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EVALUATION OF THE EFFECTIVENESS OF LIVERIN IN THE COMPLEX TREATMENT OF VARIOUS HEMODYNAMIC PHENOTYPES OF CHRONIC HEART FAILURE

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ABSTRACT

Aim of the study: to evaluate the effectiveness of Liverin's influence on the processes of fibrosis of the heart and target organs, including the liver, in different hemodynamic phenotypes of chronic heart failure.
Materials and methods: The effect of the drug Liverin on the heart and target organs, including the liver, was studied in 123 patients with CHF with various types of left ventricular ejection fraction. The patients were divided into 2 groups, the 1st group included 64 patients, the 2nd group - 59 patients with CHF. Patients of the 1st group with CHF against the background of standard treatment received the drug Liverin at a dose of 600 mg - 2 ml intravenously for 7 days, after which this drug was prescribed 2 capsules 3 times a day for 3 months. Patients in Group 2 received only standard treatment. After the therapy, 3 months later, the function of the right chambers of heart were assessed using echocardiography and the degree of liver fibrosis was assessed by liver elastography and the levels of galectin-3 and aldosterone in the blood serum were determined. **Results:** Observation showed that in patients of the 1st group, against the background of the treatment (standard treatment + liverin), central hemodynamic indices improved, there was a significant regression of left ventricular hypertrophy, mean liver density (MLD) and indicators on the Metavir scale (F) decreased, the levels of galectin - 3 and

aldosterone in the blood serum decreased significantly, which reflect the activity of fibrotic processes in the body (p <0.001). And also there was an improvement in the clinical and functional state of patients against the background of the treatment, which was reflected by a significant decrease in the diameter of the inferior vena cava and signs of its collapse during a deep breath, as well as signs of pulmonary hypertension in this patient. Patients of group 2 showed a partial improvement in clinical and functional state against the background of blockade of neurohormonal activation, but there was no statistically significant dynamics of indicators of MLD, F, pressure and volume of the right heart. **Conclusions:** For the early diagnosis of fibrosis of the heart and liver in patients with various hemodynamic types of CHF, it is necessary to perform echocardiography and elastography of the liver and determine the level of galectin-3 and aldosterone in the blood serum. The use of liverin as part of standard therapy for CHF reduces the processes of fibrosis of the heart and liver, leads to regression of cardiac remodeling, as well as an improvement in the clinical and functional state of patients.

Key words: chronic heart failure, fibrosis process, liver elastography, galectin - 3, aldosterone, Metavir scale

INTRODUCTION

Chronic heart failure (CHF) is a systemic disease, and for its treatment it is advisable to use medication groups that block all neurohormones involved in the pathogenesis of the disease in appropriate amounts and in appropriate proportions [4, 5]. Until the clinical signs of the disease appear, the renin-angiotensin-aldosterone (RAA) and sympathoadrenal (SA) systems in the body are activated in conjunction with a number of neurohormones and growth factors, causing remodeling of the cardiovascular system [3]. According to the latest recommendations of the European and Russian Association of Cardiologists, in the absence of absolute contraindications, the following neuromodulators - angiotensin converting enzyme (ACE) inhibitor or angiotensin (AT) II AT1 receptor antagonists (ARA), beta-adrenoblockers (β-blockers), mineralocorticoid receptor antagonists (MCRA), and in special cases diuretics, cardiac glycosides, peripheral vasodilators, antiarrhythmic drugs, etc. are prescribed to reduce clinical endpoints (mortality, hospitalization, need to call an ambulance) in patients with CHF [8].

Indeed, ACE inhibitors are the most appropriate drug to be prescribed to all patients diagnosed with CHF regardless of etiology and stage [4, 13]. However, their long-term use in clinical practice has been shown to increase aldosterone synthesis by ricochet pathways. This is explained by the presence of other factors that activate aldosterone synthesis that are not dependent on the ACE pathway (mainly the activation of tissue RAA system components) [2]. In this regard, in recent years, ARA representatives have been widely used in the treatment of CHF. The organ-protective and antifibrotic effects of this drug have been proven in major clinical studies such as CHARM, SOLVD, ELITE II, which have shown a significant reduction in hospital admissions and overall mortality due to their

neuromodulatory and pleiotropic effects. The pleiotropic effect of ARA is explained by its stimulation of AT2 and PPAR-γ receptors in muscle, fat, and hepatocytes [7].

It is known that as the CHF worsens, the SA system becomes more active. Combined administration of b-blockers with ACE inhibitors in the treatment of CHF leads to regression of myocardial remodeling, increased left ventricular ejection fraction (LVEF), slowing disease progression, hospitalization, and a sharp decrease in overall mortality [11, 20]. In cases where it is not possible to use drugs of this group, ivabradine, which is an inhibitor of the sinus node If - channels, is used to reduce the number of heart contractions in patients with CHF [5 – 7, 27, 28].

Secondary hyperaldosteronism (SHA), which occurs in the body, also plays an important role in the development of CHF and injury to target organs [30]. The use of ACE inhibitors, along with ARA, MKRA, in order to reduce the activity of advanced fibrous processes in organs and tissues due to SHA significantly reduces complications of the disease and the overall risk of death [8, 10, 13-15].

However, despite the widespread use of proven drugs in clinical practice, the incidence of CHF-related deaths and hospitalizations has not decreased. Timely detection of comorbidities and pathological abnormalities in the target organs in patients with CHF, the correct choice of alternative treatment methods can be one of the solutions to this situation. Consequently, in the St. Petersburg Register of the Russian Federation, 68% of patients with CHF over the age of 75 had 2 or more comorbidities, 38% had 5 or more comorbidities, similar information was found in the United States, and about 89% of cases non-cardiological drugs have been prescribed for clinical stabilization and to improve quality of life [3, 22]. Indeed, the results of a large randomized study found that extracardiac factors cause disease decompensation in 40–70% of cases in patients with emergency hospitalization CHF. This condition is more common in CHF patients with preserved and intermediate LVEF [1, 9, 25, 29].

Therefore, the use in clinical practice of drugs that reduce the activity of fibrous processes, which play an important role in the pathogenesis of the disease, along with standard treatment of CHF, may lead improvements in clinical outcomes.

The aim of the study. Evaluation of the effect of liverin on the processes of fibrosis in the heart and target organs, including the liver, in different hemodynamic phenotypes of CHF.

Materials and methods of research. A total of 123 patients diagnosed with CHF were included in the study. Diagnosis of CHF in the patients included in the

study was based on their complaints, anamnesis, objective examination and laboratory tests, the "Recommendations for the diagnosis and treatment of acute and chronic heart failure" of the European and Russian Association of Cardiologists, the New York Association of Cardiologists (New York). Heart Association, 1964) as well as the 6-minute walking test. The duration of CHF in patients was 2–6 years, with an average of 2.7 ± 1.1 years. In all cases, the development of CHF was caused by CHD and AH.

Patients involved in the study were randomly assigned to two groups. The 1st group consisted of 64 patients with CHF (22 patients with decreased LVEF, 20 with intermediate LVEF and 22 CHF patients with preserved LVEF). The 2nd group consisted of 59 CHF patients (19 patients with decreased LVEF, 18 with intermediate LVEF and 22 CHF patients with preserved LVEF). A general description of the patients is given in Table 1.

Table 1

A general description of patients with CHF

Indices	1st group, n=64		2nd, n=59	
	CHF II ФС	CHF III ФС	CHF II ФС	CHF III ФС
Age, years	62.0±1.1	63.5±1.5	66.0±1.5	64.2±1.7
BMI, kg/m^2	29.1±0.1	31.9±1.0*	30.6±0.9	28.8±0.8
LVEF, %	46.7±1.7	45.9±1.4	46.4±1.7	45.8±1.8
6MWT, m	351.5±6.4	210.8±7.2**	350.0±6.5	235.9±9.0**
CCAS, ball	5.1±0.1	8.3±0.1**	5.1±0.1	7.9±0.1**
Quality of Life, ball	45.0±1.1	59.2±1.4**	45.9±1.4	54.4±1.7**
ACE inhibitors	18 (54.5%)	17 (54.8%)	16 (57.1%)	18 (58.1%)
ARA	15 (45.5%)	14 (45.2%)	12 (42.9%)	13 (41.9%)
β – blockers	26 (78.8%)	25 (80.6%)	21 (75.0%)	24 (77.4%)
MCRA	25 (75.8%)	27 (87.1%)	21 (75.0%)	25 (80.6%)
Diuretics	21 (63.6%)	24 (77.4%)	19 (67.9%)	25 (80.6%)
Antifibrotic treatment: Liverin	33 (100%)	31 (100%)	-	-

Note: BMI – body mass index, LVEF - left ventricular ejection fraction, 6MWT – six minute walk test, CCAS - clinical condition assessment scale, ACE inhibitors – angiotensin-converting enzyme inhibitor, ARA - angiotensin receptor antagonists, β-blockers – beta adrenoblockers, MCRA - mineralocorticoid receptor antagonist; * - significance of differences between II and III ФС indices, $p<0.01$; ** - $p<0.001$.

Exclusion criteria: patients with acute MI and unstable angina, arterial hypotension, II - III degree atrioventricular block, rheumatic and congenital heart defects, strike and its complications, diffuse autoimmune and connective tissue diseases, acute and chronic inflammatory diseases, kidney disease with cardiac

dysfunction - cases of advanced chronic kidney disease, diseases of the parenchyma with liver failure, exacerbation of chronic obstructive pulmonary disease, bronchial asthma, severe respiratory failure, oncological, mental illness, alcoholism and other serious comorbidities.

In the patients in the study, all examinations were performed within the first 3 days of hospitalization and subsequent examinations after 3 months of prospective follow-up. In all patients, general analysis of blood and urine, biochemical analysis of blood, coagulogram were performed, lipid spectrum was examined, and levels of aldosterone and galectin – 3 were evaluated using enzyme-linked immunosorbent assay. All patients underwent ECG, ExoKG, and liver elastography investigations.

Enzyme-linked immunosorbent assays were performed in the laboratory of the Republican Scientific-Practical Medical Center of Pediatrics using the device Cobas-6000 (Roshe, Germany).

Serum aldosterone levels were measured by enzyme-linked immunosorbent assay using DBC Aldosterone ELISA (Canada). The test reagent used in the study to detect serum aldosterone ranged from 9.1 to 1000. Sensitivity 9.1. reference (control group) value 86.8 [47.8; 199.1] ng/ml.

Quantitative measurement of G-3 in blood serum was performed by the method of enzyme-linked immunosorbent assay using human reagent Galectin-3 ELISA (Germany). The control sensitivity was 0.29 ng/ml, and the reference was was 8.6 [3.7; 11.7] ng/ml.

Echocardiography (EchoCG) was made using transthoracic access in PHILIPS Affiniti 70 (Netherlands) device, frequency - 5-1 MHz. During echocardiography M and B modes were used and recommendations of American Society of Echocardiography (ASE, 2015) were followed. During investigation following were measured: end diastolic and end systolic size of LV (EDS and ESS), end diastolic and end systolic volume of LV (EDV and ESV), posterior wall thickness of LV (LVPWT) and interventricular septal thickness (IVST), left atrium (LA) size, left ventricle ejection fraction (LVEF), stoke volume (SV), difference between EDV and ESV, left ventricular mass (LVM) using Devereux R.B. formula - LVM =0,8 [1,04 (EDS + LVPWT + IVST)3 – EDS3] + 0,6 g.

LVM index (LVMI) using LVMI = LVM/S (body), g/m2 formula.

In order to exactly evaluate indices of central hemodynamics it was divided into body surface area. Left ventricular hypertrophy was considered when LVMI was ≥115g/m2 in men and ≥95g/m2 women. Remodeling of left ventricle was determined based on relative thickness of the ventricle wall (LVRWT =

IVST+LVPWT/EDS). The normative value of LVRWT ranged from 0.22 to 0.42. Myocardial structural geometric remodeling was determined using A. Ganau's formula, where: the normative geometry of the left ventricle was LVMI = N, LVRWT <0.42; concentric hypertrophy LVMI> N, LVRWT> 0.42; concentric remodeling LVMI = N, LVRWT> 0.42; eccentric hypertrophy LVMI> N, LVRWT <0.42. In this study, the diameter of the inferior vena cava (IVC) (N <21 mm) and its collapse (compression of more than 50% of normal) were determined in the subcostal position during deep breathing. We also indirectly assessed the increase in pressure in the right ventricle and pulmonary artery, depending on the dilation of the IVC, right ventricle (N <30 mm), and atrium (normally its diameter is up to 44 mm).

Liver elastogram was performed in real-time using two-dimensional motion wave elastography with the help of a Phillips AFFINITI 70G instrument. It is known that in pathological conditions that cause diffuse changes in the liver, its density is directly related to fibrous processes. The degree of fibrosis is one of the main criteria for determining the severity of the disease. The procedure is performed on an empty stomach 4–6 h after the patient had eaten. This is because the livers stiffness may change slightly in response to increased blood flow to the organ after a meal. It is recommended that the patient lie on his back and place his right hand behind his head so that the rib space is in an extended position. He is then asked to exhale slowly and to stop the exhalation process for 1-2 seconds during exhalation, and liver stiffness was assessed. Then, the area to be examined should be directed 1.5 - 2.0 cm from the Glisson capsule to the liver parenchyma, and its capsule should look like a clear white line perpendicular to the direction of the ultrasound rays. This situation is very important. This is because in this case the reflected signal does not reduce its intensity and returns to the transmitter without significant losses.

Fibrous changes in the liver are assessed using the METAVIR (Meta - analysis of histological data in viral hepatitis) scale (Table 2).

Table 2

Stages of liver fibrosis according to METAVIR scale

Fibrosis stage	Mean liver stiffness, kPa	Stages
No fibrosis	<5.8	F 0
Mild fibrosis	5.9 – 7.2	F 1
Moderate fibrosis	7.3 – 9.5	F 2
Severe fibrosis	9.6 – 12.5	F 3
Cirrhosis	> 12.5	F 4

On liver elastometry using the METAVIR scale, fibrosis process was considered to be nonexistent when mean liver stiffness was less than 5.8 kP.

Patients in both groups were prescribed as standard treatment - ACE inhibitors or AT II AT1 receptor antagonists - azilsartan medoxomil (edarbi), b-blockers (bisoprolol), MCRA representative spironolactone (verospiron) or eplerenone as standard treatment according to the recommendation of the European and Russian Cardiologists Association (2016). In order to evaluate the effectiveness of the antifibrotic drug - Liverin, patients of the 1st group were prescribed Liverin 600 mg - 2.0 ml intravenously for 7 days, then 2 capsules 3 times a day for 3 months. Patients of the 2nd group received only the standard treatment.

The dynamics of the clinical condition of all patients under observation was assessed during re-referral (outpatient and inpatient) and sing communication means. The study examined the clinical condition of patients (CCAS as modified by V.Yu. Mareev, 2000), quality of life (Minnesot Questionnaire), and resistance to physical exertion (6MWT).

The data obtained in the study were statistically processed using the computer program Excel - 2010, and the differences and correlations in the groups were identified. Based on the results of the study, a conclusion and practical recommendations were developed.

Research results. The study of central hemodynamic parameters in patients with CHF in the 1st group revealed the following (Table 3).

Table 3

Dynamics of central hemodynamic parameters in patients with CHF who were prescribed Liverin in addition to the standard treatment

Indices	CHF II FC, n=33		CHF III FC, n=31	
	Before the treatment	After the treatment	Before the treatment	After the treatment
EDV, ml	164.3±7.5	156.3±7.5	177.5±8.8	172.4±8.5
ESV, ml	94.4±6.4	85.6±7.2	103.6±8.3	98.5±8.2
LVEF, %	46.7±1.1	49.7±1.0*	45.9±1.1	48.0±1.0*
IVST, mm	11.2±0.2	11.1±0.2	11.3±0.2	11.1±0.2
LVPWT, mm	12.2±0.3	12.1±0.3	12.3±0.2	12.1±0.2
LVMI, g/m^2	249.4±8.5	246.3±7.4	267.6±11.3	263.1±9.4
LVRWT, units	0.41±0.01	0.40±0.01	0.43±0.008	0.41±0.007*

Note: * - significance of difference between indices before and after the treatment, $p<0.05$.

Regression of cardiac remodeling indices was observed in patients of the 1st group receiving Liverin in addition to the standard treatment after 3 months of prospective follow-up. Namely, in CHF patients with II FC EDV and ESV values decreased from 164.3±7.5 to 156.3±7.5 ml and from 94.4±6.4 to 85.6±7.2 ml respectively. While in CHF patients with III FC, EDV and ESV values decreased respectively from 177.5±8.8 to 172.4±8.5 ml and from 103.6±8.3 to 98.5±8.2 ml. Accordingly, LVEF values reliably increased from 46.7±1.1 to 49.7±1.0 and from 45.9±1.1 to 48.0±1.0% in respective functional class patients ($p<0.05$). Left ventricular hypertrophy in patients with CHF plays an important role in the development of adverse complications of the disease. In patients of this group left ventricular hypertrophy indicators – e.i. IVST, LVPWT, LVRWT and LVMI decreased in II FC patients respectively from 11.2±0.2 to 11.1±0.2, from 12.2±0.3 to 12.1±0.3, from 0.41±0.01 to 0.40±0.01 and from 249.4±8.5 to 246.3±7.4 g/m^2; while in III FC patients they changed from 11.3±0.2 to 11.1±0.2, from 12.3±0.2 to 12.1±0.2, from 0.43±0.008 to 0.41±0.007 ($p<0.05$) and from 267.6±11.3 to 263.1±9.4 g/m^2.

Table 4

Dynamics of central hemodynamic parameters in patients with CHF who were prescribed the standard treatment

Indices	CHF II FC, n=28		CHF III FC, n=31	
	Before the treatment	After the treatment	Before the treatment	After the treatment
EDV, ml	166.3±8.4	164.2±8.2	191.0±10.7	189.0±10.2
ESV, ml	98.0±8.8	96.0±8.7	118.0±10.0	116.7±10.1
LVEF, %	46.4±1.7	47.3±1.2	45.9±1.8	46.5±1.8
IVST, mm	10.6±0.1	10.9±0.1*	11.1±0.1	11.2±0.2
LVPWT, mm	11.6±0.1	11.8±0.1	12.2±0.2	12.3±0.1
LVMI, g/m^2	246.0±7.5	247.9±7.1	282.1±9.5	285.1±9.5
LVRWT, units	0.40±0.01	0.41±0.01	0.43±0.02	0.43±0.01

Note: * - significance of difference between indices before and after the treatment, $p<0.05$.

Standard treatment was prescribed to the patients of the 2nd group for three months. In II FC patients of this group, EDV and ESV values decreased from 166.3±8.4 to 164.2±8.2 ml and from 98.0±8.8 to 96.0±8.7 ml respectively. While in CHF patients with III FC, EDV and ESV values decreased respectively from 191.0±10.7 to 189.0±10.2 ml and from 118.0±10.0 to 116.7±10.1 ml. Accordingly, LVEF values increased from 46.4±1.7 to 47.3±1.2 and from 45.9±1.8 to 46.5±1.6% in respective functional class patients, although changes were not statistically significant. In II and III FC patients of this group IVST and LVPWT values increased from 10.6±0.1 to 10.9±0.1, from 11.6±0.1 to 11.8±0.1, from

11.1±0.1 to 11.2±0.2 and from 12.2±0.2 to 12.3±0.1 mm respectively. LVMI values increased respectively from 246.0±7.5 to 247.9±7.1 and from 282.1±9.5 to 285.1±9.5 g/m^2 ra in II and III FC of the disease. LVRWT values also increased in II FC patients from 0.40±0.01 to 0.41±0.01, while in III FC patients they did not change (Table 4).

In the next phase of the study, we evaluated the effect of the drug Liverin on the activity of the right ventricle and the target organs, especially fibrosis processes in the liver in patients with CHF (Table 5).

Table 5

Dynamics of indicators of activity of right chambers of the heart and fibrosis processes in the liver in patients with CHF under the influence of the drug Liverin

Indices	CHF II FC, n=33		CHF III FC, n=31	
	Before the treatment	After the treatment	Before the treatment	After the treatment
Right article, mm (transverse size)	43.6±0.6	42.6±0.6	46.7±0.5	46.5±0.5
Right ventricle, mm	31.8±0.6	30.9±0.6	34.2±0.6	33.8±0.6
Left ventricle, mm	40.0±0.7	39.1±0.7	43.3±0.6	42.9±0.6
Inferior vena cava, mm	21.9±0.3	19.9±0.3***	23.3±0.3	22.2±0.3*
Collapse of inferior vena cava, (>50%)	17.4±0.3	15.5±0.4***	19.0±0.4	18.0±0.4
Mean pressure in pulmonary artery, mm. of mercury	19.4±0.7	16.4±0.6**	21.9±0.6	19.8±0.5*
Mean liver stiffness, kPa	7.0±0.1	6.3±0.1***	7.8±0.1	7.4±0.1**
METAVIR scale	1.33±0.1	0.89±0.1***	1.90±0.1	1.50±0.1**
Galectin – 3, ng/ml	16.0±0.7	12.5±0.7**	24.7±0.9	20.6±0.8**
Aldosterone, ng/ml	459.2±14.2	417.2±12.2*	577.6±14.6	504.6±12.4***

Note: kPa – Kilopascal, * - significance of difference between indices before and after the treatment, p<0.05; **- p<0.01; ***- p<0.001.

On the basis of the treatment statistically significant decrease in mean liver stiffness, and METAVIR scale. Namely in II and III FC patients of the 1st group mean liver stiffness levels changed from 7.0±0.1 to 6.3±0.1 (p<0.001) and from 7.8±0.1 to 7.4±0.1 (p<0.01) kPa respectively. Stage of fibrosis (F) according to the METAVIR scale changed respectively from 1.33±0.1 to 0.89±0.07 (p<0.001) and from 1.90±0.1 to 1.50±0.1 (p<0.01) in II and III FC of the disease. In this group of patients, the level of fibrosis processes in the liver correlated with the activation of

a number of neurohormones in the serum. Serum levels of G-3 and aldosterone reliably decreased respectively from 16.0 ± 0.7 to 12.5 ± 0.7 (p <0.01), from 459.2 ± 14.2 to 417.2 ± 12.2 ng / ml (p <0.05), from 24.7 ± 0.9 to 20.6 ± 0.8 (p <0.01) and from 577.6 ± 14.6 to 504.6 ± 12.4 ng/ml (p <0.001) after the treatment of CHF II and III FC. In this group of patients, the level of fibrosis in the liver and the activity of neurohormones were associated with a severity of the disease, in particular, congestiontion in the large circulatory system, accompanied by strain on the right side of the heart. Namely, dimensions of right atrium and ventricle, left atrium decreased respectively from 43.6±0.6 to 42.6±0.6, from 31.8±0.6 to 30.9±0.6, from 40.0±0.6 to 39.1±0.7 mm, from 46.7±0.5 to 46.5±0.5, from 34.2±0.6 to 33.8±0.6 and from 43.3±0.6 to 42.9±0.6 mm in II and III FC of the disease. Moreover, diameter of inferior vena cava reliably decreased from 21.9±0.3 to 19.9±0.3 (p<0.001) and from 23.3±0.3 to 22.2±0.3 (p<0.05) mm respectively in II and III FC of the disease. Initially, collaps of inferior vena cava was observed in 21 (63.6%) and 13 (41.9%) patients with respective functional classes, after the treatment the values increased respectively to 78.8 and 48.4%. It is known that in patients with CHF, a 50% reduction in the collapse of the inferior vena cava during deep breathing indirectly indicates a volume and pressure strain on the right side of the heart. After the treatment, statistically significant decrease of inferior vena cava and pulmonary pressure values respectively from 17.4±0.3 to 15.5±0.4 (p<0.001) and 19.4±0.7 дан 16.4±0.6 (p<0.01) mm.hg in II FC and from 19.0±0.4 to 18.0±0.4 mm and from 21.9±0.6 to 19.8±0.5 (p<0.05) mm.hg in III FC. Before the treatment, among patients of the 1st group with II and III FC respectively 7 (21.2%) and 13 (41.9 %) patients had mild pulmonary hypertension (pressure in pulmonary artery>25 mm.hg.). After the treatment no pulmonary hypertension was found in in CHF patients of II FC. In III FC patients only 4 (12.9%) had pulmonary hypertension, which means 29.0% decrease (Table 5).

Table 6

Dynamics of indicators of activity of right chambers of the heart and fibrosis processes in the liver in patients with CHF who were prescribed standard treatment

Indices	CHF II FC, n=28		CHF III FC, n=31	
	Before the treatment	After the treatment	Before the treatment	After the treatment
Right article, mm (transverse size)	44.6±0.4	43.7±0.5	46.1±0.7	46.2±0.7
Right vetricle, mm	34.0±0.7	33.1±0.7	34.5±0.7	35.0±0.6
Left ventricle, mm	41.5±0.7	40.6±0.7	42.8±0.9	42.9±0.9
Inferior vena cava, mm	22.0±0.3	21.0±0.3*	23.2±0.3	23.3±0.3
Collaps of inferior vena cava, (>50%)	19.1±0.5	18.0±0.5	19.2±0.5	19.5±0.5

Mean pressure in pulmonary artery, mm. of mercury	20.6±0.8	20.3±0.7	21.7±0.7	22.0±0.7
Mean liver stiffness, kPa	7.3±0.08	7.2±0.1	7.6±0.1	7.5±0.1
METAVIR scale	1.5±0.1	1.4±0.07	1.70±0.08	1.65±0.09
Galectin – 3, ng/ml	17.0±0.8	15.7±0.8	23.9±0.8	22.0±0.8
Aldosterone, ng/ml	467.2±13.1	448.0±11.1	586.1±12.1	562.1±12.0

Note: kPa – Kilopascal, * - significance of difference between indices before and after the treatment, $p<0.05$; **- $p<0.01$; ***- $p<0.001$.

As a result of treatment, inferior vena cava diameter decreased from 22.0±0.3 to 21.0±0.3 ($p<0.05$) mm in II patients of the 2nd group. In III FC patients however, diameter of inferior vena cava increased from 23.2±0.3 to 23.3±0.3 mm. Before the treatment, inferior vena cava collapse was observed in 10 patients in each sub-group of II and III FC. After the treatment among III FC patients the number decreased down to six, while in II FC patients it remained unchanged.

On the basis of the treatment statistically significant decrease in mean liver stiffness, and METAVIR scale (F) in II and III FC patients of the 2nd group decreased respectively from 7.3±0.08 to 7.2±0.1, from 7.6±0.1 to 7.5±0.1 kPa, from 1.50±0.1 to 1.40±0.07 and from 1.70±0.08 to 1.60±0.09. In II and III FC patients of this group, serum levels of G-3 and aldosterone reliably decreased from 17.0±0.8 to 15.7±0.8, from 467.2±13.1 to 448.0±11.1 ng/ml, from 23.9±0.8 to 22.0±0.8 an from 586.1±12.1 to 562.1±12.0 ng/ml respectively. In II FC patients of this group, dimensions of right atrium and ventricle, left atrium decreased respectively from 44.6±0.4 to 43.7±0.5, from 34.0±0.7 to 33.1±0.7 and from 41.5±0.7 to 40.6±0.7 mm. On the contrary, these values increased respectively from 46.1±0.7 to 46.2±0.7, from 34.5±0.7 to 35.0±0.6 and from 42.8±0.9 to 42.9±0.9 mm in III FC patients. As a result of treatment, inferior vena cava diameter decreased from 22.0±0.3 to 21.0±0.3 ($p<0.05$) mm in II patients of the 2nd group. In III FC patients however, diameter of inferior vena cava increased from 23.2±0.3 to 23.3±0.3 mm. Before the treatment, inferior vena cava collapse was observed in 10 patients in each sub-group of II and III FC. After the treatment among III FC patients the number decreased down to six, while in II FC patients it remained unchanged. In this group pressure in pulmonary artery increased from 20.6±0.8 to 20.3±0.7 mm.hg. in II FC patients, while it increased from 21.7±0.7 to 22.0±0.7 mm.hg. in III FC patients. Before the treatment, 9 patients of the 2nd group of II FC had mild pulmonary hypertension. After the treatment only in 2 patients pulmonary hypertension persisted. In III FC patients, in contrast, number of patients with pulmonary hypertension increased from 11 to 16 (Table 6).

A comparison of the clinical condition, quality of life and resistance to physical activity of the patients involved in the study revealed the following (Table 7, 8).

Table 7

Dynamics of clinical and functional status of patients with CHF who were prescribed Liverin in addition to the standard treatment

Indices	CHF II FC, n=33		CHF III FC, n=31	
	Before the treatment	After the treatment	Before the treatment	After the treatment
CCAS, ball	5.1±0.2	4.1±0.2**	8.3±0.1	7.0±0.2***
Quality of life, ball	45.0±1.1	32.8±1.1***	59.2±1.4	46.2±1.4***
6MWT, meters	351.5±6.4	385.8±6.5***	210.8±7.2	254.0±7.4***

Note: CCAS – clinical condition assessment scale, 6MWT – six minute walk test; ** - significance of difference between indices before and after the treatment, p< 0.01; *** - p< 0.001.

As a result of the treatment values of CCAS and Quality of Life decreased respectively from 5.1±0.2 to 4.1±0.2 (p<0.01), form 45.0±1.1 to 32.8±1.1 (p<0.001), from 8.3±0.1 to 7.0±0.2 (p<0.001) and from 59.2±1.4 to 46.2±1.4 (p<0.001) ball in II and III FC of CHF patients of the 1st group. Meanwhile, tolerance to physical activity reliably increased respectively from 351.5±6.4 to 385.8±6.5 (p<0.001) and from 210.8±7.2 to 254.0±7.4 (p<0.001) meters.

Table 8

Dynamics of clinical and functional status of patients with CHF who were prescribed the standard treatment

Indices	CHF II FC, n=28		CHF III FC, n=31	
	Before the treatment	After the treatment	Before the treatment	After the treatment
CCAS, ball	5.1±0.1	4.5±0.2*	7.9±0.1	7.5±0.2
Quality of life, ball	45.7±1.4	39.8±1.4**	54.4±1.7	48.2±1.4**
6MWT, meters	350.0±6.5	371.1±6.6*	235.9±7.8	257.0±9.0

Note: CCAS – clinical condition assessment scale, 6MWT – six minute walk test; ** - significance of difference between indices before and after the treatment, p< 0.01; *** - p< 0.001.

As a result of the treatment values of CCAS and Quality of Life decreased respectively from 5.1±0.2 to 4.5±0.2 (p<0.05), form 45.7±1.4 to 39.8±1.4 (p<0.01), from 7.9±0.1 to 7.5±0.2 and from 54.4±1.7 to 48.2±1.4 (p<0.01) ball in II and III FC of CHF patients of the 2nd group. Meanwhile, tolerance to physical

activity increased respectively from 350.0±6.5 to 371.1±6.6 ($p<0.05$) and from 235.9±7.8 to 257.0±9.0 meters.

Discussion. Patients with CHF develop fibrous processes not only in the cardiovascular system, but also in a number of target organs, especially the liver, due to chronic activation of the sympathoadrenal and local concentric circulatory RAA system. It is known that the functional state of the liver, fibrous processes in it play an important role in the course of the disease and the occurrence of unpleasant complications, [16, 17, 26]. Naturally, its consideration in the treatment of the disease leads to an improvement in the clinical condition of patients. Recent studies have examined the effectiveness of the Liverin to reduce fibrous processes in the liver, the effect of which is assessed by hepatocyte necrosis and inflammation, a decrease in fibrous processes through laboratory tests and fibroscan examination [21]. It is known that transforming growth factor (TGF-b1) is actively involved in cell proliferation, apoptosis, collagen formation and inflammatory processes in the body [12, 23]. Chinese scientists Huang and Chen (2013) noted that Liverin reduces the process of fibrosis in organs and tissues by reducing the expression of TGF-b1, which is representative of cytokines. According to the Beijing Medical University College of Clinical Medicine and Shanghai University Hospital, the oxymatrin alkaloid has been shown to reduce various arrhythmias in patients with cardiovascular disease. This effect of the drug was explained by scientists with a decrease in the activity of the inflammatory process, blockage of sodium and calcium channels [4, 18]. In the 1st group patients of our study effective blockade of the neurohormonal system on the basis of standard treatment and improvement of central hemodynamics, reliable regression of left ventricular hypertrophy as a result of the drug was observed, and we associated this with a decrease in myocardial fibrosis and left ventricular relaxation. No such statistically significant dynamics were observed in patients of the 2nd group, who did not receive the medication Liverin.

Although there are theoretical data that Liverin reduces fibrous processes in the body, the medication was studies in very few studies in practice [4, 21]. The efficacy of the drug Liverin (oxymatrin) in the treatment of pneumonia caused by a new coronavirus infection in China has been studied and has been used in combination with drugs of national recommendation approved in experimental models. Decreased pathological lung injury and viral load, decrease in the amount IL-6 and -10 as well as TNF-α in the lung tissue, and improvement in the ratio of lymphocytes in the peripheral blood were observed patients to whom Liverin was ordered [31]. Based on the results of this study, the efficacy of the drug Liverin was studied in 40 patients with acute coronavirus infection treated at the Jingzhou

Infectious Diseases Hospital from January 30 to March 21, 2020. It has been used in combination with drugs manufactured by Chinese and European pharmaceutical companies in accordance with the national recommendation for the diagnosis and treatment of new coronavirus infection. In patients treated with Liverin, the coronavirus infection test was negative, patients had a positive change in clinical signs, normalized serum lymphocyte ratio and decreased C-reactive protein on the 10th day of treatment. Moreover, it was observed that lung tissue lesions - fibrotic shadows - in this group of patients decreased more rapidly in dynamics than in other patients. In patients who did not receive Liverin in this hospital, but who received arbidol, kaletra, and other well-known antiviral drugs instead, no positive results typical of Liverin injection were observed during the same period [24, 31]. The level of fibrosis in the liver and the activity of neurohormones in the patients involved in our study were found to be consistent with the severity of the disease, particularly with large circulatory stasis, right ventricular fibrillation. Hepatic stiffness and METAVIR scale moderately decreased in CHF patients with CHF receiving Liverin along with the standard therapy. The was also decrease in serum levels of certain neurohormones, including galectin-3 and aldosterone, which indicate the activity of fibrous processes in the body ($r < 0.001$). Moreover, in these patients, a decrease in the diameter of the inferior vena cava, its collapse in the respiratory process, the symptoms of pulmonary hypertension, with a positive change in the clinical and functional status of patients was observed and our results were consistent with previous studies [24, 31, 32]. Although partially positive changes in the clinical and functional status of patients were observed due to decreased activity of neurohormones on the basis of standard treatment prescribed in the patients of the 2nd group, who did not receive Liverin, but no statistically significant dynamics was observed in mean LS, F and right ventricular pressure and volume.

Indeed, CHF is a complex clinical syndrome in which chronic activation of neurohormones leads to pathological remodeling of the cardiovascular system, arterial hypoxemia in the body, venous stasis, and systemic inflammatory processes. Injury to target organs in CHF exacerbates the course of the disease. In this regard, in the treatment of the disease, in addition to the appropriate blockade of neurohormones, it is advisable to prescribe treatment aimed at reducing the pathological processes in the target organs, especially the liver, including fibrous processes.

In conclusion, in order to detect pathological processes in the heart and target organs in patients with CHF, special attention should be paid to the activity of the right side of the heart during EchoCG, and early liver elastography should be

conducted in early stages. It is important to monitor biologically active substances that indicate the intensity of fibrosis, e.i. serum galectin - 3 and aldosterone. It is also possible to evaluate the effectiveness of treatment, choosing an appropriate method of treatment of the disease, based on the dynamics of these indicators.

Indeed, long-term administration of the drug Liverin on the basis of standard treatment of various hemodynamic phenotypes of CHF reduces the activity of fibrous processes, regression of remodeling of the heart and target organs, improving clinical and functional status, quality of life and tolerance to physical activity.

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