LDL-C = low-density lipoprotein cholesterol, LVEF = left ventricular ejection fraction, TC = total cholesterol, TG = triglyceride, UA = uric acid.

and HFpEF groups, respectively (Fig. 1C, D). The copeptin and NT-proBNP levels were the highest in the HFrEF group. Interestingly, there were significant differences in copeptin and NT-proBNP levels between the HFrEF and HFpEF groups ($P < .001$).

The correlations between copeptin and FBG, TC, TG, Cre, UA, LVEF, and E/A in the patients with HFrEF patients are summarized in Table 2. Positive correlations could be found between the copeptin levels and the Cre or UA levels. Negative correlations could be observed between the copeptin levels and the LVEF or E/A levels.

The correlations between copeptin and FBG, TC, TG, Cre, UA, LVEF, and E/A in the patients with HFpEF are summarized in Table 3. Similar to the results found in the HFrEF group, positive correlations were found between copeptin levels and the Cre or UA levels, while negative correlations were found between the copeptin levels and the LVEF and E/A levels.

The cardiac function of all patients with CHF patients was graded according to the criteria of NYHA. The copeptin values were 11.30 ± 2.20, 14.60 ± 3.90, 17.33 ± 3.81, and 20.64 ± 2.91 pmol/L for the HFrEF patients with NYHA I (n = 19), NYHA II (n = 55), NYHA III (n = 42), and NYHA IV (n = 15), respectively (Fig. 2A). The copeptin levels were the highest and lowest in the NYHA IV and NYHA I groups, respectively. There were statistical differences between NYHA I and NYHA II groups, NYHA II and NYHA III groups, and NYHA III and NYHA IV groups in terms of their copeptin levels.

The NT-proBNP levels were 669.10 ± 349.31, 990.27 ± 305.11, 1375.22 ± 344.40, and 1610.51 ± 256.44 ng/L for the HFrEF patients with NYHA I (n = 19), NYHA II (n = 55), NYHA

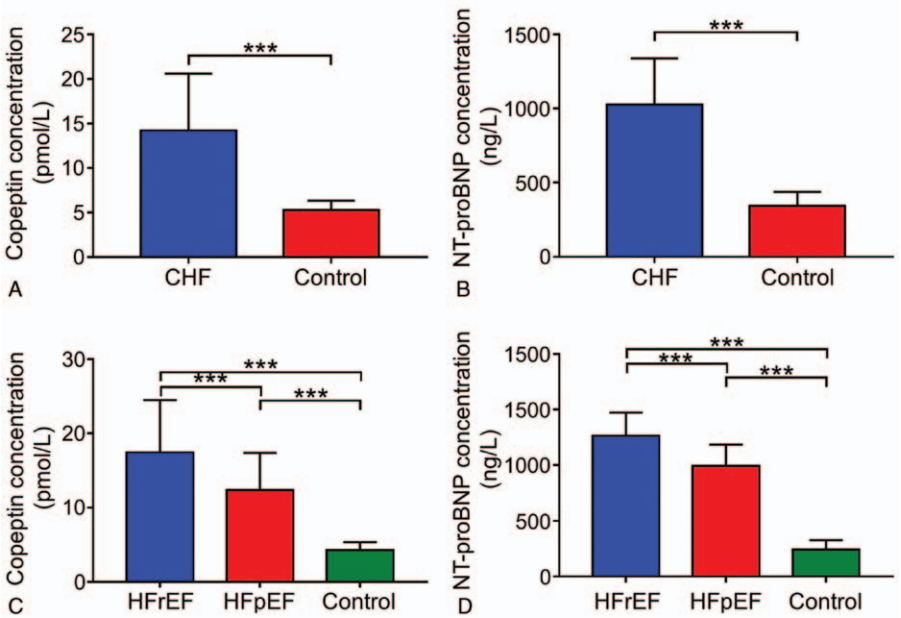

Figure 1. Copeptin and NT-proBNP levels in different groups. (A) Copeptin and (B) NT-proBNP levels in patients with CHF and healthy candidates. (C) Copeptin and (D) NT-proBNP levels in the HFrEF, HFpEF, and control groups. Data are presented as mean ± SD ($^*P < .05$, $^{**}P < .01$, $^{***}P < .001$). HFpEF = heart failure with preserved left ventricular ejection fraction, HFrEF = heart failure with reduced left ventricular ejection fraction, NT-proBNP = N-terminal pro-B-type natriuretic peptide.

Table 2

The correlation between copeptin and FBG, TC, TG, Cre, UA, LVEF, and E/A in HFrEF.

	FBG	TC	TG	Cre	UA	LVEF	E/A
r	0.22	0.33	0.40	0.58	0.62	−0.45	−0.37
P	.58	.59	.30	.01	.03	.01	.02

Cre = creatinine, E/A = the ratio of the early to late diastolic transmitral filling velocity, FBG = fasting blood glucose, HFrEF = heart failure with reduced left ventricular ejection fraction, LVEF = left ventricular ejection fraction, TC = total cholesterol, TG = triglyceride, UA = uric acid.

Table 3

The correlation between copeptin and FBG, TC, TG, Cre, UA, LVEF, and E/A in HFpEF.

	FBG	TC	TG	Cre	UA	LVEF	E/A
r	0.14	0.33	0.25	0.62	0.52	−0.43	−0.38
P	.70	.47	.32	.01	.03	.01	.01

Cre = creatinine, E/A = the ratio of the early to late diastolic transmitral filling velocity, FBG = fasting blood glucose, HFpEF = heart failure with preserved left ventricular ejection fraction, LVEF = left ventricular ejection fraction, TC = total cholesterol, TG = triglyceride, UA = uric acid.

III (n = 42), and NYHA IV (n = 15), respectively (Fig. 2B). The NT-proBNP levels increased as the NYHA grade increased, and there were significant differences between any 2 groups.

The copeptin values were 9.71 ± 3.15, 13.62 ± 4.33, 14.20 ± 3.92, and 13.90 ± 4.51 pmol/L for the HFpEF patients with NYHA I (n = 26), NYHA II (n = 50), NYHA III (n = 36), and NYHA IV (n = 15), respectively (Fig. 2C). The copeptin levels were higher in the NYHA II, NYHA III, and NYHA IV groups than that in the NYHA I group. However, no significant difference was found among the NYHA II, NYHA III, and NYHA IV groups in terms of copeptin levels.

The NT-proBNP levels were 695.30 ± 202.71, 812.62 ± 103.32, 1001.34 ± 242.52, and 1281.41 ± 281.47 ng/L for the HFpEF patients with NYHA I (n = 26), NYHA II (n = 50), NYHA III (n = 36), and NYHA IV (n = 15), respectively (Fig. 2D). There were significant differences between the NYHA I and NYHA II groups, the NYHA II and NYHA III groups, and the NYHA III and NYHA IV groups in terms of NT-proBNP levels.

The correlations between copeptin and NT-proBNP in the HFrEF and HFpEF groups are summarized in Table 4. A positive correlation between copeptin and NT-proBNP was found in the HFrEF group, but not in the HFpEF group.

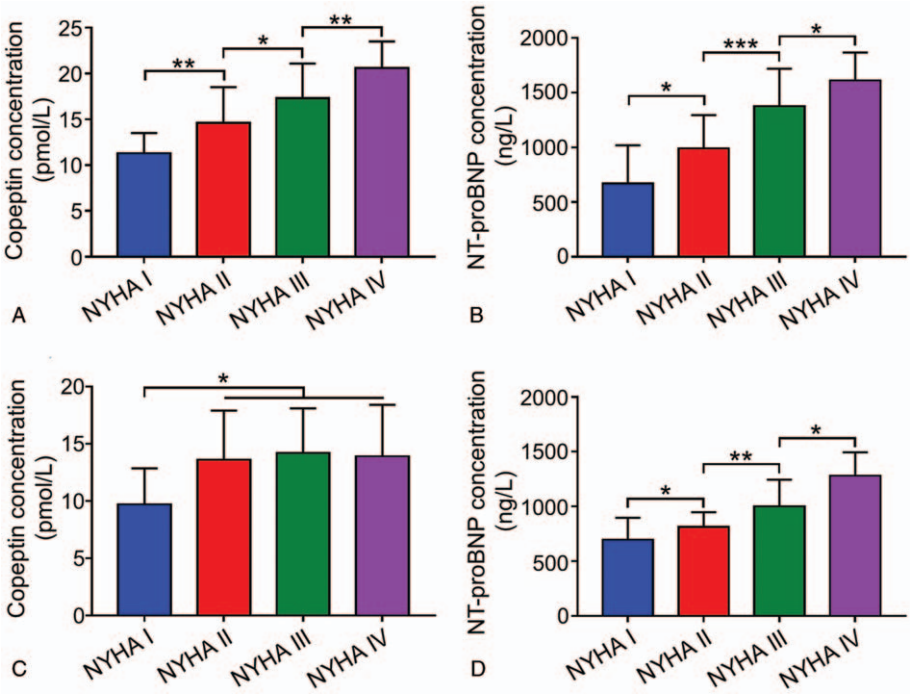

Figure 2. The copeptin and NT-proBNP levels in HFrEF and HFpEF patients with different NYHA grades. (A and B) represented HFrEF patients, and (C and D) represented HFpEF patients. Data are presented as mean ± SD ($^{*}P < .05$, $^{**}P < .01$, $^{***}P < .001$). HFpEF = heart failure with preserved left ventricular ejection fraction, HFrEF = heart failure with reduced left ventricular ejection fraction, NT-proBNP = N-terminal pro-B-type natriuretic peptide, NYHA = New York Heart Association.

Table 4

The correlation between copeptin and BNP in HFrEF and HFpEF groups.

	r	*P*
HFrEF	0.32	.02
HFpEF	0.25	.20

HFpEF = heart failure with preserved left ventricular ejection fraction, HFrEF = heart failure with reduced left ventricular ejection fraction.

4. Discussion

CHF, which seriously affects the quality of life of patients, is the final stage of various heart diseases. The number of patients with HFrEF may account for 20% to 50% of total CHF patients, and it is important to diagnose HFrEF at an early stage, to assess its severity and treat it properly.[16] The onset of HFrEF is associated with impaired active relaxation property of the left ventricle, decreased myocardial compliance, and myocardial hypertrophy with interstitial fibrosis.[16,17] As a result, for patients with HFrEF, the filling ability of the left ventricle at the diastolic phase is impaired, cardiac output is decreased, and the left ventricular end diastolic pressure is increased.

For patients with CHF, the atrial tension changes during HF, which increases the secretion of AVP.[18,19] However, the short half-life of AVP makes it difficult to preserve and test in vitro. Copeptin is part of the uncleaved pro-AVP, which is cosecreted with AVP, and emerges in equimolar amounts to AVP. Therefore, copeptin might be a promising biomarker to diagnose and assess CHF.[20] In addition, the tension of the ventricular wall increases during HF, which leads to increased secretion of NT-proBNP and BNP in the ventricular muscles. The level of serum NT-proBNP and BNP also increase, and the degree of elevation correlates positively with the severity of HF.[21,22] In 1 study, the authors evaluated the predictive value of copeptin for HF and compared it with BNP and NT-proBNP.[11] They concluded that the increased levels of copeptin were linked to excess mortality of patients with HF, and copeptin was superior to BNP and NT-proBNP to assess HF in their study. In another study, Irina et al found that plasma copeptin could predict the development of coronary artery disease and cardiovascular mortality.[12] Louise et al also found that copeptin levels could predict mortality in patients with CHF, but copeptin did not predict the end point of hospitalization independently from NT-proBNP.[23] Even though, both NT-proBNP and BNP are effective for HF assessment, the half-life of NT-proBNP is longer than BNP and NT-proBNP is more stable than BNP in serum.[24,25] In addition, NT-proBNP has higher sensitivity and specificity than BNP for the evaluation of HF.[26] As a result, in addition to copeptin, NT-proBNP was selected as another kind of biomarker for the assessment of HFrEF and HFpEF in this study.

In the present study, the clinical value of copeptin to assess HFrEF was evaluated. There were no statistical differences in the age, sex, body weight, and BMI among the 3 groups. The levels of FBG, TC, TG, LDL-C, and HDL-C increased in the HFrEF and HFpEF groups, which indicated that high levels of these materials might result in CHF. The higher levels of Cre and UA in the HFrEF and HFpEF groups demonstrated that HF might increase the amount of kidney damage. For patients with CHF, the left ventricular diastolic function is always impaired, which leads to a decrease in the LVEF. In our study, the LVEF was lower in HFrEF or HFpEF group than in the control group. For the patients with HFrEF, the left ventricular end-diastolic diameter did not increase or only slightly increased, the thickness of left ventricular wall was normal or thickened, and the LVEF was slightly changed.[27] However, the LVEF was obviously changed in the patients with HFpEF. This is consistent with the results in our study, in which the LVEF was significantly higher in the HFrEF group than in the HFpEF group. E/A is also used to assess the left ventricular diastolic function, but it is affected by many other factors (e.g., heart rate).[28] Significant differences were found between the HFrEF or HFpEF group and the control group in terms of the E/A values; however, no statistical difference was observed between the HFrEF and HFpEF groups.

The copeptin and NT-proBNP levels were higher in CHF patients than in control candidates, which indicated that plasma copeptin and NT-proBNP values might be significant for CHF diagnosis. Interestingly, there were significant differences in the copeptin and NT-proBNP levels between the HFrEF and HFpEF groups, which demonstrated that higher levels of plasma copeptin and NT-proBNP might be more significant to predict HFrEF. In both the HFrEF and HFpEF groups, the copeptin levels were positively correlated with Cre and UA, and negatively correlated with LVEF and E/A. This also indicated that the increased levels of plasma copeptin and NT-proBNP might be useful to predict CHF. In addition, the impaired heart function might deteriorate the kidney function and decrease the left ventricle function.

To better evaluate the clinical value of plasma copeptin in HFrEF assessment, the heart function of the patients was graded. For HFrEF patients, the plasma copeptin and NT-proBNP levels increased as the NYHA grade increased. However, this was different to that in the patients with HFpEF. Even though, NT-proBNP levels also increased as the NYHA grade increased, the copeptin levels did not change obviously, especially for patients with NYHA II, NYHA III, and NYHA IV HFpEF. This demonstrated that the change in plasma copeptin levels was more sensitive in patients with HFrEF. For these patients, the secretion of copeptin increased as the damage to heart function increased. However, the change in copeptin levels was not so obvious for patients with HFpEF as the damage to the heart function increased. The secretion of AVP and copeptin may be associated with the ventricular tension changes.[7] The LVEF is normal or slightly decreased for HFrEF patients, but is obviously decreased for HFpEF patients. This might demonstrate that the ventricular systolic function of HFrEF is better than that of HFpEF and the ventricular tension is seriously reduced for HFpEF patients. In addition, van Heerebeek et al[29] found that the myocardial fibrosis density was higher in HFpEF group than that in HFrEF group, which indicated that the ventricular tension of HFpEF might be lower than that of HFrEF. As for HFpEF patients in this study, the ventricular tension reduced when compared with healthy candidates. As a result, the copeptin levels were higher in the HFpEF group than that in the control group. However, as for NYHA II, III, and IV HFpEF patients, the ventricular tension decreased greatly and the tension changes might not be obvious. Therefore, the copeptin levels did not change markedly as the NYHA grade increased. In addition, the plasma copeptin levels were positively correlated with NT-proBNP levels in patients with HFrEF but not with HFpEF. All of these results indicated that the sensitivity of copeptin is higher than that of NT-proBNP for HFrEF evaluation and the plasma copeptin levels might be more applicable for the prediction of HFrEF than that of HFpEF.

There are some limitations about our study. Although our study demonstrated that copeptin levels are more sensitive for HFrEF evaluation than NT-proBNP, there were no determined

copeptin or NT-proBNP levels to differentiate HFrEF from HFpEF. As a result, further studies are still needed to provide specific copeptin levels for accurate HFrEF diagnosis. Other emerging biomarkers should also be considered to differentiate HF of different etiologies. Among these biomarkers, microRNAs (miRNAs) have been shown to be very promising for HF differentiation. For example, Ciro et al found a positive transcoronary gradient for miR-423 ($P < .001$) and miR-34a ($P < .001$) only in the ischemic HF group.[30] Whereas, a positive gradient was found for miR-21-3p ($P < .001$) and miR-30a ($P = .030$) only in the nonischemic HF group. But no significant variations were observed in both groups of miR-126 or miR-199. Furthermore, some miRNAs also showed a correlation with LV volumes as well as with systolic and diastolic LV function.[30] Therefore, the circulating levels of different miRNAs might also be differentially expressed in HFrEF and HFpEF patients. Furthermore, our study only analyzed the short-term effects of copeptin on HFrEF and HFpEF, but the long-term effects remain unknown. Maybe in further studies, we can analyze the long-term effects of copeptin on HFrEF.

5. Conclusion

Our findings indicate that the level of plasma copeptin increases with the exacerbation of HFrEF in patients. Copeptin is involved in the whole process of progression in HFrEF patients. As a result, the copeptin value might be applicable to predict and assess HFrEF in the clinic.

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Visualization: Shuo Wu.
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