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The Possibility of Non-Pharmacological Methods in Increasing Clinical Efficiency of Treating Patients with Chronic Heart Failure and Metabolic Syndrome.

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ABSTRACT

The article deals with the influence of metabolic syndrome (MS) on the clinical course, laboratory and instrumental data and the quality of life in patients with chronic heart failure (CHF). It is shown that the presence of metabolic syndrome in patients with chronic heart failure corresponds to the elevated levels of proinflammatory cytokines (interleukin-1β, interleukin-6, tumor necrosis factor), which is associated with a more severe course of chronic heart failure with more prominent symptoms. It is demonstrated that the complex treatment and rehabilitation program including dietary tips and physical training is more effective in the correction of the metabolic syndrome components and clinical symptoms of chronic heart failure than standard pharmacological therapy.

Keywords: chronic heart failure, metabolic syndrome, cytokines, NT-proBNP, rehabilitation, physical training.

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INTRODUCTION

The problem of chronic heart failure (CHF) is currently one of the most challenging pathologies [1,2]. According to the EPOCH-CHF (8 regions of Russia) and EPOCH-O-CHF (22 regions of Russia) studies, CHF was diagnosed in 7,9 million people (7,0% of the total population of the country). 4,5 percents of the population (5,1 million) had CHF of II-IV functional classes (FC) by the New York Heart Association (NYHA) classification, and 2,1% of patients (2,4 million people) suffered from most severe forms of CHF (III-IV FC) [3].

A rational approach to treatment with the assessment of all possible risks allows to greatly improve a patient's condition and lessen the severity of the course of the disease [4,5].

Lately a great interest has been taken in studying the relationship between metabolic disorders and obesity and the increase in cardiovascular complications [6,7]. Some of the risk factors for cardiovascular diseases are brought together under the term “metabolic syndrome” (MS). The prevalence of MS can be considered a pandemic: about 1,7 billion people are overweight or obese, i.e. approximately every third person in the world [8,9].

MS is characterized by the increase in the amount of visceral fat, the decrease in the sensitivity of peripheral tissues to insulin and hyperinsulinemia, which cause the development of violations of carbohydrate, fat and purine metabolism and arterial hypertension (AH) [10].

The development of the concept of MS has allowed to define an important role of hyperinsulinemia and insulin resistance in the development of CHF in patients with this syndrome [8].

AH takes 80,0% in the structure of the causes of CHF and contributes to its decompensation [2,3]. Another pathogenetic link connecting CHF and MS is the development of subclinical systemic inflammation [6,7,11,12].

Clinical guidelines for heart failure management recommend to use regular physical activity in order to increase the efficiency of the disease prevention and rehabilitation of this category of patients. It is been proved that regular physical activity improves metabolism, autonomic regulation, pulmonary ventilation, physical performance, perfusion of the heart, brain and skeletal muscles, and psycho-emotional status of the patients. As a result, the duration of the hospital stay and the need for repeated admissions to the hospital are reduced, and the quality of life (QOL) and life expectancy of patients with mild and moderate kinds of CHF [2,3,5] are improved.

An overview of recent publications has demonstrated that there are virtually no studies on the efficiency of the rehabilitation programs in patients with CHF which were designed with regard to the concomitant MS.

The aim of the study is to assess the influence of MS on the course of CHF, the results of laboratory and instrumental examinations, QOL of patients with CHF, and to develop and test a complex rehabilitation program (RP) including patients' education, physical activity and dietary recommendations developed with regard to concomitant MS.

MATERIALS AND METHODS

The study included 63 patients with CHF and MS (31 men, 32 women, an average age 64,12 ± 1,05 years). The diagnosis of CHF was made on the basis of the ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure (2016), the patients were classified using the NYHA functional classification (1994) according to the results of the six-minute test. All patients were grouped based on the functional classes (FC) as it follows: 2 patients (3,2%) had I FC, 20 patients (31,7%) - II FC, 34 patients (54,0%) - III FC, 7 patients (11,1%) - IV FC of CHF. MS was diagnosed according to the national guidelines for management of patients with MS of the Ministry of Health of the Russian Federation (2013).

According to the rehabilitation measures, 2 groups were formed. The first group consisted of 31 patients (16 men, 15 women, average age 64,06 ± 1,68 years) who took part in the complex RP for 12 months

as well as received the standard treatment of CHF. The second group consisted of 32 patients (14 men, 18 women, average age 64,19 ± 1,32 years) who received only standard therapy for 12 months and refused to take part in the RP.

With regard to the concomitant MS, a complex RP was developed which included patients' education - 5 workshops in groups of 5-6 people, lasting 60-90 minutes with a break; 4 workshops were devoted to the issues of CHF, 1 workshop – to MS, the sequence of topics of the workshops was always the same. Patients that smoked and were obese attended 1 additional workshop. All patients were given educational books, brochures, leaflets, information booklets. The complex RP also included physical training - aerobic exercise (walking at an individually selected pace under the control of heart rate for 30-40 minutes 5 days a week) - which took place for 8 weeks after the educational seminars. The patients were recommended to keep up physical training on their own later. The evaluation of the condition of cardiovascular and respiratory systems as well as the correction of the physical training were made using a cardiorespiratory analysis complex, assessing such parameters as pulse oximetry and electrocardiography during the six minute test.

Complex clinical and laboratory examination of patients conducted at the stage of enrollment and after 12 months of follow-up included:

- assessment of anthropometric parameters: waist circumference, body mass index (BMI);
- measurement of the blood pressure (BP) level taken three times;
- assessment of the level of compliance of patients suffering from chronic diseases using the questionnaire "Compliance level"(R.V. Kadyrov et al., 2014);
- evaluation of clinical manifestations severity of CHF using the scale for evaluation of the clinical condition of patients with CHF by V.Yu. Mareev (SECC);
- assessment of tolerance to physical exercise and the level of dyspnea using the six-minute test and the Borg scale;
- bioimpedance measurement using a TANITA BC body composition analyzer with the assessment of total body fat, visceral fat, and body water;
- echocardiography (echo);
- assessment of quality of life of the patients using the Minnesota living with heart failure questionnaire (MLHFQ);
- biochemical analysis of venous blood samples including determination of glucose level and the lipid profile - triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) by the direct determination using reagent kits and the MINDRAY BC 5300 automatic analyzer (Mindray, China);
- determination of the concentration of amino-terminal pro–B-type natriuretic peptide (NT-proBNP) and the levels of proinflammatory cytokines (IL-1β, IL-6, TNF-α) in the blood serum with the help of the "sandwich" solid-phase enzyme immunoassay using reagent kits and IMMULITE 2000 automatic analyzer (Siemens Diagnostics, USA).

Statistical analysis of the data was performed using STATISTICA 12.0. The quantitative data (with the normal distribution of the feature) is represented in the form of M ± Co, where M is the sample mean, Co is the standard deviation. Qualitative variables were compared using the Fisher's exact test. The comparison of the quantitative indicators was carried out using the Wilcoxon signed-rank test (for dependent variables) and the Mann-Whitney U-test (for independent groups). For the analysis of the dependencies between the parameters characterizing CHF and MS components, the parameters of clinical, instrumental and laboratory examinations of patients Spearman's nonparametric method was used. The Chaddock scale was used for the assessment of the significance of the correlation between two variables.

RESULTS AND DISCUSSION

Correlation analysis was used for the evaluation of the statistical correlation between the qualities of the test subjects in order to identify and study the link between the parameters characterizing CHF (FC, SECC, NT-proBNP, parameters of echo, six-minute test, the Borg scale, the MLHFQ questionnaire) and components of MS (waist circumference, BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), TG, HDL-C, LDL-C), the results of clinical, instrumental examinations (bioimpedance measurement) and cytokine status (IL-1β, IL-6,

TNF-α) examinations. The results are presented in Table 1.

Table 1: The results of the correlation analysis between the clinical and laboratory characteristics of the patients with CHF and MS

Parameters	FC CHF FC CHF	SECC	NT-proBNP	LV EF	6-min test	Dyspnea (Borg's scale)	MLHFQ
	R	R	R	R	R	R	R
WC	0,63	0,60	0,52	-0,51	-0,75	0,59	0,64
TG	0,35	0,39	0,40	-0,36	-0,55	0,40	0,31
HDL-C	-0,39	-0,40	-0,35	0,35	0,60	-0,33	-0,30
Endogenous fat mass	0,75	0,52	0,48	-0,67	-0,85	0,80	0,67
Body water	0,77	0,43	0,49	-0,45	-0,83	0,87	0,66
IL-1β	0,71	0,75	0,81	-0,80	-0,64	0,50	0,71
IL-6	0,89	0,88	0,90	-0,92	-0,62	0,48	0,80
TNF	0,79	0,74	0,78	-0,74	-0,68	0,45	0,74

Note. R is the value of the Spearman coefficient.

In the patients examined, multiple correlations were established between the components of MS and clinical, laboratory and instrumental markers of CHF. For instance, a strong and very strong positive correlation between such values as FC of CHF, SECC, LV EF, NT-proBNP and the levels of proinflammatory cytokines (IL-1β, IL-6, TNF) in the blood serum was found. In turn, the mass of endogenous fat and the content of the body water have a strong positive correlation with the results of six-minute test, dyspnea on the Borg scale, QOL according to the questionnaire MLHFQ.

The results of the performed correlation analysis has led to a conclusion that such components of MS as obesity with visceral fat accumulation, hypertension, impaired carbohydrate and lipid metabolism; fluid retention, activation of the systemic inflammation (increased levels of proinflammatory cytokines (IL-1β, IL-6, TNF)) have a negative impact on the course of CHF; there is a significant increase in the severity of the clinical symptoms of CHF; the cardiovascular remodeling is potentiated; there is a decrease in the exercise tolerance; which adversely affect quality of life of the patients.

The complex RP contributed greatly to the decrease in the severity of the components of MS in patients with CHF while only negative changes have been noted in patients with CHF and MS who received only standard treatment of cardiovascular pathology.

For instance, after 12 months in the group of patients with CHF and MS who participated in the complex RP the waist circumference was reduced by 6,55 cm in men (p=0,012) and by 6,58 cm (p=0,0013) in women, the BMI decreased by 1,55 kg/m2 (p<0,001).

The dynamics of the components of MS was significantly more negative for the patients with CHF and MS who received only standard treatment of cardiovascular pathology. For example, the waist circumference increased by 3,75 cm (p<0,001) in men and by 8,06 cm (p<0,001) in women. The BMI increased significantly by 1,3 kg/m2 (p<0,001) (Table 2).

After 12 months WC and BMI were significantly lower in the patients who took part in the complex RP than in the group receiving only standard pharmacological therapy (Table 2).

Table 3 shows the positive dynamics trending to significance of the lipid profile parameters in the participants of the RP.

For instance, the concentration of TG decreased by 0,13 mmol/l (p=0,053), the HDL-C concentration increased by 0,07 mmol/l (p=0,058), the LDL-C l level decreased by 0,12 mmol/l (p=0,06). In the patients who

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didn't take part in the RP the dynamics of the lipid profile values was, in turn, negative. The TG concentration increased by 0,3 mmol/l (p<0,001), the HDL cholesterol concentration decreased by 0,21 mmol/l (p<0,001), the LDL cholesterol level increased by 0,35 mmol/l (p<0,001) (Table 3).

Table 2: Dynamics of WC and BMI

Parameters	Complex RP (n=31)		Standard pharmacological therapy (n=32)		p(2-4)
	before	after 12 months	before	after 12 months	
	1	2	3	4	
WC in men, cm	106,61±11,8	100,06±7,5	106,56±8,0	110,31±7,9	<0,001
p	0,012		<0,001		
WC in women, cm	105,23±10,6	98,65±2,3	104,25±6,1	112,31±5,83	<0,001
p	0,0013		<0,001		
BMI, kg/m^2	32,39±1,1	30,84±1,0	32,16±1,3	33,46±1,1	<0,001
p	<0,001		<0,001		

Table 3: Dynamics of the lipid profile parameters

Parameters, mmol/l	Complex RP (n=31)		Standard pharmacological therapy (n=32)		p(2-4)
	before	after 12 months	before	after 12 months	
	1	2	3	4	
TG	2,22±0,05	2,09±0,04	2,26±0,05	2,56±0,02	<0,001
p	0,053		<0,001		
HDL-C	0,79±0,02	0,86±0,02	0,80±0,02	0,59±0,01	<0,001
p	0,058		<0,001		
LDL-C	3,90±0,03	3,78±0,06	3,76±0,05	4,11±0,03	<0,001
p	0,06		<0,001		

Note: p (2-4) – the differences after 12 months are significant with p<0,05.

Based on the results of the second follow-up after 12 months the levels of TG and LDL-C were significantly lower, and the HDL-C concentration was significantly higher in the group of patients who took part in the complex RP than in the group receiving only standard pharmacological therapy.

The patients with CHF and MS who took part in the complex RP changed their attitude towards smoking. The percentage of the patients who smoked dropped by 25,8% after 12 months (χ^2=6,86; p=0,032). Among the patients with CHF and MS who received only standard treatment of cardiovascular diseases, the attitude to smoking did not change (Table 4).

Table 4: Attitude to smoking

Parameters	Complex RP (n=31)				Standard pharmacological therapy (n=32)				p (3-7)
	before		after 12 months		before		after 12 months		
	1	2	3	4	5	6	7	8	
	Abs.	%	Abs.	%	Abs.	%	Abs.	%	
Smokers	17	54,8	9	29,0	18	56,3	18	56,3	<0,05
Non smokers	14	45,2	22	71	14	43,7	14	43,7	<0,05

After 12 months in the group of patients who took part in the complex RP, the average severity of clinical symptoms of CHF decreased significantly from 6,83 ± 0,24 to 5,03 ± 0,14 points on the SECC scale, i.e. in 1,4 times (p<0,001).

The dynamics of the same parameter in the group of patients who didn't participate in the RP was significantly negative: the number of points on the SECC scale rose from 6,81±0,31 to 8,53±0,27, i.e. in 1,2 times (p<0,001).

After 12 months exercise tolerance based on the results of the six minute test in the patients with CHF and MS who were the participants of the RP became significantly better: an average 6-minute walking distance changed from 222±14,8 to 263±8,5 m, i.e. the difference was 41 m (p=0,009). In the group of patients with CHF and MS who received only standard pharmacological therapy, exercise tolerance changed to the worse: an average 6-minute walking distance dropped from 221±8 to 201±9,2 m, i. e. by 20 m (p=0,0118).

In the complex RP participants, the level of dyspnea after a six-minute test assessed using the Borg scale decreased from 4,74±0,19 to 3,68±0,13, i.e. in 1,3 times (p<0,001). In the group of patients that received standard treatment only, the dynamics of the parameter in question was significantly negative, raising from 4,71±0,16 to 5,59±0,14, i.e. in 1,2 times (p<0,001).

The NT-proBNP levels of the patients that took part in the complex RP did not change significantly after 12 months: 1991±56 and 2046±41 pg/ml respectively (p=0,15); while in the patients with CHF and MS who received only standard treatment of cardiovascular pathology negative dynamics was noted with the differences trending to significance: 1995±69 to 2173±32 pg/ml (p=0,054).

After 12 months, in the participants of the rehabilitation program the activity of the systemic inflammatory response decreased: IL-1β by 7,3% (p<0,001), IL-6 by 3,4% (p<0,001), TNF by 3,1% (p=0,038) (Table 5). Dynamics of the levels of the proinflammatory cytokines in the second group was significantly negative: the average concentration of IL-1β increased by 16,3% (p<0,001), IL-6 by 4,6% (p<0,001), TNF by 4,1% (p=0,0014) (Table 5).

Table 5: Dynamics of the inflammatory cytokines

Parameters, pg/ml	Complex RP (n=31)		Standard pharmacological therapy (n=32)		p(2-4)
	before	after 12 months	before	after 12 months	
	1	2	3	4	
IL-1β	19,13±1,41	17,74±1,55	18,16±1,63	21,13±1,01	<0,001
p	<0,001		<0,001		
IL-6	31,16±1,55	30,19±1,02	31,06±1,55	32,50±1,54	<0,001
p	<0,001		<0,001		
TNF	32,16±2,75	31,13±0,96	32,25±1,81	33,59±1,38	<0,001
p	0,038		0,0014		

The results of the bioimpedance measurement in patients who took part in the complex RP have showed a decrease in the total fat by 6,07% (p<0,001), a decrease in the visceral fat by 2,55% (p<0,001), and a decrease in the body water by 4,53% (p<0,001) (Table 6). As for the second group, the results of the bioimpedance measurement have demonstrated an increase in the total fat by 4,58% (p<0,001), in the visceral fat by 4,92% (p<0,001), in the body water by 5,25% (p<0,001) (Table 6).

Table 6: Dynamics of the body composition parameters

Parameters	Complex RP (n=31)		Standard pharmacological therapy (n=32)	
	before	after 12 months	before	after 12 months
Total fat, %	37,91±0,89	31,84±0,24	37,44±0,87	42,02±0,72
Endogenous fat, %	16,09±0,59	13,54±0,27	16,05±0,73	20,97±0,68
Body water, %	45,75±1,27	48,77±0,83	46,13±1,09	51,38±0,99

According to the echo results, there was no significant difference in the parameters under study for the patients of the first group. For example, the average LV EF was 40,03±0,69% initially and 40,74±0,56% after 12 months of the rehabilitation (p=0,69).

It's worth noting that there was certain negative dynamics of the echo parameters in the second group trending to significance (p≥0,05) (Table 7).

Table 7: Dynamics of the echocardiography parameters

Parameters	Complex RP (n=31)		Standard pharmacological therapy (n=32)	
	before	after 12 months	before	after 12 months
LVEDD, cm	5,63±0,25	5,60±0,34	5,62±0,33	5,84±0,47
	p=0,56		p=0,058	
LVESD, cm	4,34±0,57	4,37±0,26	4,32±0,49	4,38±0,12
	p=0,61		p=0,059	
LA, cm	4,36±0,44	4,32±0,61	4,34±0,66	4,40±0,59
	p=0,49		p=0,058	
LV EF, %	40,03±0,69	40,74±0,56	40,04±0,81	38,86±0,46
	p=0,69		p=0,06	

The MLHFQ score of the patients that took part in the complex RP decreased significantly from 63,13±2,72 to 50,03±1,02 points (p<0,001), which is considered to be positive dynamics. As for the patients who only received standard treatment, there was a statistically significant increase of the MLHFQ score from 63,22±2,05 to 81,28±1,64 points (p<0,001), which means it changed to the worse.

The results of the trial of the rehabilitation program for patients with CHF adapted with regard to concomitant MS demonstrated clinical efficiency of the suggested approach in the correction of the parameters of the clinical, instrumental, laboratory status of the patients. It should be emphasized that weight loss was due to the decrease in the body water and fat mass confirmed by the data obtained from bioimpedance measurements. The progress of cardiac and vascular remodeling seemed to slow down which was demonstrated by the echo measurements and the NT-proBNP serum levels. Positive dynamics of the clinical and functional state parameters of the patients who participated in the complex rehabilitation program was accompanied by a decrease in the activity of the systemic inflammatory response, one of the key pathogenetic links connecting CHF and MS.

As for the patients with CHF and MS who received only standard treatment of cardiovascular pathology, negative dynamics of the parameters in question was noted after 12 months, which shows that it's highly advisable to use the complex RP designed with regard to the concomitant pathology in order to improve the somatic status, quality of life and psychosocial adaptation of this category of patients.

CONCLUSIONS

- Obesity with the accumulation of predominantly endogenous fat, dyslipidemia, fluid retention, increased activity of the systemic inflammatory response in patients with MS cause a more severe course of CHF with prominent clinical manifestations and a lower QOL of the patients.
- Complex rehabilitation program for patients with CHF and MS including patients' education, physical training and dietary recommendations contributes to the correction of MS components that tend to be reversible.
- Complex rehabilitation program contributes to a significant improvement in the clinical course of CHF, slowing down the progression of cardiovascular remodeling, reducing the activity of the systemic inflammatory response, reducing the total body fat mass, the endogenous fat mass, the body water content, and increasing the exercise tolerance.
- Complex rehabilitation program allowed to improve QOL and physical capabilities of the patients with CHF.

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