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Level of copeptin and NT-proBNP in patients with decompensated heart failure in the post-infarction period under the influence of treatment

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Abstract
Copeptin is a C-terminal fragment of pro-vasopressin and a part of vasopressin precursor - pre-pro-vasopressin. The precursor is cleaved, while copeptin and vasopressin are released in equal equimolar amounts. The advantages of using copeptin include its stability, easy and rapid measurements. Its mean plasma concentration is 4.2 pmol/l. Copeptin is a promising biomarker of diagnosis and clinical course of heart failure and its decompensation.
The aim of the study was to assess the feasibility of using copeptin and NT-proBNP in the patients with decompensated heart failure in the early and late post-infarction periods and to determine changes in their correlation during the rehabilitation process.
Materials and Methods: There were examined 120 patients with Q-QS wave and non-Q wave myocardial infarction, stage II A-B decompensated chronic heart failure according to the classification proposed by Vasylenko V.Kh. and Strazhesko M.D., the New York Heart Association functional class III-IV.
Study groups were homogenous by age, gender, disease severity, duration of the post-infarction period, clinical signs of decompensation, that served as a basis for inclusion of the patients in the study.
All the patients underwent the six-minute walk test in a quiet 30-50-m long hospital corridor in the morning. In all the patients, serum concentration of N-terminal pro-brain natriuretic peptide (pg/mg) was determined using commercial ELISA kit for Human N-terminal pro-brain natriuretic peptide (Biomedica, Slovakia S.R.O.). The results obtained were statistically processed on the personal computer by means of an advanced analytics software package STATISTICA-7 and a statistical software package "Microsoft-Excel" using the statistical variation analysis. During 2 months of treatment, plasma copeptin levels decreased in all the study groups.
Results and Discussion: When studying a dynamic of changes in blood level of N-terminal pro-brain natriuretic peptide, there was observed its significant reduction in all the groups after treatment. The combined use of succinic acid and arginine preparations when treating the patients with Q wave and non-Q wave myocardial infarction and decompensated heart failure allowed us to reduce blood levels of N-terminal pro-brain natriuretic peptide by 41.03% and 41.61% 2 months after the beginning of treatment. The combined use of succinic acid and arginine preparations in combination therapy for decompensated heart failure allowed us to reduce blood levels of N-terminal pro-brain natriuretic peptide under conditions of graded exercises. Thus, during treatment of the patients of all the study groups, there was observed a gradual reduction in the concentration of N-terminal pro-brain natriuretic peptide in the blood both at rest and during graded exercises.
Conclusions: Copeptin and N-terminal pro-brain natriuretic peptide levels can be used both for the prediction of heart failure in the post-infarction period and quality assessment of treatment performed.

Keywords: Decompensated heart failure, myocardial infraction, copeptin, pro-brain natriuretic peptide, succinic acid, arginine preparations

Introduction
Heart failure (HF) and its decompensation are pathological conditions that develop in response to changes in myocardial structure and function, or hemodynamic overload resulting in disturbance of the heart's pumping function [27]. Chronic HF is a syndrome resulting from the inability of the heart to provide enough blood for normal metabolism on the background of normal venous outflow and cardiac filling pressure [10]. In HF, some changes in atrial pressure, increased levels of arginine vasopressin (AV), activation of the renin-angiotensin-aldosterone system and sympathetic nervous system are observed [6, 11]. Due to this, plasma levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) and AV are found to be elevated [24]. Rapid and reliable risk stratification is of paramount importance both for the patients with acute coronary syndrome [18] and those in the post-infraction period complicated by

decompensated HF. For this purpose, considering the mortality rate, natriuretic peptides are usually used. In recent years, new prognostic markers of cardiovascular stress have emerged; among them, copeptin and pro-vasopressin deserve special attention [13, 14, 17].

Copeptin was firstly described by Holwerda in 1972 as a 39-amino acid glycopeptide with leucine-rich core segment [1]. Copeptin is a C-terminal fragment of pro-vasopressin and a new neurohormone of AV system [3]. It is a part of vasopressin precursor – pre-pro-vasopressin [9]. Pre-pro-vasopressin is cleaved, while copeptin and vasopressin are released in equal equimolar amounts [2], and its concentration correlates with that of the latter [19]. AV is a key hormone that possesses osmoregulatory, hemodynamic and endocrinological effects, plays an important role in the maintenance of the intravascular volume and pressure and is involved in stress response [26]. AV, also called antidiuretic hormone, is synthesized in the hypothalamus and is released from the posterior pituitary in response to hemodynamic and osmotic changes. The circulation of this hormone increases in certain pathologic conditions, especially cardiovascular diseases [25]. Its main physiological function is the maintenance of body water homeostasis that can be explained by specific relationships with at least three G protein–coupled receptors [4]. The main stimuli for its secretion are an increase in osmotic pressure and a decrease in circulating blood volume [2]. Despite this, the determination of AV circulation is impractical due to its short half-life and instability in blood plasma.

The advantages of using copeptin include its stability, easy and rapid measurements. Normal copeptin value was firstly determined on the basis of its measurement in 359 healthy volunteers under normal osmotic conditions; the mean plasma copeptin concentration was found to be 4.2 pmol/l ranging from 1.0 pmol/l to 13.8 pmol/l [4]. Therefore, copeptin is a promising biomarker of diagnosis and clinical course of HF [22].

Overstretching of the ventricular wall results in increased secretion of NT-proBNP and BNP by cardiac muscle [20]. The increase in plasma concentrations of these enzymes has a positive correlation with the severity of HF course [6].

There is a correlation between renal dysfunction and copeptin and vasopressin concentrations as well; plasma concentration of both peptides increases with the increase in the glomerular filtration rate, although the level of increase in copeptin concentration is higher than the level of increase in vasopressin concentration [16]. High copeptin level is known to serve as a marker of unfavorable clinical course in sepsis, shock, pneumonia, stroke, acute coronary syndrome [15, 23], as well as a diagnostic marker for disturbances of sodium and water homeostasis. Currently, insufficient data are available to prove the feasibility of determining copeptin as a prognostic biomarker for the development and clinical course of decompensated HF in the post-infraction period.

Despite recent advances in treatment of HF in the post-infarction period, the mortality rate of HF decompensation is high [12]; this is mainly due to the growth and ageing of the population [26]. Therefore, the search for new drugs is reasonable. According to 2016 European Society of Cardiology Guidelines, pharmacological therapy for HF with reduced left ventricular ejection fraction should include beta-blockers, angiotensin-converting-enzyme inhibitors, ivabradine, mineralocorticoid receptor antagonist, diuretics [8]. Modern therapeutic approaches are still aimed at reducing heart load and improving its contractibility, that, certainly, increases energy consumption by the weakened heart. In the fields of medicine such as oncology and immunology, therapeutic interventions at the level of cellular metabolism are implemented at the stage of preclinical studies [15]. As the heart is one of the most highly energy consuming organs, adjuvant therapy that is aimed at increasing energetic metabolism, possesses cytoprotective and adaptive effects, reduces endothelial dysfunction and has a great potential [7]. Several preparations with antioxidant, antiinflammatory, antiplatelet and hypolipidemic properties are known [21]. Among the groups of such preparations, succinic acid and arginine preparations deserve special attention.

This study was carried out to assess the feasibility of using copeptin and NT-proBNP in the patients with decompensated HF after prior myocardial infarction (MI) and to determine changes in their correlation during the rehabilitation process.

Materials and Methods

There were examined 120 patients with Q-QS wave and non-Q wave MI, stage II A-B decompensated chronic HF according to the classification proposed by Vasylenko V. Kh. and Strazhesko M.D., the New York Heart Association (NYHA) functional class (FC) III-IV. The patients with Q-QS wave MI (60 individuals) were divided into 4 groups depending on the treatment method: Group I included 15 patients who received basic therapy in accordance with the protocols of the Ministry of Health of Ukraine (lisinopril - 10 mg once a day; bisoprolol fumarate - 10 mg once a day; eplerenone - 50 mg once a day; valsartan - 40 mg twice a day; ivabradine - 5 mg twice a day); Group 2 comprised 15 patients who, on the background of basic therapy, received a preparation of succinic acid according to the proposed scheme; Group 3 included 15 patients who, on the background of basic therapy, received arginine preparations according to the proposed scheme; Group 4 comprised 15 patients who, on the background of basic therapy, received a preparation of succinic acid and arginine preparations according to the proposed scheme. The patients with non-Q wave MI (60 individuals) were divided into 4 analogous groups. Tivortin - arginine hydrochloride manufactured by Yuria-Pharm, Kyiv, Ukraine; approved by the Order of the Ministry of Health of Ukraine of September 18, 2009 No 528, registration number UA/8954/01/01. An intravenous infusion of 4.2% Tivortin solution was administered at a dose of 100 ml once a day at a drip rate of 10 drops per minute within the first 10-15 minutes by increasing drip rate to 30 drops per minute (within the first 10 days). Tivortin aspartate - L-arginine aspartate, aspartic acid manufactured by Yuria-Pharm, Kyiv, Ukraine; approved by the Order of the Ministry of Health of Ukraine of July 18, 2009, registration number UA/9941/01/01. The preparation was administered orally at a dose of 5 ml 5 times per day with a meal (the maximum daily dose is 8 g) since the 11th day of randomization for 15 days. Mexicor - 3-hydroxy-6-methyl-2-ethylpyridine succinate, solution for injections manufactured by LLC "Ekofarminvest", Russian Federation; approved by the Order of the Ministry of Health of Ukraine of July 18, 2006, registration number UA/4971/01/01. The solution diluted in either sodium chloride or 5% dextrose in water was infused slowly at a dose of 100-150 ml for 30-90 minutes 3 days per day every 8 hours within the first 10 days. The recommended daily therapeutic dose is 6-9 mg; the maximum single dose is 2 mg/kg of body weight. The maximum daily dose should not

exceed 800 mg; the maximum single dose is 250 mg. Mexicor - ethyl-methyl-hydroxypyridine succinate, capsules manufactured by LLC "Ekofarminvest", Russian Federation; approved by the Order of the Ministry of Health of Ukraine of March 06, 2015, registration number UA/4971/02/01. The preparation was administered orally at a dose of 100 mg 3 times per day since the 10th day of hospitalization for 5 months. The maximum therapeutic dose is 800 mg; the maximum single dose is 200 mg. The daily dose was divided into 3 doses given during the day. The patients were observed on the 1st day of hospitalization and within the 1st and 2nd months after outpatient treatment.

Study groups were homogenous by age, gender, disease severity, duration of the post-infarction period, clinical signs of decompensation, that served as a basis for inclusion of the patients in the study.

All the patients underwent the six-minute walk test (6 MWT) in a quiet 30-50-m long hospital corridor in the morning. Before performing the 6 MWT, heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured and the standard 12-lead electrocardiogram (ECG) was recorded. Criteria for immediate stopping the test included chest pain, severe shortness of breath, limb cramps, dizziness, unsteady gait, sweating, severe pallor, $SpO_2 < 86\%$. In all the patients, serum concentration of NT-proBNP (pg/mg) was determined using commercial ELISA kit for Human NT-proBNP (Biomedica, Slovakia S.R.O.). The results obtained were statistically processed on the personal computer by means of an advanced analytics software package STATISTICA-7 and a statistical software package "Microsoft-Excel" using the statistical variation analysis. There were calculated the arithmetic mean M, the mean squared error δ, the standard error of the arithmetic mean m, the sample size (n), the probability of the difference between two arithmetic means "p". P-value was considered significant at $p<0.05$. To compare the probability of appearing clinical signs and changes during physical examination between study groups, the Fisher's exact test was used.

Results and Discussion

When studying a dynamic of changes in blood level of NT-proBNP, there was observed its significant reduction in all the groups after treatment (Table 1). Thus, in the patients, who received standard therapy, the concentration of NT-proBNP reduced gradually from (948.33±2.99) pg/ml at the beginning of treatment to (780.33±3.18) pg/ml ($p<0.05$) and (710.33±2.89) pg/ml ($p<0.05$) 1 and 2 months after the beginning of treatment, respectively, constituting 25.15% of the initial values. In the patients, who received a preparation of succinic acid, there was observed a similar reduction in blood levels of NT-proBNP (by 29.09%) – from (951.27±3.10) pg/ml before treatment to (700.33±3.44) pg/ml and (674.53±2.61) pg/ml 1 and 2 months after the beginning of treatment, respectively ($p<0.05$). There were no significant differences in the dynamics of changes in NT-proBNP level in the patients who, on the background of basic therapy, received arginine preparations. The level of NT-proBNP was (952.00±2.33) pg/ml before treatment, while 1 month after the beginning of treatment, it was (749.53±3.60) pg/ml, and 2 months after the beginning of treatment, it was (721.07±2.84) pg/ml. The combined use of a preparation of succinic acid and arginine preparations, when treating the patients with Q wave MI and decompensated HF, allowed us to reduce blood levels of NT-proBNP by 41.03% 2 months after the beginning of treatment. In this group, the level of NT-proBNP was (949.73±3.67) pg/ml before treatment, (620.07±3.43) pg/ml 1 month after the beginning of treatment ($p<0.05$) and (560.07±3.10) pg/ml 2 months after the beginning of treatment ($p<0.05$).

When analyzing a dynamic of changes in NT-proBNP level during graded exercises, the differences in the effect of treatment on the dynamics of changes in the indicators were observed. Thus, in the patients with Q MI and decompensated HF, who received standard therapy during all the observation periods, the level of NT-proBNP reduced gradually by 9.25% and 20.75% 1 and 2 months after the beginning of treatment, respectively, that was significantly lower as compared to the patients before exercising. In the patients, who received a preparation of succinic acid, the level of NT-proBNP was (1045.53±2.28) pg/ml before treatment and (761.53±2.88) pg/ml 2 months after the beginning of therapy ($p<0.05$), constituting 27.16% of the initial values. Significant differences in the dynamic of changes in NT-proBNP levels after graded exercises were observed in the patients, who, on the background of basic therapy, received arginine preparations. Thus, before treatment, NT-proBNP level was (1049.00±2.48) pg/ml, while 1 and 2 months after the beginning of treatment, it was (919.33±3.15) pg/ml and (800.53±3.16) pg/ml, respectively ($p<0.05$). The combined use of succinic acid and arginine preparations in combination therapy for decompensated HF allowed us to reduce blood levels of NT-proBNP under conditions of graded exercises. In these patients, before treatment, the level of NT-proBNP was (1046.13±2.92) pg/ml, whereas 1 and 2 months after the beginning of treatment, it was (730.00±2.90) pg/ml and (609.80±3.12) pg/ml, respectively ($p<0.05$).

When analyzing a dynamic of changes in blood level of NT-proBNP, its significant reduction during a 2-month observation period was observed in all the groups (Table 2). Thus, in the patients, who received standard therapy, the concentration of NT-proBNP reduced gradually from (951.40±2.59) pg/ml at the beginning of treatment to (770.00±2.98) pg/ml ($p<0.05$) and (705.80±2.93) pg/ml ($p<0.05$) 1 and 2 months after the beginning of treatment, respectively, constituting 25.81% of the initial values. In the patients, who received a preparation of succinic acid, there was observed a similar reduction in blood level of NT-proBNP (by 29.43%) – from (950.27±3.28) pg/ml before treatment to (670.60±3.22) pg/ml 2 months after the beginning of treatment ($p<0.05$). There were no significant differences in the dynamics of changes in NT-proBNP level in the patients who, on the background of basic therapy, received arginine preparations. Thus, the level of NT-proBNP was (948.87±3.46) pg/ml before treatment, while 1 month after the beginning of treatment, it was (734.33±3.27) pg/ml, and 2 months after the beginning of treatment, it was (714.80±2.93) pg/ml. The combined use of succinic acid and arginine preparations in combination therapy for non-Q MI and decompensated HF allowed us to reduce blood levels of NT-proBNP almost twofold – by 41.61% 2 months after the beginning of treatment. In this group, the level of NT-proBNP was (951.13±2.28) pg/ml before treatment, (610.40±2.85) pg/ml 1 month after the beginning of treatment ($p<0.05$) and (555.40±2.75) pg/ml 2 months after the beginning of treatment ($p<0.05$).

The study of changes in NT-proBNP level during graded exercises showed certain differences in the effect of rehabilitation therapy on changes in the indicators. Thus, in

the patients with decompensated HF, who received standard therapy, the level of NT-proBNP reduced gradually by 12.41% and 22.86% 1 and 2 months after the beginning of treatment, respectively. In the patients, who received a preparation of succinic acid, the level of NT-proBNP was (1048.87±3.16) pg/ml before treatment and (730.27±3.53) pg/ml 2 months after the beginning of therapy ($p<0.05$), constituting 30.38% of the initial values. In the patients, who, on the background of basic therapy, received arginine preparations, blood level of NT-proBNP was (1048.40±2.38) pg/ml before treatment, (900.47±3.02) pg/ml 1 month after the beginning of treatment ($p<0.05$), and (790.53±3.07) pg/ml 2 months after the beginning of treatment ($p<0.05$). The combined use of succinic acid and arginine preparations in combination therapy for HF allowed us to reduce blood levels of NT-proBNP under conditions of graded exercises. In these patients, before treatment, the level of NT-proBNP was (1048.93±3.43) pg/ml, whereas 1 and 2 months after the beginning of treatment, it was (706.67±3.02) pg/ml and (602.33±3.29) pg/ml, respectively ($p<0.05$).

During 2 months of treatment, in all the groups, the reduction in copeptin level was observed. According to the results of examining the patients, who received standard therapy (Table 3), their level of copeptin reduced gradually from (18.13±0.12) pmol/l before treatment to (16.47±0.07) pmol/l and (15.23±0.11) pmol/l 1 and 2 months after the beginning of treatment, respectively ($p<0.05$). In the patients, who received a preparation of succinic acid, there was observed a similar reduction in blood level of copeptin (by 27.33%) – from (18.07±0.13) pmol/l before treatment to (13.15±0.18) pmol/l 2 months after the beginning of treatment ($p<0.05$). Before treatment, the level of copeptin in the patients who, on the background of basic therapy, received arginine preparations was (18.15±0.06) pmol/l, while 1 month after the beginning of treatment, it was (15.04±0.18) pmol/l ($p<0.05$), and 2 months after the beginning of treatment, it was (14.11±0.21) pmol/l ($p<0.05$). The combined use of succinic acid and arginine preparations in combination therapy for Q wave MI allowed us to reduce blood level of copeptin by 38.90%. In these patients, before treatment, the level of copeptin (18.09±0.15) pmol/l, whereas 1 and 2 months after the beginning of treatment, it was (12.22±0.14) pmol/l and (11.20±0.17) pmol/l, respectively ($p<0.05$).

The analysis of the concentration of copeptin in the blood showed its significant reduction in all the groups (Table 4). Thus, in the patients, who received standard therapy, the concentration of copeptin reduced gradually from (18.13±0.10) pmol/l at the beginning of treatment to (16.29±0.15) pmol/l ($p<0.05$) and (15.09±0.14) pmol/l 1 and 2 months after the beginning of treatment, respectively, constituting 16.77% of the initial values. In the patients, who received a preparation of succinic acid, the concentration of copeptin reduced by 27.95% - from (18.07±0.15) pmol/l before treatment to (13.81±0.12) pmol/l and (13.02±0.14) pmol/l 1 and 2 months after the beginning of treatment, respectively ($p<0.05$). Before treatment, the level of copeptin in the patients who, on the background of basic therapy, received arginine preparations was (18.15±0.06) pmol/l, while 1 month after the beginning of treatment, it was (14.92±0.15) pmol/l ($p<0.05$), and 2 months after the beginning of treatment, it was (14.03±0.24) pmol/l ($p<0.05$). The combined use of succinic acid and arginine preparations allowed us to reduce the concentration of copeptin in the blood by 39.54% after 2 months of treatment. In these patients, before treatment, the level of copeptin (18.11±0.14) pmol/l, whereas 1 and 2 months after the beginning of treatment, it was (11.94±0.13) pmol/l and (10.95±0.09) pmol/l, respectively ($p<0.05$).

Thus, during treatment of the patients of all the study groups, there was observed a gradual reduction in the concentration of NT-proBNP in the blood both at rest and during graded exercises. Good results were achieved in the patients with prior Q wave and non-Q wave MI complicated by decompensated HF, who, on the background of standard therapy, received succinic acid and arginine preparations according to the proposed scheme.

Table 1: Dynamics of changes in NT-proBNP indicators in the patients with decompensated HF and prior Q-QS wave MI during the course of treatment

Group of patients / Complaints	Standard treatment (n=15)			Standard treatment + succinic acid (n=15)			Standard treatment + arginine preparations (n=15)			Standard treatment + succinic acid + arginine preparations (n=15)		
	Before treatment	1 month	2 months	Before treatment	1 month	2 months	Before treatment	1 month	2 months	Before treatment	1 month	2 months
NT–proBNP, pg/ml, before exercises	948.33±2.99	780.33±3.18 p1*	710.33±2.89 p1*, p2*	951.27±3.10	700.33±3.44 p1*	674.53±2.61 p1*, p2*	952.00±2.33	749.53±3.60 p1*	721.07±2.84 p1*, p2*	949.73±3.67	620.07±3.43 p1*	560.07±3.10 p1*, p2*
Δ1,%	-	-17.71	-25.15	-	-26.38	-29.09	-	-21.27	-24.26	-	-34.71	-41.03
NT–proBNP, pg/ml, after exercises	1047.60±5.18	950.20±2.86 p1*	830.27±3.10 p1*, p2*	1045.53 ±2.28	850.20±3.14 p1*	761.53±2.88 p1*, p2*	1049.00 ±2.48	919.33±3.15 p1*	800.53±3.16 p1*, p2*	1046.13 ±2.92	730.00 ±2.90 p1*	609.80±3..12 p1*, p2*
Δ1,%	-	-9.25	-20.75	-	-18.68	-27.16	-	-12.34	-23.69	-	-30.22	-41.71
Δ2,%	10.47	21.77	16.88	9.90	21.39	8.73	10.18	22.65	11.02	10.15	17.72	8.87

Notes: 1. the reliability of difference scores p_1 – as compared to the indicators before treatment; p_2 – as compared to the indicators 1 month after the beginning of treatment; * – $p<0.05$, ** – $p>0.05$.
2. Δ_1 – the increase or reduction (-) in the indicator during the course of treatment as a percentage to the values before treatment
3. Δ_2 – the increase or reduction (-) in the indicator during the course of treatment as percentage depending on physical exercises

Table 2: Dynamics of changes in NT-proBNP indicators in the patients with decompensated HF and prior non-Q wave MI during the course of treatment

Group of patients / Complaints	Standard treatment (n=15)			Standard treatment + succinic acid (n=15)			Standard treatment + arginine preparations (n=15)			Standard treatment + succinic acid + arginine preparations (n=15)		
	Before treatment	1 month	2 months	Before treatment	1 month	2 months	Before treatment	1 month	2 months	Before treatment	1 month	2 months
NT-proBNP, pg/ml, before exercises	951.40±2.59	770.00±2.98 p_1*	705.80±2.93 p_1*, p_2*	950.27±3.28	694.60±2.87 p_1*	670.60±3.22 p_1*, p_2*	948.87±3.46	734.33±3.27 p_1*	714.80±2.93 p_1*, p_2*	951.13±2.28	610.40±2.85 p_1*	555.40±2.75 p_1*, p_2*
Δ1,%	-	-19.07	-25.81	-	-26.90	-29.43	-	-22.61	-24.67	-	-35.82	-41.61
NT-proBNP, pg/ml, after exercises	1050.00±3.38	919.73±3.24 p_1*	810.00±3.51 p_1*, p_2*	1048.87±3.16	811.20±3.17 p_1*	730.27±3.53 p_1*, p_2*	1048.40±2.38	900.47±3.02 p_1*	790.53±3.07 p_1*, p_2*	1048.93±3.43	706.67±3.02 p_1*	602.33±3.29 p_1*, p_2*
Δ_1,%	-	-12.41	-22.86	-	-22.66	-30.38	-	-14.11	-24.68	-	-32.63	-42.58
Δ_2,%	10.36	19.45	14.76	10.38	11.68	8.89	10.49	10.59	9.57	10.28	15.77	8.45

Notes: 1. the reliability of difference scores p_1 – as compared to the indicators before treatment; p_2 – as compared to the indicators 1 month after the beginning of treatment; * – $p<0.05$, ** – $p>0.05$.
2. Δ_1 – the increase or reduction (-) in the indicator during the course of treatment as a percentage to the values before treatment
3. Δ_2 – the increase or reduction (-) in the indicator during the course of treatment as a percentage depending on physical exercises

Table 3: Dynamics of changes in copeptin indicators in the patients with decompensated HF and prior Q-QS wave MI during the course of treatment

Group of patients / Indicator	Standard treatment (n=15)			Standard treatment + succinic acid (n=15)			Standard treatment + arginine preparations (n=15)			Standard treatment + succinic acid + arginine preparations (n=15)		
	Before treatment	1 month	2 months	Before treatment	1 month	2 months	Before treatment	1 month	2 months	Before treatment	1 month	2 months
Copeptin, pmol/l	18.13±0.12	16.47±0.07 p_1*	15.23±0.11 p_1*, p_2*	18.07±0.13	14.05±0.14 p_1*	13.15±0.18 p_1*, p_2*	18.15±0.06	15.04±0.18 p_1*	14.11±0.21 p_1*, p_2*	18.09±0.15	12.22±0.14 p_1*	11.20±0.17 p_1*, p_2*
Δ,%	-	-9.16	-15.99	-	-22.25	-27.33	-	-17.13	-22.26	-	-32.45	-38.09

Notes: 1. the reliability of difference scores p_1 – as compared to the indicators before treatment; p_2 – as compared to the indicators 1 month after the beginning of treatment; * – $p<0.05$, ** – $p>0.05$.
2. Δ – the increase or reduction (-) in the indicator during the course of treatment as a percentage to the values before treatment

Table 4: Dynamics of changes in copeptin indicators in the patients with HF and prior non-Q wave MI during the course of treatment

Group of patients / Indicator	Standard treatment (n=15)			Standard treatment + succinic acid (n=15)			Standard treatment + arginine preparations (n=15)			Standard treatment + succinic acid + arginine preparations (n=15)		
	Before treatment	**1 month**	**2 months**	**Before treatment**	**1 month**	**2 months**	**Before treatment**	**1 month**	**2 months**	**Before treatment**	**1 month**	**2 months**
Copeptin, pg/ml	18.13±0.10	16.29±0.15 p_1*	15.09±0.14 p_1*, p_2*	18.07±0.15	13.81±0.12 p_1*	13.02±0.14 p_1*, p_2*	18.15±0.06	14.92±0.15 p_1*	14.03±0.24 p_1*, p_2*	18.11±0.14	11.94±0.13 p_1*	10.95±0.09 p_1*, p_2*
Δ,%	-	-10.15	-16.77	-	-23.57	-27.95	-	-17.88	-22.78	-	-34.07	-39.54

Notes: 1. the reliability of difference scores p_1 – as compared to the indicators before treatment; p_2 – as compared to the indicators 1 month after the beginning of treatment; * – $p<0.05$, ** – $p>0.05$.

2. Δ – the increase or reduction (-) in the indicator during the course of treatment as a percentage to the values before treatment

Conclusions

In the patients with prior MI, the level of increase in exercise tolerance and the reduction in NT-proBNP level depend both on the duration and type of rehabilitation treatment. Succinic acid and arginine preparations in combination with standard therapy for the patients with prior MI and decompensated HF allow improving the effectiveness of treatment within 2 months, as indicated by reduced levels of NT-proBNP and copeptin. Since copeptin is directly involved in the progression of HF, its level can be used both for the prediction of this syndrome and quality assessment of treatment performed.

Prospects for further research

Since the main limits of changes in the indicators of NT-proBNP and copeptin before and after treatment of the patients in the early and late post-infarction period complicated by decompensated HF have been determined, we plan to develop practical guidelines for using these peptides with the aim of diagnosing the progression of this syndrome in the patients whose FC was lowered and quality assessment of treatment performed.

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