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Copeptin and NTproBNP in patients with acute Q - myocardial infarction complicated by acute heart failure with hyperglycemia on admission

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Abstract

Introduction. Acute heart failure is a complication of Q-myocardial infarction that affects the acute period and long-term outcome of the disease. The study of new predictors and outcomes of acute heart failure remains an urgent problem. **Objective.** To assess the levels of copeptin and NTproBNP in acute period of Q - myocardial infarction complicated by acute heart failure with hyperglycemia (HG) on admission. **Materials and methods.** The study involved 139 patients with acute MI Q-complicated by acute heart failure, who were divided into two groups: normoglycemia (n = 31) and HG on admission (n = 108). There were selected subgroups of HG: stress HG (n = 34), impaired glucose tolerance (IGT) (n = 26), new-onset type 2 diabetes (n = 25), type 2 diabetes mellitus (DM) in history (n = 23). The control group included 26 healthy individuals. The general clinical examination, echocardioscopy, continuous daily monitoring of ECG and blood pressure were performed, the levels of insulin, copeptin and NTproBNP were determined. **Results.** Compared with control group the patients with normoglycemia showed significantly higher level of copeptin

on the first day by 27% (p = 0.03), in the group of HG on admission by 57% (p = 0.0001), in the stress HG group by 62% (p = 0.0001), in the group of new-onset diabetes by 49% (p = 0,001), in DM type 2 in history by 54% (p = 0,01). In patients with stress HG copeptin by 49% (p = 0.02), and in patients with GH on admission it was 2.3 times higher than in the normoglycemia group. On the 12thday the copeptin level was significantly higher than the values in the control group by 56% (p = 0.0009) in patients with normoglycemia, by 51% (p = 0,007) in group with the HG on admission, by 51% (p = 0.003) in stress HG patients. NTproBNP level was significantly higher that in the control on the first and 12th days in all groups. On the first day in patients with normoglycemia – 8,6 times (p = 0.00001), in group of HG on admission – 9,9 times (p = 0,00001), in stress HG patients – 11,2 times (p = 0.00001), in the group of IGT – 7,4 times (p = 0.0001), in patients with new-onset diabetes – 10,7 times (p = 0.00001), in the type 2 diabetes in history group – 12,2 times (p = 0.0001). On the 12th day NTproBNP level in patients with normoglycemia – 4.8 times (p = 0.001), in the group with HG on admission – 11.3 times (p = 0.00001), in stress HG – 11.1 times (p = 0.00001), in group of IGT – 12.8 times (p = 0.001), with new-onset diabetes – 7.14 times (p = 0.0002), in patients with DM type 2 in history – 11.7 times (p = 0.0001) higher than in the control group. In order to identify factors affecting the level of copeptin, a model of multiple linear regression was made. **Conclusions.** The most significant changes of copeptin were identified in groups of hyperglycemia on admission and stress HG. On the 12th day the increase of copeptin level, compared with the control group, retained in normoglycemia, hyperglycemia on admission and stress hyperglycemia patients. NTproBNP level was significantly increased in all patients, regardless of the presence and type of hyperglycemia. Systolic blood pressure in the pulmonary artery, the presence of the clinical manifestations of heart failure and hyperglycemia on admission have a predictive property, that allows to use them in the linear regression model to predict copeptin level.

Key words: Q-myocardial infarction, acute heart failure, hyperglycemia, copeptin.

Introduction. Q-myocardial infarction (Q-MI) is one of the most common causes of hospitalization and death in the world. Each year, there are more than 15 million new cases of heart attacks in the world, and more than 50 thousands in Ukraine [1]. The most severe complication Q-MI, affecting the acute period and long-term outcome of the disease, is acute heart failure (AHF) [2]. With the development of AHF hospital mortality of patients with Q-MI increases from 7% to 12% and a year mortality from 12% to 40% [3, 4]. Early

identification of predictors of the development of AHF at Q-MI remains a major challenge for the timely implementation of treatment measures. The determination of the concentration of NTproBNP in the development of AHR in patients with Q-MI has been convincingly proven due to its high diagnostic and prognostic value [5]. The study of new predictors of the development and outcomes of AHF in patients with Q-MI is still relevant. Copeptin is the C-terminal residue of a provazopressin molecule, that is reflecting the level of endogenous stress [6]. The role of copeptin has been proven as an additional marker for early diagnosis, risk stratification and medium-term outcome in patients with MI [7-9]. A direct link between the level of copeptin and the severity of AHF was established in patient with MI [10] and also an association with a level of hyperglycemia (GH), which is an additional risk factor [11].

Objective. To assess the levels of copeptin and NTproBNP in acute period of Q - MI, complicated by AHF with against HG on admission.

Materials and methods. The study was conducted in the intensive care unit for the treatment of patients with acute coronary insufficiency KU "City Clinical Hospital of Emergency and Ambulance in Zaporizhzhia" on the clinical basis of the Department of Internal Diseases No. 1 of ZSMU (Zaporizhzhia State Medical University). The study design was coordinated with the local ethics committee (Minutes №9, December 7, 2016) with the conclusion of compliance moral and ethical standards of bioethics.

Inclusion criteria were patients with acute Q-MI complicated by AHF (class I-III for Killip)

Exclusion criteria were patients with non Q-myocardial infarction.

After signing the informed consent, the study included 139 patients in the acute period of Q-MI, average age 66 ± 0.97 years (M ± m), male – 59% (n = 83) and 26 healthy persons (control group), average age 62.5 ± 1.57 years (M ± m), 58% was a male. The patients were divided into groups depending on the presence of HG on admission (according to recommendations of the American Association of Endocrinology and the American Diabetes Association [12]) and the type HG. Normoglycemia group consisted of 31 patients, average age 63 ± 1.86 years (M ± m). Group HG on admission included 108 patients, average age 67 ± 1.12 years (M ± m). After the examination (on the 12th day, an oral glucose tolerance test was performed) in the group of HG on admission, the following subgroups were identified: stress HG - 34 patients, average age 70 ± 2.1 years (M ± m), impaired glucose tolerance (IGT) - 26 persons, average age 65 ± 2.35 (M ± m), new-onset type 2 diabetes (NOD) group - 25 patients, average age 65 ± 2.47 years (M ± m), diabetes mellitus (DM) type 2 in history group – 23 patients, average age 67 ± 1.86 years (M ± m).There were no significant differences in

age and sex between observed groups. All patients with HG on admission were divided according to the class of AHF by Killip classification: Killip I - n = 24, average age 61 ± 2.69 (M ± m), Killip II - n = 45, average age 69 ± 1,36 (M ± m), Killip III - n = 33, average age 69 ± 1.70 (M ± m). The average age of patients in group Killip II and Killip III was significantly higher, than in Killip I.

All patients underwent general clinical examination, the levels of glycemia and insulin were determined on the day of hospitalization. During the first 48 hours of the development of clinical symptoms and on the 12th day of the disease, it was performed transthoracic dopplerechocardioscopy (ECS) on an ultrasound scanner “MyLab50” (“Esaote”, Italy) in M; B; PW; CW; CFM modes, according to the recommendations of the American Society of Echocardiography [13], the levels of copeptin and NTproBNP were determined. The study of plasma samples for copeptin was determined using a set of reagents produced by Phoenix Pharmaceuticals by competitive enzyme immunoassay. NTproBNP levels in serum were determined by ELISA using a standard set of reagents NTproBNP ELISA Kit («Biomedica», Slovakia). The research was carried out according to the instructions for sets at the Training medical and laboratory center of Zaporizhzhia State Medical University (Director - MD, Professor A. Abramov). Blood sampling was carried out from a peripheral vein into Vacutainer tubes with K2 EDTA and proteolysis inhibitor aprotinin to obtain plasma and Vacutainer tubes to obtain serum and it was centrifuged for 15 min at 1600 rpm speed. The resulting plasma was frozen at -70°C, the serum at -20°C, followed by cross-sectional study of all samples. As reference NTproBNP values, the manufacturer suggested a median of 5,8 pmol/l. There were no reference values for the copeptin set in the instruction. According to examination of healthy persons (control group of this study), the reference value for copeptin was considered a median of 0,94 ng/mL. On the 10-12 day Holter ECG and blood pressure (BP) monitoring were performed on the unit "EC-3H / ABP" ("Labtech", Hungary) according to the Ukrainian Heart Association Recommendations [14, 15] with the evaluation of standard ECG parameters (minimum, maximum and average heart rate, number of ventricular and supraventricular extrasystoles, the duration of ischemic episodes, QT max, QT min), analysis of frequency and time characteristics of heart rate variability (HRV), mean values of systolic (SBP) and diastolic (DBP) blood pressure for a day, in the daytime and nighttime, and the standard deviation of BP averages measures (BP variability), hypertension time index (TI) and diastolic index (DI).

Statistical analysis was performed by the program Statistica 13.0 (StatSoftInc., № JPZ8041382130ARCN10-J) and Microsoft Excel. Normal distribution of quantitative traits

was assessed using the Shapiro-Wilk test. The data are presented as M ± m (arithmetic mean ± error average) and Me (Q25; Q75) (median upper and lower quartiles). The significance of differences quantitative variables between two independent groups were evaluated using the Mann-Whitney test. To evaluate the relationship between quantitative measures Spearman and Gamma correlation analysis methods were used. To determine the factors, influencing the level of copeptin the model of multiple logistic linear regression was made. The differences at the level of $p<0,05$ were considered significant.

Results

The study showed that in patients with acute myocardial infarction on the 1st day copeptin level – 2,1 times and NTproBNP – 8,5 times higher than in the control group, and on the 12th day – 2 times and 9,3 times, respectively (Table 1).

Table 1 – The dynamic of copeptin and NTproBNP levels in patients with Q-myocardial infarction complicated by acute heart failure, Me (Q25; Q75)

Indicator, units	Control group, n = 26	MI, n = 139	P value
Copeptin on the 1st day, ng/ml	0,94 (0,6, 1,0)	1,99 (0.76; 3.19) *	0.0003
Copeptin on the 12th day, ng/ml		1.94 (0.66; 4.05) *	0.0009
NTproBNP on the 1st day, pmol/l	4,47 (1,47; 11,75)	* 40.64 (21.73; 115.1)	0.00001
NTproBNP on the 12th day, pmol/l		41.78 (10.48; 86.81) *	0.00001

Note. 1. * - significant differences with the control group, $p<0.05$;

Copeptin and NTproBNP levels in groups depending on the type of HG are shown in Table 2. In comparison with the control group, in the group of normoglycemia, copeptin level on the 1st day was significantly higher by 27% ($p = 0.03$), in group HG on admission by 57% ($p = 0.0001$), in the group of stress HG by 62% ($p = 0.0001$), in the NOD group by 49% ($p = 0.001$), in the group with type 2 DM in history by 54% ($p = 0.01$). In IGT group, copeptin was by 51 % higher on the first day than in the control group, but the difference was not significant ($p = 0.07$).

Table 2 – Copeptin and NTproBNP levels depending on the type of HG, Me (Q25; Q75)

Indicator,units	Control group, n = 26	Normoglycemia, n = 31	HG on admission			
			Stress HG, n = 34	IGT, n = 26	NOD, n = 25	Type 2 DM in history, n = 23
Copeptin on the 1st day, ng/ml	0.94 (0.6, 1.0)	1.3 (0.76; 2.6) *	2.17 (0.77; 3.32) *&			
			2.53 (1.25; 3.3) & *	1,86 (0,59; 2,96)	1.83 (0.69; 3.87) *	2.04 (0.77; 3.32) *
Copeptin on the 12th day, ng/ml		2,15 * (1.15; 3.81)	1.9 (0.58; 4.17)*			
			1.9 (0.89; 4.17) *	1.9 (0.55; 3.78)	2.68 (0.49; 4.05)	1.12 (0.59; 4.33)
NTproBNP on the 1st day, pmol/l	4.47 (1.47; 11.75)	3.46 (18.1, 135.9) *	44.18 (23.2; 111.7) *			
			50.19 (15.1; 140.1) *	33.14 (18.4; 80.7) *	47.65 (20.6; 106) *	54.32 (38.3, 127.3) *
NTproBNP on the 12th day, pmol/l		21.26 (13.4; 87.1) *	50.5 [0.54; 4.17] *			
			49.78 (8.4, 82.2) *	57.19 (5.3; 86.8) *	31.95 (11.6; 61.2) *	52.38 (2.6, 134.2) *

Note. 1. * - significant differences with the control group, $p < 0.05$;

2. & - significance differences with normoglycemia group, $p < 0.05$

Comparing the level of copeptin between normoglycemia group and the groups with different types of HG, significant differences were revealed with stress HG group, where copeptin was by 49% higher ($p = 0.02$) and in patients with HG on admission – 2,3 times higher ($p = 0.04$).

On the day 12th, copeptin level was significantly higher than the values in the control group by 56% ($p = 0.0009$) in patients with normoglycemia, by 51% ($p = 0.007$) in HG on admission group, by 51% ($p = 0.003$) in patients with stress HG. The significant differences were not found in groups of IGT, NOD and type 2 DM in history comparing with the control group.

NTproBNP level on the 1st and 12th days was significantly higher in all groups than in the control group. It was higher on the first day in patients with normoglycemia – 8.6 times ($p = 0.00001$), in group of HG on admission – 9.9 times ($p = 0.00001$), in stress HG patients – 11.2 times ($p = 0.00001$), in the group of IGT – 7,4 times ($p = 0.0001$), in patients with NOD

– 10.7 times (p = 0.00001), in type 2 DM in history group – 12.2 times (p = 0.0001). On the 12th day NTproBNP levels in patients with normoglycemia – 4.8 times (p = 0.001), in the group with HG on admission – 11.3 times (p = 0.00001), in stress HG – 11.1 times (p = 0.00001), in group of IGT – 12.8 times (p = 0.001), with NOD – 7.14 times (p = 0.0002), in patients with DM type 2 in history – 11.7 times (p = 0.0001) than in the control group.

Table 3 - Copeptin and NTproBNP levels by classes of AHF (Killip classification) in patients with HG on admission, Me (Q25; Q75)

Indicator, units	Killip I, n = 28	Killip II, n = 45	Killip III, n = 33
Copeptin on the 1st day, ng/ml	0.76 (0.46; 2.74)	2.53 (1.12; 3.8) *	2.17 (1.51; 3.32) *
Copeptin on the 12th day, ng/ml	0.94 (0.44; 1.9)	2.68 (0.9, 4.33) *	3.19 (0.71; 4.8) *
NTproBNP on the 1st day, pmol/l	33.7 (8.05; 69.6)	40.32 (24.4; 85.5)	101.7 (38.2; 223) * #
NTproBNP on the 12th day, pmol/l	26.4 (4.52; 70)	53.51 (8.39; 86.6)	54.34 (39.04; 109.6) *

Note: * - significant differences with the group Killip 1

- significance differences with the group Killip 2

On the 1st day, copeptin level in the group Killip II was significantly higher than in the group Killip I – 3.3 times (p = 0.002) and on the 12th day – 2.9 times (p = 0.01). The level of copeptin in group Killip III on the 1st day was significantly higher than in Killip I – 2.9 times (p = 0.006) and on the 12th day – 3.4 times (p = 0.01). On the 1st day NTproBNP level in the group Killip III was significantly higher than in Killip I group – 3 times (p = 0.03) and Killip II group – in 2.5 times (p = 0.03). NTproBNP level on the day 12th in Killip III group was significantly higher than in Killip I group – 2.1 times (p = 0.02).

The correlation analysis of the group HG on admission revealed the following relationships. Copeptin level on the 1st day has a significant positive correlation with the class of AHF by Killip (γ = + 0.25) and insulin levels (r = + 0.42); with indicators of ECS - positive connection with a systolic pulmonary artery pressure (SPAP) during the day of admission (r = + 0.29) and a negative relationship with left ventricular ejection fraction (LVEF) on 12th day (r = -0.26). Level of copeptin on the 12th day has a significant positive correlation with the class of AHF by Killip (γ = + 0.26), insulin level (r = + 0.42); with indicators of ECS on the first day - positive connection with SPAP (r = + 0.27), on the 12th day-negative connection with shock index (r = -0.44), stroke volume (SV) (r = -0.41), systolic index (SI) (r = -0.29)

and LVEF (r = -0.37). The following indicators of daily monitoring of BP correlated with the level of copeptin at the 1th day: DBP in the daytime (r = + 0.37), DBP in the nighttime (r = + 0.34), DI SBP (r = + 0.49) and DI DBP (r = + 0.44). Copeptin did not significantly correlate with the performance of daily monitoring of ECG.

NTproBNP level on the first day has a significant positive correlation with the class of AHF by Killip (+0.23). With indicators of ECS on the day of admission – a positive connection with the left ventricular mass index(LVMI) (r = + 0.25), peak E (r = + 0.23), and E / A (r = + 0.30), negative relationship with the LVEF in the day of admission (r = -0.25); negative correlation with the number of episodes of ventricular tachycardia (r = -0.34). The following indicators of daily monitoring of BP correlated with the NTproBNP level on the 1st day: the average level of the SBP in the daytime (r = + 0.33), the standard deviation of the average SBP in the daytime (r = + 0.31), the TI SBP in the daytime (r = + 0.36).

NTproBNP level on the12th day has a significant positive correlation with the exponent E / A (r = + 0,36) and a negative relationship with peak A (r = -0,28) and LVEF (r = -0.27); negative correlation connection with the sympathetic-parasympathetic balance (LF / HF) (r = -0.34) and a positive with high-frequency components of the spectrum (HFn) (r = + 0.35); a positive relationship with the average level of SBP in the daytime (r = + 0.31), hypertension TI of SBP (r = + 0.36) and DBP (r = + 0.35) in the day time.

To determine the factors that independently influence the level of copeptin, the multiple linear regression analysis was made. In all patients with Q-MI complicated by AHF a significant effect on the level of copeptin was determined only for two factors: SPAP and the presence of HG on admission (Table. 4).

Table 4 – The results from regression analysis of patients with Q-MI complicated by AHF

Indicator	Coefficients	Standard error	t-statistics	P-Value
SPAP	0.059024	0.009588	6.155853	1.04E-08
HG on admission	0.785487	0.318393	2.467038	0.015047

A linear multiple regression model:

Level of copeptin =0.059 x SPAP + 0.78 x HG on admission

The coefficient of determination R-square is equal to 0.67, that confirms the quality of the model.

The resulting equation shows that with the increase of SPAP by 10 mmHg copeptin levels increase on average by 0.59 ng/ml, and when the patient has HG on admission the copeptin increases by 0.78 ng/ml. To determine the coupling strength between features the coefficient of elasticity was calculated: for SPAP e = 0.73, for the HG on admission e = 0.26. Thus, a greater effect on the magnitude copeptin has SPAP. With an increase in SPAP by 1% copeptin level increases by 0.73%.

In patients with HG on admission the factors, that significantly influence the levels of copeptin on the 1st day, was SPAP value and availability of clinical manifestations of AHF (Table. 5). The coefficient of determination R-squared equals 0.69.

Table 5 – The results of the regression analysis of patients with Q-infarction complicated by acute heart failure and hyperglycemia on admission

Indicator	Coefficients	Standard error	t-statistics	P-Value
SPAP	0.057016	0.012222	4.665008	1.08E-05
AHF symptoms	1.054799	0.422182	2.498444	0.01431

A linear multiple regression equation:

Level of copeptin= 0.057 x SPAP+ 1.05 x symptoms of AHF

The model suggests that with an increase of SPAP by 10 mmHg copeptin level increases by 0.57 ng/ml and with the presence of clinical symptoms of AHF – by 1.05 ng/ml. Estimating the coefficient of elasticity (for SPAP e = 0.66, for the clinical manifestations of AHF e = 0.32) SPAP has greater impact on the level copeptin. When SPAP increases by 1%, the level of copeptin increases on average by 0.66%.

Discussion. According to the literature, the level of copeptin is associated with the level of glycemia [11], the presence of metabolic syndrome and obesity, especially by visceral type [16]. However, the effect of vasopresin on glucose metabolism is indirect and mediated by other hormonal systems [17]. The study [18] evaluated predictor role of copeptin in the development of type 2 diabetes. There was revealed a lot of correlations: with parameters of insulin resistance, components of the metabolic syndrome, C-reactive protein and others. But significant correlation with blood glucose levels has not been identified. Similar data were obtained in our study. On the background of HG, the stress response causes an active synthesis of growth hormone, which inhibits the action of insulin and leads to insulin

resistance [19]. Reflecting the level of endogenous stress, copeptin is associated with the presence of HG on admission and insulin levels, but not with the level of glycemia.

The study [20] found that copeptin level in patients with Q-MI and HG was significantly higher than in the control group, but did not significantly differ from normoglycemia groups. The authors noted a high predictive value of copeptin in patients with MI against HG. At the same time, they indicated that increased level of copeptin is a marker of stress, but not a pathogenetic factor in the development of HG. In our study the copeptin levels in patients with HG on admission and stress HG are significantly different from the group of normoglycemia, but by the 12th day the significance of the difference disappears.

The study [10] defined a threshold of a prognostic level of copeptin (2.95 ng / ml) for developing severe AHF in patients with acute coronary syndrome without ST segment elevation recovery in the first 3 hours from the onset of the pain syndrome. Previously, we [21] also evaluated the predictive value of copeptin in development of AHF in acute Q-MI. Our data indicate, that copeptin is dependent predictor of AHF with a threshold value of 0.53 ng / ml.

In patients with heart failure with preserved LVEF [22] copeptin level was increased, compared with the control group, correlated with NTproBNP, has prognostic value, but was not a marker of diastolic dysfunction. In our study, the association of the level of copeptin and LV diastolic function was also not obtained, unlike NTproBNP.

In patients with systolic dysfunction and LVEF $\leq$ 40 % after Q-MI an increase in the level of copeptin is associated with the development of AHF, a worse prognosis, and the risk of recurrence of MI [23]. The study [24] confirmed that copeptin concentration related to the degree of left ventricular dysfunction after MI. Accordingly copeptin level inversely correlated with the LVEF at discharge ($r = -0.188$, $p = 0.03$) and further observation ($r = -0.270$, $p < 0.001$). There is a positive relationship with the volume of the left ventricle during systole and diastole. Patients with increased left ventricular end systolic volume have higher concentrations of copeptin (average 6.30 pmol/l vs 5.75 pmol / l; $p = 0.012$), that confirms the link between copeptin level and ventricular remodeling. In our study the level of copeptin inversely correlated with LVEF, shock index, SV and SI, that reflects the association between the concentration of copeptin and the development of left ventricular systolic dysfunction.

According to the literature [25], patients with pulmonary hypertension have a higher level of copeptin and its concentration correlates with the severity of disease and survival of patients [26]. In patients with chronic heart failure copeptin concentration correlates with the SPAP [27] and increases with class by NYHA [28]. After constructing a logistic regression

model in our study, the SPAP was defined as a factor, that has the greatest impact on the level of copeptin, both in patients with HG on admission and in the entire patients with acute Q-IM, complicated by AHF.

Conclusion

1. In patients with acute Q-myocardial infarction on the 1st day of disease the level of copeptin was significant higher comparing with the control group. The most significant changes were found in groups HG on admission and stress HG. A significant increase of copeptin in relation to the normoglycemia group was detected in patients with stress HG and HG on admission. NTproBNP level was significantly increased in all patients, regardless the presence and type of hyperglycemia.

2. The copeptin level was significantly increased on the 1st and 12th days in patients with HG and presence of clinical manifestations of acute heart failure on admission. The significant increase of NTproBNP was revealed only at class III AHF by Killip classification.

3. There is an association between copeptin level and AHF class by Killip, insulin concentration during hospitalization, SPAP magnitude, left ventricular systolic dysfunction severity, an increase on the average level and load of diastolic blood pressure during daytime and a better decrease in blood pressure at night.

4. NTproBNP level was associated with the class of AHF by Killip, development of type 2 diastolic dysfunction, left ventricular systolic dysfunction, increase in systolic blood pressure in the day time, its variability, hypertension index time of systolic and diastolic blood pressure in the day and the activity of the parasympathetic nervous system.

5. Systolic blood pressure in the pulmonary artery, the presence of the clinical manifestations of heart failure and hyperglycemia on admission have a predictive property, that allows to use them in the linear regression model to predict copeptin level.

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