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The relationship between cardiac resynchronization therapy and serum levels of copeptin

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Abstract. *Background:* Chronic heart failure (CHF) is a complex syndrome characterized by an abnormal neurohormonal activation, including arginine vasopressin (AVP). Copeptin is an indicator of AVP activation, which levels are elevated in CHF and have prognostic importance. Cardiac resynchronization therapy (CRT) is an important device therapy for patients with advanced CHF, left ventricular (LV) systolic dysfunction and evidence of electromechanical dyssynchrony. The aim of the present study was to determine the possible relationship between CRT and serum copeptin levels.
Methods: We included CRT patients with ischemic as well as nonischemic etiology of CHF. The levels of copeptin were measured at baseline and 12 months respectively after CRT implantation. Echocardiography was also performed pre and 12 months post CRT implantation. A CRT response was defined as a ≥ 15% reduction in LV end-systolic volume (LVESV).
Results: The study population consisted of 41 patients. The mean copeptin level was 20.50 ± 15.77 pmol/l. Copeptin levels positively correlated with New York Heart Association class, left atrial diameter, creatinine levels and NT-proBNP levels. CRT responders have significant reduction in copeptin levels from baseline to 12 months (from 16.96 ± 12.80 pmol/l to 6.20 ± 6.44 pmol/l, $p < 0.001$). No significant changes in copeptin levels were observed in CRT nonresponders. Reduction > 45% in copeptin levels was significantly associated with CRT-response (OR 6.72, 95% CI 1.01 – 18.11, $p = 0.045$). Fig. 1, Tab. 2, Ref. 23, on-line full text (Free, PDF) www.cardiologyletters.sk
Conclusion: The copeptin serum levels can be a useful biomarker in the evaluation of the CRT response.
Key words: heart failure – biomarker – copeptin – cardiac resynchronization – responder

Chronic heart failure (CHF) is a complex syndrome characterized by an abnormal neurohormonal activation, including arginine vasopressin (AVP) (1). Copeptin, also known as C-terminal section of AVP precursor (CT-proAVP), consists of 39-amino acid glycopeptides and is an indicator of the activity of AVP (2-4). Several clinical studies have demonstrated that levels of copeptin are elevated in CHF and have prognostic importance (5-10). Cardiac resynchronization therapy (CRT) is an important device therapy for patients with advanced CHF, left ventricular (LV) systolic dysfunction and evidence of electromechanical dyssynchrony (11). This therapy can improve cardiac function (12) and reduce morbidity and mortality (13-15). It has been shown that CRT can also reduce levels of multiple biomarkers that are elevated in CHF (16). However, to the best of our knowledge, the relation of CRT to the levels of copeptin has never been assessed before. The aim of this study is to investigate the possible relationship between CRT and serum levels of copeptin in CHF patients. We performed

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measurement of copeptin levels before and after CRT implantation and we have linked their possible changes with CRT response.

Methods

Study population and follow-up

In this prospective study we included 41 consecutive CHF patients receiving CRT from May 2017 to November 2018 according to guidelines of the European Society of Cardiology. The mean age was 65 ± 7 years and 33 patients (80%) were men. The ischemic etiology of CHF was present in 18 patients (44%). Twenty-one patients (51%) were in NYHA class II and 20 patients (49%) were in NYHA class III. The mean LVEF was 26 ± 4% and the mean QRS duration before CRT implantation was 157 ± 16 ms. The mean level of N-terminal pro-B-type natriuretic peptide (NT-proBNP) was 2006 ± 2213 pg/ml. Most patients had optimal CHF pharmacological therapy with betablocker (98%), angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) (39%) or angiotensin receptor neprilysin inhibitor (ARNI) (46%) and mineralocorticoid receptor antagonist (MRA) (95%). History of myocardial infarction or percutaneous angioplasty/coronary bypass surgery within the last 3 months, malignancies, or chronic renal disease requiring dialysis were exclusion criteria for this study. All CRT devices were with defibrillation function (CRT-D) and were implanted by the standard transvenous technique. Blood samples to determine copeptin levels were obtained from all the patients at baseline and 12 months after CRT implantation. In addition, a two-dimensional echocardiography was performed pre and 12 months post CRT implantation for the assessment of CRT response. Responders were defined as patients who exhibited LV reverse remodeling, defined as a ≥ 15% reduction in LV end-systolic volume (LVESV). During follow-up period, all patients had follow-up 1, 3, 6 and 12 months after CRT implantation, with additional visits in our centre as required in cases of palpitations, syncope, spontaneous CRT-D shock, or decompensated heart failure. All study procedures conformed to the ethical principles of the Declaration of Helsinki and written informed consent was obtained from each participating patient.

Copeptin levels assay

All blood samples were obtained by venipuncture using ethylenediamine tetraacetic acid (EDTA) tubes and were immediately centrifuged at 1000 x g for 15 minutes at 4 °C. After centrifugation, serum samples were stored at – 80 °C until analysed. Serum levels of copeptin were measured using a sandwich enzyme-linked immuno--sorbent assay (ELISA) technology (Human Copeptin ELISA Kit, Abbexa Ltd, Cambridge, UK). According to the description of this assay by manufacturer, the functional assay sensitivity (intra-assay coefficient of variance < 0%, inter-assay coefficient of variance < 12%) was < 0.69 pmo/l and the range of assay was from 1.87 pmol/l to 120 pmol/l. Increased levels of copeptin were defined > 7.1 pmol/l for women and > 9.4 pmol/l for men (10).

Statistical analysis

Variables were expressed as mean ± standard deviation and percentages. Statistical differences between 2 groups were compared using Chi-square test for categorical variables and unpaired Student's t-test for continuous variables. The comparison of continuous variables before and after CRT in the same group was performed by paired Student's t-test. The association between copeptin levels and baseline variables was analyzed using Pearson correlation. Receiver operating characteristic (ROC) analysis was used to determine the best cut-off values for all continuous variables. Logistic regression analysis was used to determine independent predictors of response to CRT. All variables with p value < 0.1 in the univariate analysis were subsequently included into multivariate analysis. The criterion for statistical difference was set to $p < 0.05$. Analyses were performed using SPSS 20 (IBM, Inc., USA) statistical software.

Results

Association between baseline copeptin levels and baseline variables

In this study, copeptin level was detected in all patients and 31 participants (76%) had elevated copeptin levels. The mean copeptin level was 20.50 ± 15.77 pmol/l. Correlation analysis showed that copeptin levels positively correlated with NYHA class ($r = 0.347$, $p = 0.033$), left atrial diameter (LAD) ($r = 0.275$, $p = 0.045$), creatinine levels ($r = 0.641$, $p < 0.001$) and NT-proBNP levels ($r = 0.441$, $p = 0.011$), respectively. There was no significant correlation between copeptin levels with age ($r = 0.107$, $p = 0.521$), LVEF ($r = 0.076$, $p = 0.648$) and QRS duration ($r = 0.211$, $p = 0.203$). Finally, copeptin levels were not statistically different between women and men (15.44 ±10.00 pmol/l vs. 22.41 ± 17.04 pmo-

l/l, p = 0.143) and between patients with ischemic and nonischemic etiology of CHF (24.81 ± 20.50 pmol/l vs.17.82 ± 10.91 pmol/l, p = 0.181).

Relation between copeptin levels and CRT response

Based on predefined changes in the LVESV from baseline to 12 months, 28 patients (68%) were defined as CRT responders and 13 patients (32%) were defined as CRT nonresponders. Mean LVESV reduced from 149 ± 36 ml to 108 ± 34 ml (p < 0.001) and mean LVEF improved from 26 ± 4% to 33 ± 7% (p < 0.001). Significant reduction in LVESV (from 149 ± 33 ml to 98 ± 27 ml, p < 0.001) and significant improvement in LVEF (from 26 ± 4% to 34 ± 7%, p < 0.001) were observed in CRT responders. In contrast, no significant changes in LVESV (from 147 ± 45 ml to 143 ± 36 ml, p = 0.403) and LVEF (from 27 ± 5% to 26 ± 6%, p = 0.720) were observed in CRT nonresponders. As summarized **Table 1**, CRT nonresponders were older (68 ± 3 years vs. 64 ± 8 years, p = 0.007), had larger LAD (50 ± 5 mm vs. 46 ± 4 mm, p = 0.051) and had higher creatinine level (120 ± 45 μmol/l vs. 85 ± 14 μmol/l, p = 0.025) compared to the CRT responders. In addition, CRT nonresponders were less likely to receive a betablocker (85% vs. 100%, p = 0.033) and an ARNI therapy (23% vs. 57%, p = 0.041). There was no significant difference in the baseline copeptin levels between CRT responders and CRT nonresponders (16.96 ± 12.80 pmol/l vs. 25.03 ± 10.30 pmol/l, p = 0.131). After 12 months of CRT, the mean copeptin level decreased significantly from 20.50 ± 15.77 pmol/l to 8.80 ± 8.43 pmol/l (p < 0.001). As shown in **Figure 1**, there was a significant reduction in copeptin levels in CRT responders (from 16.96 ±

Table 1 Comparison of baseline characteristic of the study population according to CRT response

	responders n = (28)	nonresponders n = (13)	p value
Mean age (years)	64 ± 8	68 ± 3	0.007
Sex (male), n (%)	21 (75 %)	12 (92 %)	0.193
NYHA class III, n (%)	14 (50 %)	6 (46 %)	0.817
CAD, n (%)	10 (36 %)	8 (62 %)	0.121
Atrial fibrillation, n (%)	10 (36 %)	8 (62 %)	0.121
Hypertension, n (%)	22 (78 %)	12 (92 %)	0.276
Diabetes mellitus, n (%)	7 (25 %)	3 (23 %)	0.893
Mean creatinine level (μmol/l)	85 ± 14	120 ± 45	0.025
Mean LAD (mm)	46 ± 4	50 ± 5	0.051
Mean LVEF (%)	26 ± 4	27 ± 5	0.764
Mean LVESV (ml)	149 ± 33	147 ± 45	0.860
Mean LVEDV (ml)	201 ± 33	190 ± 54	0.423
Mean QRS width (ms)	159 16	154 19	0.379
LBBB, n (%)	19 (68 %)	7 (54 %)	0.386
Betablocker, n (%)	28 (100 %)	11 (85 %)	0.033
Amiodarone, n (%)	9 (32 %)	5 (38 %)	0.691
Digoxin, n (%)	1 (4 %)	1 (8 %)	0.568
ACEi/ARB, n (%)	10 (36 %)	6 (46 %)	0.523
ARNI, n %	16 (57 %)	3 (23 %)	0.041
MRA, n (%)	27 (96 %)	12 (92 %)	0.568
Diuretics, n (%)	28 (100 %)	13 (100 %)	1.000
Statin, n (%)	19 (68 %)	5 (38 %)	0.075
Mean NT-proBNP level (pg/ml)	1653 ± 1931	2987 ± 2745	0.111
Mean copeptin level (pmol/l)	16.96 ± 12.80	25.03 ± 10.30	0.131

ACEi – angiotensin converting enzyme inhibitor, ARB – angiotensin receptor blocker, ARNI – angiotensin receptor neprilysin inhibitor, CAD – coronary artery disease, LAD – left atrial diameter, LBBB – left bundle branch block, LVEDV – left ventricular end-diastolic volume, LVEF – left ventricular ejection fraction, LVESV – left ventricular end-systolic volume, MRA – mineralocorticoid receptor antagonist, NT-proBNP – N-terminal pro-B-type natriuretic peptide, NYHA – New York Heart Association

12.80 pmol/l to 6.20 ± 6.44 pmol/l, p < 0.001). In contrast, no significant change from baseline to 12 months after CRT implantation in copeptin levels was observed in CRT nonresponders (from 25.03 ± 10.30 pmol/l to 17.72 ± 12.98 pmol/l, p = 0.131). According to the ROC analysis, a 49% reduction in copeptin levels was shown to have the optimal accuracy in prediction of CRT response (area under curve (AUC) = 0.77, p = 0.011). Logistic regression analysis (as summarized in **Table 2**) determined significant association between a > 49% reduction in copeptin level and CRT response (OR 6.72, 95% CI 1.01 – 18.11, p = 0.045).

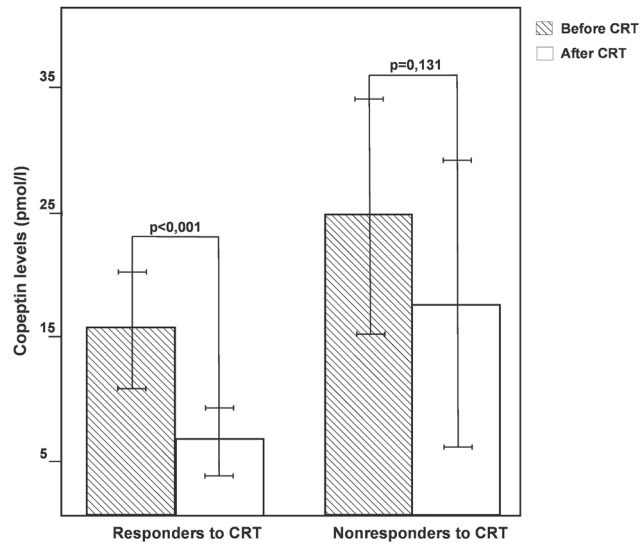

Figure 1 Changes in copeptin levels in CRT responders and nonresponders after 12 months.
Horizontal lines depict ± standard deviations.

Discussion

CHF is a complex syndrome in which an abnormal activation of AVP is an important pathogenic mechanism leading to progression of LV dysfunction due to contributing to the water retention, peripheral vasoconstriction and LV remodelling (17). In CHF patients, elevated levels of AVP correlate with the severity of the disease and have a prognostic value (18). However, AVP measurement is not commonly used in clinical practice due to small molecular size, very short half-life time in serum and in the method´s measurement difficulties (19). Copeptin is a 39-amino acid long glycopeptide derived from a pre-pro-hormone, consisting of AVP, neurophysin II and copeptin. During CHF, levels of copeptin are also increased and correlate positively with the AVP levels. Unlike AVP, copeptin is more stable and can be easily immunologically tested. Therefore, copeptin can be used as a surrogate biomarker of AVP (20-22). Indeed, several clinical studies have already shown that copeptin levels have prognostic importance in CHF. Elevated levels of copeptin were significantly associated with worse prognosis in CHF patients (5-10). Part of these studies compared predictive value of copeptin with natriuretic peptides for the outcome of CHF patients. For example, Stoiser et al evaluated the ability of copeptin and BNP to predict death, rehospitalization due to heart failure, and the combination of these two endpoint factors. The study showed that copeptin is an excellent predictor of outcome in patients with advanced heart failure. In addition, copeptin was superior to BNP in predicting death, while BNP was superior for predicting CHF rehospitalization (8). In another study, Neuhold et al evaluated the prognostic importance of copeptin and compared it with the BNP and the NT-proBNP. The authors found that increased levels of copeptin were linked to higher mortality in CHF patients, and copeptin was a superior compared to the BNP and the NT-proBNP (10). In the present study, we have aimed to determine the possible relation of the CRT to the levels of copeptin. We have provided a measurement of copeptin levels at baseline and 12 months after CRT implantation in 41 CHF patients. Our study population represented a real-world cohort of patients with ischemic as well as nonischemic

Table 2 Variables associated with CRT response (logistic regression analysis)

	univariate		multivariate	
	OR (95% CI)	p value	OR (95% CI)	p value
Age < 67 years	4.00 (0.88 – 6.25)	0.057	3.25 (1.21– 5.22)	0.127
CAD	0,27 (0.06 – 1.15)	0.071	0.37 (0.07 – 2.01)	0.146
LAD < 48 mm	3,46 (0.77 – 8.24)	0.079	3.21 (0.55 – 6.23)	0.123
LBBB	1,50 (0.39 – 5.6)	0.056	1.45 (0.55 – 6.21)	0.343
Reduction in level of copeptin > 49%	4.44 (1.05 – 11.55)	0.042	6.72 (1.01 – 18.11)	0.045

CAD – coronary artery disease, LAD – left atrial diameter, LBBB – left bundle branch block

etiology of CHF and comorbidities, including atrial fibrillation, diabetes mellitus and chronic renal disease. We have observed that copeptin level was detected in all patients and elevated levels were detected in 76 % of the participants. In line with previous studies (5, 6, 23), we have found that copeptin levels positively correlated with NYHA class, LAD, creatinine levels and NT-proBNP levels, respectively. These findings point out that levels of copeptin correlate with progression of cardiac and renal dysfunction. We have also evaluated the impact of CRT response on levels of copeptin. In the present study population, 68% of the patients were CRT responders and 32 % of the patients were CRT nonresponders. No difference in baseline levels of copeptin was observed between CRT responders and nonresponders. However, we have found that copeptin levels significantly decreased in CRT responders, whereas no significant changes in copeptin levels were observed in CRT nonresponders. In addition, we have found that a change in copeptin level was significantly associated with CRT response. In the present study population, patients who had a more than 45% reduction in copeptin level from baseline to 12 months were more likely to be CRT responders (OR 6.72). The observed relation between the response to CRT and the changes in copeptin levels can be explained by an improvement of the LV systolic function as a result of the CRT induced LV reverse remodeling. Subsequently, an increase of the cardiac output leads to decreased levels of copeptin. To the best of our knowledge, this is the first prospective study which has reported a relationship between the CRT and copeptin serum levels. We expect that measurement of copeptin levels before and after CRT implantation can help to evaluate the response of CHF patients to the CRT. Because of the limited number of patients, further studies are needed to confirm our findings.

Conclusion

The copeptin serum levels can be a useful biomarker in the evaluation of the CRT response.

Study limitations

The single-centre study and the small number of patients are main limitations of the present study.

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