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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

Severe mitral regurgitation is associated with increased copeptin levels in heart failure with reduced ejection fraction

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Abstract

Background and aim: The objective of this study was to assess the potential role of mitral regurgitation (MR) in the release of copeptin in heart failure patients with reduced ejection fraction (HFrEF).

Methods: The study included 63 patients of whom 33 had functional mild MR (Group 1) and 30 had functional severe MR (Group 2). The functional class of both groups was New York Heart Association (NYHA) Class III. Blood samples for the determination of plasma copeptin and B-type natriuretic peptide (BNP) levels were obtained on the same day with the echocardiographic examination. Standard echocardiographic studies were performed.

Results: Copeptin and BNP levels showed a substantial agreement in the whole study group (Kappa level: 0.607, $p < 0.0001$). Also, copeptin and BNP showed a strong correlation and were both increased and significantly higher in Group 2 than in Group 1 ($p < 0.001$ and $p < 0.05$, respectively). Left ventricular global longitudinal strain and left ventricular ejection fraction values were similar in both groups. The study population were divided into two subgroups on the basis of copeptin median level (6.4 ng/mL), and the prevalence of severe MR was significantly higher in the above-median-copeptin subgroup. A linear regression analysis showed that the presence of severe MR was the only independent predictor of high circulating plasma copeptin level (OR 7.5, 95% CI 2.8–12.1; $p = 0.002$).

Conclusions: Severe MR is an independent predictor of elevated plasma copeptin level in HFREF irrespective of systolic function.

Key words: copeptin, heart failure, functional mitral regurgitation

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INTRODUCTION

Heart failure (HF) is a complex clinical syndrome with high mortality and morbidity. The prognostic evaluation of patients remains a critical issue in heart failure (HF) management. An accurate means of predicting the high-risk patients who will benefit from the invasive treatment options would be of value. In recent years there has been a remarkable increase in the number of biomarkers available in HF which can provide additional prognostic information and thus may be of great interest in clinical practice [1–4].

Copeptin, a surrogate for arginine vasopressin secretion, is a novel biomarker that has shown great potential in a spectrum of cardiovascular disease including HF [3–6]. Although a number of studies demonstrated that higher circulating copeptin levels were associated with the risk of increased mortality and morbidity in HF patients, the exact mechanism of this association between copeptin and mortality is not fully understood yet [7–9].

Functional mitral regurgitation (FMR) is a common complication of left ventricular dysfunction. Although FMR is associated with a poor prognosis in patients with HF, it remains unclear whether this relationship is due to the mitral regurgitation (MR) itself or to the advanced degree of HF. The objective of this study was to assess the potential role of MR

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in the release of copeptin in HF patients with reduced ejection fraction (HFrEF).

METHODS

Patient population

Patients referred to Kartal Kosuyolu Heart Education and Research Hospital with ischaemic or non-ischaemic functional MR and ejection fraction (EF) < 40% were enrolled in this study, prospectively. Patients were excluded from the study if they had organic MR caused by degenerative, rheumatic, or senile degenerative heart valve disease, mitral annular calcification, infective endocarditis, or aortic valve regurgitation of more than mild degree. The study included 63 patients of whom 33 had mild MR (Group 1, five patients with non-ischaemic cardiomyopathy and 28 with ischaemic cardiomyopathy) and 30 had functional severe MR (Group 2, four patients with non-ischaemic cardiomyopathy and 26 patients with ischaemic cardiomyopathy). The functional classes of the groups were both New York Heart Association (NYHA) Class III. The Local Ethics Committee approved this study, and all the patients gave written, informed consent.

Copeptin measurement

Blood samples for the determination of plasma copeptin levels were obtained on the same day with echocardiographic examination. The samples were collected using pyrogen-free tubes containing EDTA and centrifuged at 5000 rpm for 10 min. The plasma samples were stored at –20ºC until the analysis. The analysis was performed with a commercially available human copeptin ELISA kit (SHANGHAI YEHUA Biological Technology Co., Ltd., Shanghai China). The assay range was within the range 0.05–20 ng/mL.

Echocardiography

Standard echocardiographic studies were performed using a 1–5 MHz X5-1 transducer (iE33, Philips Healthcare, Inc., Andover, MA). Patients were examined in the left lateral position, and measurements were averaged over three consecutive heart cycles. All standard two-dimensional (2D) transthoracic echocardiographic images were obtained, including the parasternal long axis, short axis, and apical four-, three-, and two-chamber views. Colour Doppler and tissue Doppler images were triggered to the QRS complex and stored in a cine loop format. The left ventricular (LV) end-diastolic diameter (LVEDD) and LV end-systolic diameter (LVESD) were measured from parasternal long-axis window using M-mode echocardiography. EF was calculated according to biplane Simpson's method. LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVESV) were measured in the apical four- and two-chamber views by tracing of the blood tissue interface. At the mitral valve level, the contour was closed by connecting the two opposite sections of mitral ring with a straight line. Stroke volume (SV) was determined as the product of the time-velocity integral from LV outflow tract and cross-sectional area of the aortic annulus. Stroke volume index (SVI) was calculated by dividing the stroke volume by the body surface area.

Mitral inflow velocities were measured by pulsed wave Doppler, with the sample volume placed at the tips of the mitral valve in the left ventricle. E and A wave velocities were recorded and the E/A ratio was calculated. The mitral annular velocities were measured by pulsed wave tissue Doppler imaging, with the sample volume placed at the level of the lateral and septal mitral annulus. Septal and lateral E' and A' wave velocities were recorded, and the E/E' ratio for the mitral annulus was calculated with averaging septal and lateral E' velocities, and an average E/E' value was calculated.

The quantification of MR was performed as recommended previously [10]. The proximal isovelocity surface area was visualised from the apical four-chamber view, and its radius was measured at mid-systole using the first aliasing. Regurgitant volume and effective regurgitant orifice area were obtained using the standard formulas, with values > 30 mL and > 0.2 cm^2, respectively, considered as indicating severe MR [11].

The configuration of the mitral leaflets was assessed from the parasternal long axis and apical views. The systolic tenting area was measured in mid-systole as the area between the mitral annulus and the mitral leaflets body. The coaptation depth was measured between the mitral annular plane and coaptation point in the apical four-chamber view. Right ventricular (RV) systolic function was assessed by measuring the tricuspid annular plane systolic excursion (TAPSE) in the apical four-chamber view and the tricuspid annulus peak systolic velocity (TAPSV) with tissue Doppler imaging. Additional to the standard echocardiographic study, the LV global longitudinal peak systolic strain (GLS) was assessed by applying 2D speckle-tracking echocardiography to the apical four-, three-, and two-chamber views.

The examiners performing the echocardiograms were blinded to the copeptin levels.

Statistical analysis

Data management and analysis were performed using SPSS Statistics version 17.0 (SPSS Inc., Chicago, IL). Continuous variables are expressed as mean with standard deviation (SD) or median with interquartile range (IRQ) according to the variable distribution. Normal distributions were confirmed using the Kolmogorov-Smirnov test. A t-test or Mann-Whitney U test was applied to test the differences between groups depending on the distribution of the normality of the variable. The agreement between the copeptin and B-type natriuretic peptide (BNP) is assessed by Kappa test. Correlations were tested by Pearson or Spearman's correlation analysis, as appropriate. A p value < 0.05 was considered statistically significant. A median value was calculated for copeptin and then the study population were divided into two groups according to have below/above plasma copeptin levels than the median. This two group were compared for the differences by using

Table 1. The demographic characteristics and laboratory data of the study population

Variable	Group 1	Group 2	p
Age [years]	57.0 ± 13.2	57.6 ± 14.0	NS
Gender (female)	6 (18%)	8 (26%)	NS
Systolic blood pressure [mm Hg]	108.2 ± 9.6	112.6 ± 8.4	NS
Diastolic blood pressure [mm Hg]	70.2 ± 5.9	71 ± 5.3	NS
Diabetes mellitus	13 (39%)	9 (30%)	NS
Hypertension	11 (33%)	13 (40%)	NS
Atrial fibrillation	2 (6%)	13 (43%)	0.0001
Urea [mg/dL]	51.08 ± 37.1	66.85 ± 49.8	NS
Creatinine [mg/dL]	1.25 ± 1.03	1.19 ± 0.77	NS
Uric acid [mg/dL]	7.3 ± 1.9	5.6 ± 1.13	0.04
Na [mmol/L]	135.6 ± 3.05	135.8 ±2.85	NS
Haemoglobin [g/dL]	12.48 ± 2.02	12.98 ± 2.29	NS
C-reactive protein [mg/dL]	0.6 (0.34–1.38)	0.35 (0.34–1.8)	NS
Log B-type natriuretic peptide	2.5 ± 0.26	2.7 ± 0.37	0.0024
Log copeptin	0.7 ± 0.21	1.09 ± 0.27	0.0001

t-test, Mann-Whitney U, or χ^2 as appropriate. A linear regression analysis was performed to define the predictors of high circulating plasma copeptin levels.

RESULTS

The patients' clinical characteristics and laboratory data are shown in Table 1. The age and the gender ratio were not different between the two patient groups. While the prevalence of diabetes mellitus and hypertension was similar in the two groups, atrial fibrillation was significantly more common in Group 2. The systolic and diastolic blood pressure levels and the laboratory results were not significantly different between the two groups. Copeptin and BNP levels were both increased and significantly higher in Group 2 ($p < 0.001$ and $p < 0.05$, respectively; Fig. 1). The echocardiographic parameters were presented in Table 2. While LVEDD and EF were similar, left atrial (LA) diameter, LA volume, LVESD, and LVEDV were significantly higher in Group 2 compared to Group 1 (both $p < 0.005$). LVESV and SV were not statistically different in both groups although these parameters showed a trend to decrease in Group 2. Importantly, although LV GLS measured lower in Group 2, this difference did not reach statistical significance ($p < 0.05$). Both TAPSE and TAPSV were significantly lower in Group 2, indicating worse RV systolic function. Finally, the mitral valve geometrical alteration parameters such as the tenting area and the coaptation distance were significantly higher in Group 2.

When we performed a linear regression analysis with variables that were significantly different within two groups, the presence of severe MR was the only independent predictor of high circulating plasma copeptin level (OR 7.5, 95% CI 2.8–12.1, $p = 0.002$).

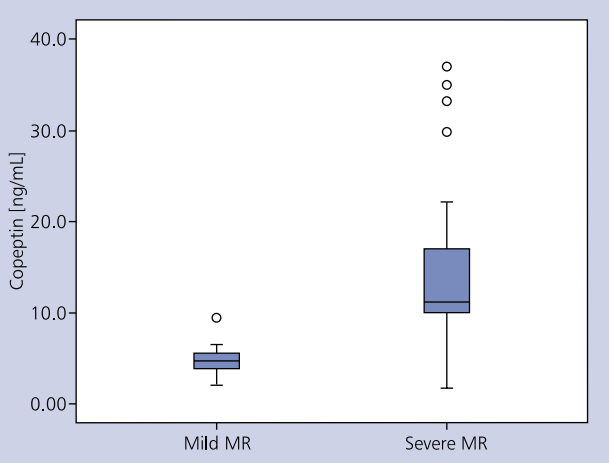

Figure 1. Box plots (medians and interquartile ranges) of serum copeptin levels. The median serum copeptin level in patients with mild mitral regurgitation (MR) was significantly lower than in patients with severe MR (4.9 ng/mL [25th and 75th percentiles 3.8 and 5.7] vs. 11.2 ng/mL [25th and 75th percentiles 9.9 and 18], respectively, $p < 0.0001$

The subgroup analysis of Group 2 revealed that there was no significant difference between the patients with and without atrial fibrillation regarding their BNP and copeptin values ($p = 0.46$ and $p = 0.11$, respectively).

Copeptin and BNP levels showed a substantial agreement (Kappa level: 0.607, $p < 0.0001$). In addition, copeptin and

Table 2. The standard echocardiographic, tissue Doppler, and two-dimensional speckle imaging data of the study population

Variable	Group 1	Group 2	p
Left atrial diameter [cm]	4.04 ± 0.56	4.69 ± 0.78	< 0.0001
Left atrial volume [mL]	56.6 ± 19.9	96.8 ± 43.4	< 0.0001
LVEDD [cm]	6.12 ± 0.93	6.53 ± 0.76	NS
LVESD [cm]	4.65 ± 0.94	5.17 ± 0.70	< 0.05
LVEDV [mL]	154.3 ± 42.8	226.1 ± 75.3	0.010
LVESV [mL]	109,0 ± 43	147.3 ± 65.1	0,131
Stroke volume index [mL/m^2]	26.2 ± 8.9	20.0 ± 5.9	0,095
Ejection fraction [%]	32.0 ± 9.71	33.1 ± 8.4	NS
E/A ratio	1.69 ± 1.57	2.86 ± 2.5	NS
E/E' ratio	10.0 ± 4.03	11.1 ± 2.88	NS
Tenting area [cm^2]	2.07 ± 0.49	2.5 ± 0.64	< 0.01
Coaptation depth [cm]	1.1 (1.07–1.2)	1.2 (1.03–1.45)	< 0.0001
Regurgitant volume [mL]		48.8 ± 13.87	
Effective regurgitant orifice [mm^2]		32.2 ± 10.9	
TAPSE [mm]	19.35 ± 5.9	17.4 ± 4.38	< 0.05
TAPSV [cm/s]	11.9 ± 3.9	9.88 ± 2.38	< 0.05
Global longitudinal strain [%]	–10.1 ± 4.5	–6 ± 7.9	NS

LVEDD — left ventricular end-diastolic diameter; LVESD — left ventricular end-systolic diameter; LVEDV — left ventricular end-diastolic volume; LVESV — left ventricular end-systolic volume; TAPSE — tricuspid annular plane systolic excursion; TAPSV — tricuspid annulus peak systolic velocity

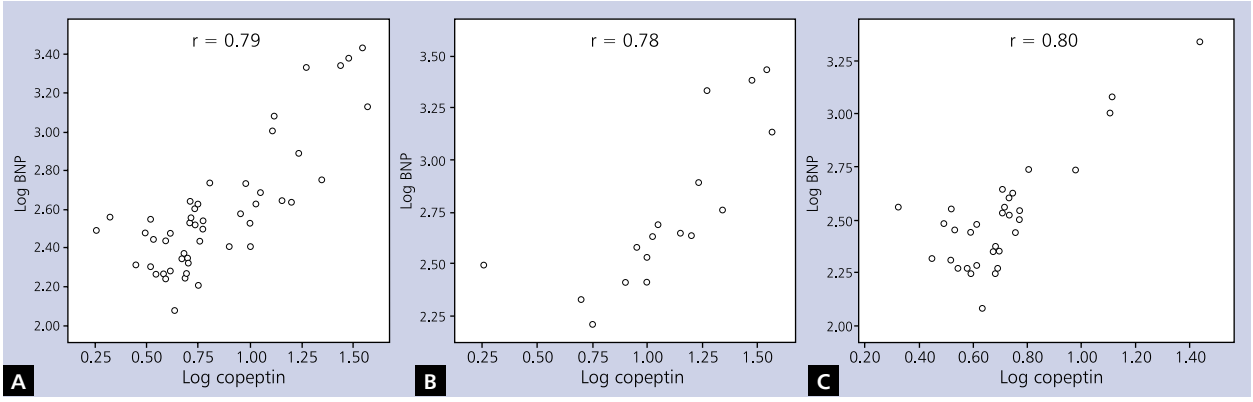

Figure 2. Correlation of copeptin and B-type natriuretic peptide (BNP) in both groups (**A**), in the severe mitral regurgitation group (**B**), and in the mild mitral regurgitation group (**C**)

BNP showed a strong correlation within and between Group 1 and Group 2 (Fig. 2). Copeptin was positively correlated with LA diameter (r = 0.37, p = 0.0001), LA volume (r = 0.45, p = 0.0001), E/A (r = 0.44, p = 0.003), and E wave (r = 0.36, p = 0.007) and negatively correlated with TAPSE (r = –0.28, p = 0.029).

When the study population were divided into two subgroups on the basis of copeptin median (6.4 ng/mL), diastolic blood pressure, LA diameter, and volume TAPSE, TAPSV, and the prevalence of severe MR were significantly higher in the above-median-copeptin subgroup (Table 3, Fig. 3).

DISCUSSION

In this study, we examined the potential role of severe MR in the release of copeptin in HF patients. This study demonstrated that HFrEF patients with significant MR have increased plasma copeptin levels compared to patients with non-significant MR, despite having similar NYHA class and EF, and more importantly the presence of significant MR was an independent predictor of increased copeptin level.

Functional MR occurs secondary to ventricular dilation and dysfunction. As demonstrated in many studies, severe functional MR is a predictor of increased mortality and mor-

Table 3. Comparison of the subgroups divided on the basis of copeptin median value

	Below median	Above median	p
Age	57.8 ± 11.6	56.2 ± 15.5	NS
Gender (female)	8 (26%)	5 (16%)	NS
Systolic blood pressure [mm Hg]	107.6 ± 9.8	113.1 ± 8.0	< 0.05
Diastolic blood pressure [mm Hg]	67.5 (65.0–75.0)	70.0 (70.0–75.0)	< 0.05
Urea [mg/dL]	39.0 (32.7–58.7)	42.7 (35.5–61)	NS
Creatinine [mg/dL]	0.98 (0.79–1.43)	0.99 (0.75–1.34)	NS
Uric acid [mg/dL]	1.2 ± 0.44	1.1 ± 0.37	NS
Na [mmol/L]	135.7 ± 2.9	135.7 ± 3.1	NS
Haemoglobin [g/dL]	12.4 ± 2.1	12.9 ± 2.1	NS
C-reactive protein [mg/dL]	0.6 (0.34–1.38)	0.35 (0.34–1.8)	NS
Log B-type natriuretic peptide	2.4 ± 0.14	2.8 ± 0,34	< 0.001
Left atrial diameter [cm]	4.09 ± 0.67	4.6 ± 0.74	< 0.05
Left atrial volume [mL]	62.7 ± 33.4	90 ± 40.8	< 0.05
LVEDD [cm]	6.2 ± 0.95	6.4 ± 0.81	NS
LVESD [cm]	4.7 ± 0.97	5.08 ± 0.76	NS
Ejection fraction [%]	32.2 ± 9.5	32.7 ± 8.8	NS
E/A ratio	1.69 ± 1.6	2.5 ± 2.4	NS
E/E' ratio	9.5 ± 3.7	11.3 ± 3.3	NS
Tenting area [cm^2]	2.1 ± 0.64	2.3 ± 0.53	NS
Coaptation depth [cm]	1.1 (1.07–1.3)	1.16 (1.0–1.2)	NS
Regurgitant volume [mL]	36.0 ± 8.4	50.2 ± 14.0	NS
Effective regurgitant orifice [mm^2]	25.0 ± 7.07	33.4 ± 11.0	NS
TAPSE [mm]	19.8 ± 5.8	16.9 ± 4.5	< 0.05
TAPSV [cm/s]	11.9 ± 3.7	9.7 ± 2.5	< 0.05
Global longitudinal strain [%]	–9.9 ± 4.3	–9.3 ± 4.0	NS
Severe mitral regurgitation prevalence	3 (10%)	26 (83%)	< 0.001

LVEDD — left ventricular end-diastolic diameter; LVESD — left ventricular end-systolic diameter; TAPSE — tricuspid annular plane systolic excursion; TAPSV — tricuspid annulus peak systolic velocity

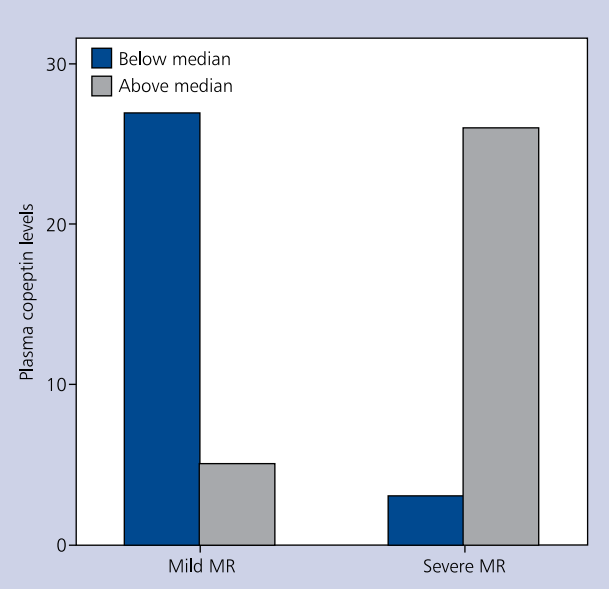

Figure 3. Plasma copeptin levels in both groups according to median copeptin level; MR — mitral regurgitation

bidity in HF, independent of EF [12–16]. In line with this data, we also demonstrated that despite significantly increased copeptin levels, the severe MR group had similar EF to the mild MR group. This finding could explain the confounding results regarding the relationship between the degree of HF and copeptin levels. In the study of Pzosonyi et al. [17], although being an independent prognostic marker in HFrEF, plasma copeptin level did not increase proportionally with the progression of the disease. In this study, LV systolic function was assessed with EF measured by echocardiography; however, the presence of functional MR was not reported. In our study, the severe and mild MR groups had similar degrees of HF regarding the NYHA class and LVEF. We assessed the systolic LV function also by measuring the deformation, and we demonstrated that although the severe MR group had slightly reduced GLS it did not reach a significant level. In keeping with these findings, neither LVEF nor LV GLS was different when we divided the group based on the median copeptin value. However, the prevalence of significant MR was significantly higher in the group with above-median copeptin.

Group 2 revealed increased LVESD, LA diameter and LA volume, LVEDV, restrictive ventricular filling, and worsening of RV systolic function as expected. This alterations are the inevitable consequences of long-standing MR. Ventricular remodelling and enlargement causes dilation of the mitral valve annulus, which compromises the competence of mitral valve closure and leads to MR; the progression of the regurgitation can then lead to cardiac pathophysiological changes, such as reduced LV impedance, increased ventricular wall-stress (thus creating an elevated LA pressure), pulmonary hypertension, and impaired RV function [18]. It is important to note that in our study, copeptin not only increased proportionally to the severity of MR, but also significantly correlated with all these parameters.

Another very important finding of our study was the good agreement between BNP and copeptin. Moreover, BNP and copeptin were closely correlated within and between the severe and mild MR groups. BNP and N-terminal (NT) pro-BNP levels were increased in HF and correlated well with ventricular wall stress and the severity of HF [19], and novel biomarkers including NT-proBNP, pro-adrenomedullin, and copeptin may correlate strongly with each other in certain conditions [20, 21]. Stoiser et al. [4] found copeptin to be an excellent predictor of outcome in advanced HF patients and also to be superior to BNP in predicting death and a combined endpoint. A similar result was found in another study, in which copeptin was shown to be a reliable outcome predictor in advanced HF, which was at least comparable with (and closely related to) BNP [7]. Combining the measurement of plasma copeptin together with BNP concentration could further improve the prediction of outcome for HF patients and may improve risk classification strategies [17, 22]. Vasopressin (thus its surrogate copeptin) and BNP reflect different pathophysiological aspects of HF. While BNP is produced by cardiac myocytes in response to stretch, vasopressin is produced in the posterior hypothalamus as a response to changes in plasma osmolality [23–25]. Besides osmotic stimuli, non-osmotic factors such as intra-cardiac and intra-arterial pressures also can trigger the secretion of vasopressin. Although non-osmotic mechanisms do not usually play an important role in healthy individuals, in HF the non-osmotic stimuli are thought to be the dominant mechanism of vasopressin production [26–28]. Indeed, prior studies have shown that although arginine vasopressin was major contributor to hyponatraemia, there was no correlation between sodium and copeptin concentrations in the HF population [29–30]. Accordingly, in our study, the patients had sodium levels within normal ranges despite elevated plasma copeptin level. In the presence of severe MR, through the reduced afterload, the left ventricle overcomes the volume overload by increasing the total cardiac output. Decreased forward SV is an expected finding in patients with severe MR, and this is also compatible with our finding of lower strain values in patients from the severe MR group than the mild MR group, despite having similar EF. However, in our study, although there was a tendency to decreased forward SV, there was no statistical difference in SVI of both groups, probably due to the limited number of patients. As a result, severe MR probably strengthens the stimuli of copeptin release by causing a constant increase in preload, which then increases ventricular wall stress/pressure.

Limitations of the study

The major limitation of our study is the relatively low number of patients included. Our study included HFrEF patients with similar functional status and those with the same symptomatic stage. There is no adequate comparable data between severe, mild, and moderate MR and also in different functional classes. Another limitation of our study is the lack of copeptin evaluation after long-term follow-up. Larger clinical trials assessing the value of copeptin in the prognosis of HFrEF patients with significant MR would be of great interest.

CONCLUSIONS

Severe MR is an independent predictor of elevated plasma copeptin level in HFrEF, irrespective of systolic function. The presence of severe MR together with elevated copeptin levels, can be used to define a high-risk patient group independent of LV systolic function for targeting a closer follow-up.

Conflict of interest: *none declared*

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Związek między ciężką niedomykalnością mitralną a zwiększonym stężeniem kopeptyny w niewydolności serca ze zmniejszoną frakcją wyrzutową

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Streszczenie

Wstęp i cel: Badanie przeprowadzono w celu oceny potencjalnego wpływu niedomykalności mitralnej (MR) na uwalnianie kopeptyny u chorych z niewydolnością serca i zmniejszoną frakcją wyrzutową lewej komory (HFrEF).

Metody: Do badania włączono 63 chorych, spośród których u 33 stwierdzono łagodną czynnościową MR (grupa 1), a u 30 — ciężką funkcjonalną MR (grupa 2). Pacjenci z obu grup byli w III klasie niewydolności serca wg klasyfikacji *New York Heart Association* (NYHA). Próbki krwi w celu oznaczenia stężeń kopeptyny i peptydu natriuretycznego typu B (BNP) pobrano w tym samym dniu, w którym wykonano standardowe badanie echokardiograficzne.

Wyniki: Stężenia kopeptyny i BNP były zgodne w całej badanej populacji (współczynnik kappa: 0,607; $p < 0,0001$). Ponadto stężenia kopeptyny i BNP były silnie skorelowane oraz przyjmowały istotnie wyższe wartości w grupie 2 niż w grupie 1 (odpowiednio, $p < 0,001$ i $p < 0,05$). Wartości globalnego odkształcenia podłużnego lewej komory i frakcji wyrzutowej lewej komory były podobne w obu grupach. Uczestników badania podzielono na dwie podgrupy w zależności od mediany stężenia kopeptyny (6,4 ng/ml) i stwierdzono istotnie częstsze występowanie MR w podgrupie ze stężeniami kopeptyny powyżej mediany. W analizie regresji liniowej wykazano, że występowanie ciężkiej MR było jedynym niezależnym czynnikiem predykcyjnym wysokiego stężenia kopeptyny w osoczu (OR: 7,5; 95% CI 2,8–12,1; $p = 0,002$).

Wnioski: Ciężka MR jest niezależnym czynnikiem predykcyjnym zwiększonego stężenia kopeptyny w osoczu u chorych z HFrEF niezależnie od czynności skurczowej.

Słowa kluczowe: kopeptyna, niewydolność serca, czynnościowa niedomykalność mitralna

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