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, HFrEF = 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] NT-proBNP and BNP play an important role in CHF assessment.

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.[1] Copeptin is a homologous peptide to AVP. It is more stable and easier to detect in serum.[9,11] Copeptin was superior to BNP in predicting death.
caused by CHF. Zhong et al[9] also found that there was a significant positive correlation between increased 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. 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) ≥ 45%, the left ventricular (LV) end-diastolic volume index < 97 mL/m², 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 ≤ 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 5.29 ± 92.35 ng/L and 345.15 ± 209.33 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
and HFrEF 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 III (n = 42), and NYHA IV (n = 15), respectively (Fig. 2A). The NT-proBNP levels were significantly higher in NYHA IV compared to NYHA I, and the differences were more prominent in NYHA IV compared to NYHA I and NYHA III.

### Table 1

| 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% (64)      | 52% (65)      | 50% (54)        |
| Body weight, kg | 64.1 ± 9.7    | 65.6 ± 9.1    | 63.2 ± 10.3     |
| BMI, kg/m²      | 25.6 ± 3.9    | 26.9 ± 3.7    | 26.1 ± 3.1      |
| FBG, (mmol/L    | 484.66 ± 34.3 | 466.91 ± 14.2 | 346.22 ± 34.3   |
| TC, mmol/L      | 5.20 ± 0.82   | 5.11 ± 1.31   | 4.00 ± 1.21     |
| TG, mmol/L      | 3.21 ± 0.66   | 3.27 ± 0.98   | 2.36 ± 0.18     |
| HDL-C, mmol/L   | 1.56 ± 0.30   | 1.50 ± 0.19   | 1.16 ± 0.20     |
| 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 ± 8.23  | 42.11 ± 5.18  | 69.33 ± 4.57    |
| E/A             | 0.77 ± 0.26   | 0.70 ± 0.56   | 1.62 ± 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, HFrEF = heart failure with preserved left ventricular ejection fraction, HFpEF = heart failure with reduced left ventricular ejection fraction, TC = total cholesterol, TG = triglyceride, UA = uric acid.
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.

| 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 transmural 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 transmural 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.
which increases the secretion of AVP.\textsuperscript{18,19} However, the short is impaired, cardiac output is decreased, and the left ventricular HFrEF, the independently from NT-proBNP.\textsuperscript{23} Even though, both NT-
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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{21,22} In 1 study, the authors evaluated the predictive value of copeptin for HF and compared it with BNP and NT-proBNP.\textsuperscript{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, Irima et al found that plasma copeptin could predict the development of coronary artery disease and cardiovascular mortality.\textsuperscript{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.\textsuperscript{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.\textsuperscript{12,24} In addition, NT-proBNP has higher sensitivity and specificity than BNP for the evaluation of HF.\textsuperscript{26} As a result, in addition to copeptin, NT-proBNP was selected as another kind of biomarker for the assessment of HFrEF and HFP EF 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, TG, TC, HDL-C, and LDL-C increased in the HFrEF and HFP EF groups, which indicated that high levels of these materials might result in CHF. The higher levels of Cre and UA in the HFrEF and HFP EF groups demonstrated that HF might increase the amount of kidney damage. For patients with CHF, the left ventricular systolic function is always impaired, which leads to a decrease in the LVEF. In our study, the LVEF was lower in HFrEF or HFP EF 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.\textsuperscript{27} However, the LVEF was obviously changed in the patients with HFP EF. This is consistent with the results in our study, in which the LVEF was significantly higher in the HFrEF group than in the HFP EF 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).\textsuperscript{28} Significant differences were found between the HFrEF or HFP EF group and the control group in terms of the E/A values; however, no statistical difference was observed between the HFrEF and HFP EF 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 HFP EF groups, which demonstrated that higher levels of plasma copeptin and NT-proBNP might be more significant to predict HFrEF. In both the HFrEF and HFP EF 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 HFP EF. 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 HFP EF. This demonstrated that the change in plasma copeptin levels was more sensitive in patients with HFP EF. 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 HFP EF as the damage to the heart function increased. The secretion of AVP and copeptin may be associated with the ventricular tension changes.\textsuperscript{7} The LVEF is normal or slightly decreased for HFrEF patients, but is obviously decreased for HFP EF patients. This might demonstrate that the ventricular systolic function of HFrEF is better than that of HFP EF and the ventricular tension is seriously reduced for HFP EF patients. In addition, van Heerebeek et al\textsuperscript{29} found that the myocardial fibrosis density was higher in HFP EF group than that in HFrEF group, which indicated that the ventricular tension of HFP EF might be lower than that of HFrEF. As for HFP EF patients in this study, the ventricular tension reduced when compared with healthy candidates. As a result, the copeptin levels were higher in the HFP EF group than that in the control group. However, as for NYHA II, III, and IV HFP EF 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 HFP EF but not with HFrEF. All of these results indicated that the sensitivity of copeptin is higher than that of NT-proBNP for HF assessment and the plasma copeptin levels might be more applicable for the prediction of HFrEF than that of HFP EF.

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

| Table 4: The correlation between copeptin and BNP in HFrEF and HFP EF groups. |
|-----------------|-----------------|-----------------|
|                  | r               | P               |
| HFrEF            | 0.32            | .02             |
| HFP EF           | 0.25            | .20             |
| HFrEF = heart failure with preserved left ventricular ejection fraction, HFP EF = heart failure with reduced left ventricular ejection fraction. |
copetin or NT-proBNP levels to differentiate HFrEF from HfPEF. As a result, further studies are still needed to provide specific copetin 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-376c (P < .001) only in the ischemic HF group.30 However, 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 copetin on HFrEF and HfPEF, but the long-term effects remain unknown. Maybe in further studies, we can analyze the long-term effects of copetin on HFrEF.

5. Conclusion

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

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References

[1] Ziaean B, Fonarow GC. Epidemiology and aetiology of heart failure. Nat Rev Cardiol 2016;13:368–78.
[2] Herrmann-Lingen C. Chronic heart failure and depression. Internist 2018;59:443–51.
[3] van Riet EE, Hoes AW, Wagenaar KP, et al. Epidemiology of heart failure: the prevalence of heart failure and ventricular dysfunction in older adults over time. A systematic review. Eur J Heart Fail 2016;18:242–52.
[4] Wolok F, Cleggert B, Pfeffer MA, et al. Role of B-type natriuretic peptide and n-terminal prohormone BNP as predictors of cardiovascular morbidity and mortality in patients with a recent coronary event and type 2 diabetes mellitus. J Am Heart Assoc 2017;6 pii: e004743.
[5] Vella CS, Santini F, Oldani M, et al. BNP, Galectine-3 and ST-2 cut-off values for long term risk assessment in chronic heart failure patients. Eur J Heart Fail 2017;19:477–1477.
[6] Pan Y, Li D, Ma J, et al. NT-proBNP test with improved accuracy for the diagnosis of chronic heart failure. Medicine (Baltimore) 2017;96:e9181.
[7] Fenske WK, Schneyder I, Koch G, et al. Release and decay kinetics of copetin vs AVP in response to osmotic alterations in healthy volunteers. J Clin Endocrinol Metab 2018;103:503–13.
[8] Kadota M, Is T, Yagi S, et al. Response prediction and influence of tolvaptan in chronic heart failure patients considering the interaction of the renin-angiotensin-aldosterone system and arginine vasopressin. Int Heart J 2016;57:461–6.
[9] Zhong Y, Wang R, Yan L, et al. Copetin in heart failure: review and meta-analysis. Clin Chim Acta 2017;475:36–43.
[10] Sola E, Kerber AJC, Verspaget HW, et al. Plasma copetin as biomarker of disease progression and prognosis in cirrhosis. J Hepatol 2016;65:914–20.
[11] Neuhold S, Huesmann M, Strunk G, et al. Comparison of Copetin, B-type natriuretic peptide, and amino-terminal pro-B-type natriuretic peptide in patients with chronic heart failure: prediction of death at different stages of the disease. Eur Heart J 2008;29:178–9.
[12] Tasevska J, Enhorning S, Persson M, et al. Copetin predicts coronary artery disease cardiovascular and total mortality. Heart 2016;102:127–32.
[13] Duengen H-D, Tscholl V, Obradovic D, et al. Diagnostic performance of serial in-hospital measurements of copetin and multiple novel biomarkers among patients with worsening heart failure: results from the MOLITOR study. ESC Heart Fail 2018;5:288–96.
[14] Winther JA, Brynildsen J, Høsseth AD, et al. Diagnostic and prognostic significance of copetin in acute exacerbation of chronic obstructive pulmonary disease and acute heart failure: data from the ACE 2 study. Respir Res 2017;18:184.
[15] Mueller C, Mockel M, Giannitsis E, et al. Use of copetin for rapid rule-out of acute myocardial infarction. Eur Heart J Acute Cardiovasc Care 2017[Epub ahead of print].
[16] Muenzel T, Gori T, Keaney JF Jr, et al. Pathophysiological role of oxidative stress in systolic and diastolic heart failure and its therapeutic implications. Eur Heart J 2015;36:2555–64.
[17] Borlaug BA. The pathophysiology of heart failure with preserved ejection fraction. Nat Rev Cardiol 2014;11:507–15.
[18] Xiaoyi YY, Li Z, Hua Z, et al. Assessment of obstestin and arginine vasopressin (AVP) levels in acute renal failure and acute heart failure. Eur Rev Med Pharmacol Sci 2017;21:3277–81.
[19] Vinod P, Krishnappa V, Chauvin AM, et al. Cardiorenal syndrome: role of arginine vasopressin and vaptans in heart failure. Cardiol Res 2017;8:87–95.
[20] Morgenstern NG, Struck J, Alonso C, et al. Assay for the measurement of copetin, a stable peptide derived from the precursor of vasopressin. Clin Chem 2006;52:112–9.
[21] Troughton RW, Frampton CM, Brunner-La Rocca H-P, et al. Effect of B-type natriuretic peptide-guided treatment of chronic heart failure on total mortality and hospitalization: an individual patient meta-analysis. Eur Heart J 2014;35:1559–67.
[22] van Veldhuisen DJ, Linssen GCM, Jaarsma T, et al. B-type natriuretic peptide and prognosis in heart failure patients with preserved and reduced ejection fraction. J Am Coll Cardiol 2013;61:1498–506.
[23] Billling L, Kistorp C, Schou M, et al. Plasma copeptin levels and prediction of outcome in heart failure outpatients: relation to hyponatremia and loop diuretic doses. J Cardiac Fail 2012;18:351–8.
[24] Boomsma F, van den Meiracker AH. Plasma A- and B-type natriuretic peptides: physiology, methodology and clinical use. Cardiovasc Res 2001;51:442–9.
[25] Lam CSP, Burnett JC, Costello-Boerrigter L, et al. Alternate circulating pro-B-type natriuretic peptide and B-type natriuretic peptide forms in the general population. J Am Coll Cardiol 2007;49:1193–202.
[26] Lee JA, Kim DH, Yoo SJ, et al. Association between serum N-terminal pro-brain natriuretic peptide concentration and left ventricular dysfunction and extracellular water in continuous ambulatory peritoneal dialysis patients. Perit Dial Int 2006;26:360–5.
[27] Oki T, Tanaka H, Imashita T, et al. Associations between left ventricular diastolic function and right ventricular function in patients with and without preserved left ventricular ejection fraction. J Echocardiogr 2018;16:81–6.
[28] Pandey A, Parashar A, Kumbhani DJ, et al. Exercise training in patients with heart failure and preserved ejection fraction meta-analysis of randomized control trials. Circ Heart Fail 2015;8:33–40.
[29] van Heerebeek L, Borbely A, Niesweg HR, et al. Myocardial structure and function differ in systolic and diastolic heart failure. Circulation 2006;113:1966–73.
[30] de Rosa S, Eposito F, Carella C, et al. Transcoronary concentration gradients of circulating microRNAs in heart failure. Eur J Heart Fail 2018;20:1000–10.