Central Asian Journal of Medicine

Volume 2021 | Issue 2 Article 2

7-1-2021

THE IMPORTANCE OF INTESTINAL MICROBIOTA AND EDOTOXINEMIA IN THE DEVELOPMENT AND COURSE OF VARIOUS HEMODYNAMIC PHENOTYPES OF CHRONIC HEART FAILURE

Abdukodir K. Kurbonov
Tashkent Medical Academy, Tashkent, 100109, Uzbekistan, a.qurbonov@apgmu.uz

Adigaffar G. Gadayev
Tashkent Medical Academy, Tashkent, 100109, Uzbekistan, abgadaev@yahoo.com

Mukhammad M. Ernazarov
Tashkent Medical Academy, Tashkent, 100109, Uzbekistan, ernazarov.muxammad@mail.ru

Rustam I. Turakulov
Tashkent Medical Academy, Tashkent, 100109, Uzbekistan, Rustam_434@mail.ru

Central Asian Journal of Medicine

THE IMPORTANCE OF INTESTINAL MICROBIOTA AND EDOTOXINEMIA IN THE DEVELOPMENT AND COURSE OF VARIOUS HEMODYNAMIC PHENOTYPES OF CHRONIC HEART FAILURE

Abdukodir K. Kurbonov[1], Adigaffar G. Gadayev[2], Mukhammad M. Ernazarov[3], Rustam I. Turakulov[4]

1 M.D, Assistant of the Department of Internal Diseases № 3, the Tashkent Medical Academy, Uzbekistan
E-mail: a.qurbonov@apgmu.uz

2 M.D, Professor of the Department of Internal Diseases № 3, the Tashkent Medical Academy, Uzbekistan
E-mail: Abgadaev@yahoo.com

3 Head of the cardiac resuscitation department of the multidisciplinary clinic, the Tashkent Medical Academy, Uzbekistan
E-mail: ernazarov.muxammad@mail.ru

4 PhD, Assistant of the Department of Internal Diseases № 3, the Tashkent Medical Academy, Uzbekistan
E-mail: Rustam_434@mail.ru

ABSTRACT

Aim of the study: to assess the relationship between the degree of disturbance of the intestinal microbiota and dysbiosis, as well as endotoxinemia in various hemodynamic phenotypes of chronic heart failure (CHF). **Materials and methods.** The disturbance of the intestinal microbiota composition and changes in the degree of dysbiosis and endotoxin concentration in the blood serum and their interrelation with the course and severity of the disease were studied in 123 patients with CHF with reduced, intermediate and preserved left ventricular ejection fraction. **Results.** The aggravation of the violation of the composition of the intestinal microbiota in the form of a decrease in the number of normative obligate anaerobic microorganisms, in particular bifidobacteria, lactobacilli and lactose-positive Escherichias, and an increase in the number of conditionally pathogenic microorganisms - lactose-negative Escherichia, Staphylobacteriasis, and Candida phenotypes were determined. It was also found that the degree of intestinal dysbiosis and levels of endotoxinemia were associated with the severity of CHF. **Conclusion.** It is advisable to control the level of intestinal microbiota, the degree of dysbiosis and endotoxinemia to assess the effectiveness of the treatment for various hemodynamic phenotypes of CHF.

Key words: chronic heart failure, intestinal microbiota, intestinal dysbiosis, microorganisms, endotoxinemia.

INTRODUCTION

Chronic heart failure (CHF) is a clinical syndrome caused by cardiovascular disease and other comorbidities [14]. Chronic activation of neurohormones, especially sympathoadrenal, renin-angiotensin-aldosterone and immune-inflammatory systems, plays an important role in its occurrence and course. Under the influence of these neurohormones, various pathological changes occur not only in the cardiovascular system, but also in a number of target organs, aggravating the course of the disease [8].

Studies have shown that changes in the composition of the intestinal microflora in patients with CHF activate the immune-inflammatory system. Bacterial lipopolysaccharides (BLPS), an endotoxin that is a by-product of the cell wall of gram-negative bacteria in the gut, play an important role in this. In CHF, structural changes in the intestinal wall, ischemia and arterial hypoxemia, venous stasis and edema lead to impaired motor-evacuation of the intestine, leading to an increase in its permeability [2, 9, 22]. Moreover, in the course of the disease there is a quantitative and qualitative change in the intestinal microflora, including an increase in the number of gram-negative microorganisms. This in turn leads to an increase in the production of endotoxins by them in the gut. Under physiological conditions, when BLPS enters the bloodstream, it is bound and neutralized by a special lipopolysaccharide-binding protein synthesized in the liver. In patients with CHF, BLPS is absorbed into the bloodstream due to abrupt changes in intestinal microbiota, increased intestinal permeability, and decreased liver detoxification, leading to activation of the immune system and cytokinemia [10]. However, almost all studies to date have involved CHF patients with low left ventricular ejection (LVEF) and have not studied the relationship between intestinal microbiota status and endotoxinemia levels in intermediate and preserved hemodynamic phenotypes of the disease.

The aim of the study. Assessment of the interdependence of intestinal microbiota composition, degree of dysbiosis, the amount of endotoxinemia in different hemodynamic phenotypes of CHF.

Materials and methods of the study. A total of 123 patients diagnosed with CHF were included in the study. Patients were divided into 3 groups based on clinical status and central hemodynamic parameters: the 1st group consisted of 41 CHF patients with decreased left ventricular ejection fraction (LVEF< 40%) (22 patients with II FC, mean age 61.6±1.3 years 8 men and 14 women; 19 patients with III FC, mean age 65.3 ± 2.6 years, 9 men and 10 women), the 2nd group

consisted of 38 CHF patients with intermediate LVEF (41- 49%) (18 patients with II FC, mean age 65 ± 1.9, 14 men and 4 women; 20 patients with III FC, mean age 60.4 ± 1.9, 15 men and 5 women), and the 3rd group consisted of 44 CHF patients with preserved LVEF (>50%) (21 patients with II FC, mean age 65.1± 1.7, 12 men and 9 women; 23 patients with III FC, mean age 65.6 ± 1.2, 12 men and 11 women). The control group consisted of 20 healthy volunteers.

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 hypertension. Among the patients of the 1st group 16 (39%) had myocardial infarction more than 6 month ago, 5 (12.2 %) had undergone coronary stenting or shunting operation, 9 (21.9%) had rhythm and conduction disorders, 3 (7.3%) had heart aneurism. Moreover, 13 patients (31.7 %) had obesity and 6 (14.6 %) had anemia. Among the patients of the 2nd group 31 (81.6%) had myocardial infarction more than 6 month ago, 5 (13.2%) had undergone coronary stenting or shunting operation, 6 (15.8%) had rhythm and conduction disorders, 6 (15.8%) had heart aneurism. Moreover, 13 patients (34.2%) had obesity and 3 (7.9%) had anemia. Among the patients of the 3rd group 17 (38.6%) had myocardial infarction more than 6 month ago, 4 (9.1%) had undergone coronary stenting or shunting operation, 7 (15.9%) had rhythm and conduction disorders, 1 (2.3%) had heart aneurism. Moreover, 14 patients (31.8%) had obesity and 2 (4.5%) had anemia. A general description of the patients is given in Table 1.

Table 1

A general description of patients with chronic heart failure involved in the study

Indices	Total	1st group	2nd group	3rd group
Number of patients	123	41	38	44
Age, years	63.4 ±1.2	63.3±1.4	62.6±1.9	65.4±1.0
BMI, kg/m^2	30.8±0.9	27.9±0.6	31.9±1.3	30.5±0.7
Sex, man/woman	70/53	17/24	29/9	24/20
CHF duration, years	3.6 ±1.2	4.2±1.8	3.2±1.3	2.9±0.9
Exertion stenocardia II FC III FC	123 33 90	41 9 32	38 6 32	44 18 26

Hypertension	123	41	38	44
PICS, %	64 (52%)	16 (39%)	31 (81.6%)	17 (38.6%)
Coronary stenting and coronary bypass, %	14 (11.4%)	5 (12.2%)	5 (13.2%)	4 (9.1%)
Rhythm and conduction disorders, blockade, atrial fibrillation, ventricular extrasystole,%	22 (17.9%)	9 (21.9%)	6 (15.8%)	7 (15.9%)
Heart aneurism, %	10 (8.1%)	3 (7.3%)	6 (15.8%)	1 (2.3%)
LVEF, %	47.9±0.9	36.5±0.4	46.1±0.4	59.6±0.6
Obesity	40 (32.5%)	13 (31.7%)	13 (34.2%)	14 (31.8%)
Anemia	11 (8.9%)	6 (14.6%)	3 (7.9%)	2 (4.5%)

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.

Based on the complaints, anamnesis and objective examination of all three groups of patients with CHF, their clinical and functional status was assessed, the general and biochemical analysis of blood and urine, coagulogram, lipid spectrum were determined. Serum endotoxin LAL (Limulus Amebocyte Lysate) was chromogenically detected in patients using test reagents. The reference level was - 0.07 - 0.21 EU/ml.

The composition of the colon microbiota was studied bacteriologically. In its examination, the modified methodological recommendations of A.Z.Smolyanskaya (1984) and N.M.Gracheva and co-authors (1986) were used as a basis for analysis. The analysis revealed the ratio of aerobic and anaerobic, as well as the total number of obligate (bifidobacteria, lactobacilli, lactose-positive Escherichia) and conditionally pathogenic microbes (hemolytic Escherichia, streptococcus, staphylococcus, Candida fungi, etc.) in 1 gram of feces. Tests for the detection of asporogenic anaerobes and microaerophilic microorganisms were cultured in the following media: Blaurokk - for bifidobacteria; MRS-4 - for the isolation of lactobacilli and milk streptococci. 5% blood agar, as well as Endo, Saburo medium and yellow-salt agar were used to isolate aerobic and facultative-anaerobic microorganisms. Types and groups of isolated microorganisms after a

specified time are determined on the basis of their growth in selective and differential-diagnostic media in accordance with official guidelines, based on microscopic data in Gram-stained smears. The number of microorganisms was calculated according to the following formula: K = A x 200 x P (CFU/g). In this formula: K - the number of bacteria of a particular species; A - the number of colonies in the last cup culture in which the microbes grew; 200 – the coefficient that corresponds to 1 ml of sedimentary culture (volume – 0.005 ml); P – degree of dilution. The number of bacteria in each species was expressed in CFU / g.

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.

MS Excel (2007) computer software was used for statistical processing of the data obtained in the study. The arithmetic mean and standard deviations (M ± m) of the indicators were calculated. The significance of difference between the compared groups was assessed according to the Student's criterion, where p <0.05.

Results of the study and discussion. The indicators of central hemodynamics and cardiac remodeling in patients with CHF involved in the study differed statistically significantly (Table 2).

Table 2

Clinical-functional status and central hemodynamic parameters of patients with chronic heart failure

Indices	1st group, CHF with decreased LVEF, n=41	2nd group, CHF with intermediate LVEF, n=38	3rd group, CHF with preserved LVEF, n=44
CCAS, ball	6.4±0.3	6.9±0.4	6.7±0.3
QoL, ball	47.5±1.6	52.1±1.9	53.7±1.5 ##
6MWT, meters	289.5±12.0	285.1±16.1	285.2±12.1
Indicators of central hemodynamics			
EDS, sm	6.8±0.08	6.2±0.1 ***	5.3±0.05 ###
EDV, ml	211.3±4.4	181.2±9.7**	135.2±2.9 ###
ESS, sm	5.6±0.1	4.9±0.1 ***	3.6±0.05 ###
ESV, ml	146.8±4.9	107.0±7.5 ***	59.9±1.9 ###
IVST, mm	10.4±0.2	11.0±0.2*	11.7±0.2 ###
LVPWT, mm	11.2±0.2	12.3 ±0.2 ***	12.6±0.2 ###
LVMI, g/m^2	278.0±8.8	269.3±8.6	239.2±6.5 ##
LVRWT, unit	0.33±0.01	0.47±0.01 ***	0.45±0.01 ###
LVEF, %	35.9±0.4	45.4±0.4 ***	56.5±0.6 ###

Note: significance of differences between the 1st and the 2nd groups: * - p<0.05; ** - p<0.01; *** - p<0.001; significance of differences between the 1st and the 3rd groups: # - p<0.05; ## - p<0.01; ### - p<0.001; CCAS – clinical condition assessment scale, QoL – quality of life, 6MWT – six minute walk test, EDS – end diastolic size, EDV – end diastolic volume, ESS - end systolic size, ESV – end systolic volume, IVST – interventricular septal thickness, LVPWT – left ventricular posterior wall thickness, LVRWT –left ventricular relative wall thickness, LVEF – left ventricular ejection fraction

LVEF, which represents the inotropic properties of the myocardium, was found to be 35.9 ± 0.4% in the 1st group patients and decreased by 9.5 and 20.6%, respectively, compared to those in the 2nd and 3rd groups (p <0.001). In the 1st group patients, EDS and EDV were 9.6 (6.8 vs. 6.8 cm, p <0.001) and 16.6 (181.2 vs. 211.3 ml, r <0.01)% and 28.3 (5.3 vs. 6.8 cm) compared with those in the 2nd and 3rd groups respectively (p <0.001) and increased by 56.3 (135.2 vs. 211.3 ml, p <0.001)%. In this group of patients, ESS and ESV were 14.2 (vs. 5.6 cm, p <0.001) and 37.1 (107.0 vs. 146.8 ml, p <0.001)% and 55.5 (3.6 vs. 5.6), respectively, compared with those in the 2nd and 3rd groups (p <0.001) and increased by 145.1%

(596 vs. 146.8 ml, p <0.001). The clear development of left ventricular hypertrophy (LVH) in patients with CHF is a direct indication of the high risk of developing its complications. All patients in the 1st group had eccentric hypertrophy (EH), 29 patients in the 2nd group had concentric hypertrophy (CH), 9 patients had EH, 29 patients in the 3rd group had EH, and 15 patients had EH. In patients of the 3rd group, IVST, LVPWT, and LVRWT were 6.7 (11.7 vs. 11.7 mm, p <0.001), 9.7 (11.2 vs. 12.6 mm, p <0.001), and 29.4% (0.33 vs. 0.45, respectively) compared with the 1st group patients. (p<0.001), it was found that in this group the symptoms of LVH were more pronounced. These values were found to be 5.7 (p <0.05), 9.8 (p <0.001) and 42.4% (p <0.001) higher in the 2nd group patients than the 1st group, respectively.

Bacteriological analysis revealed that the composition of the intestinal microbiota in patients in all three groups of followers changed statistically significantly compared to the control group.

In II and III FC of CHF patients with decreased LVEF numbers of normal obligate microflora such as Bifidobacteria, Lactobacilli and Lactose positive Escherichia decreased respectively from 4.8 x 10^8 to 1.1 x 10^7 and 4.7 x 10^6 (p<0.01); from 1.6 x 10^8 to 2.4 x 10^7 (p<0.01) and 9.0 x 10^6 (p<0.001); from 1.1 x 10^8 to 6.3 x 10^6 (p<0.01) and 9.2 x 10^5 (p<0.001) CFU/g compared to reference values. On the contrary, it was found that numbers of Lactose negative Escherichia, Enterobacteria, Staphylococcus and Fungi increased respectively from 2.0 x 10^4 to 7.0 x 10^6 and 8.1 x 10^7 (p<0.05); from 5.3 x 10^3 to 7.6 x 10^5 and 6.9 x 10^6 (p<0.05); from 6.0 x 10^3 to 5.1 x 10^5 (p<0.01) and 1.2 x 10^5 (p<0.001); and from 4.1 x 10^3 to 3.1 x 10^4 (p<0.05) and 5.0 x 10^4 (p<0.01) CFU/g (Table 3).

Table 3

Qualitative and quantitative description of intestinal microbiota in CHF patients with decreased LVEF

Name of microflora	Group of microflora	Reference indicator, n=20	CHF II FC, n=22	CHF III FC, n=19
		CFU/g		
Bifidobacteria	Normal gram-positive	4.8±1.6x10^8 [1.2x10^5;1.8x10^9]	1.1±0.5x10^7 [1.1x10^3; 1.1x10^8]	4.7±1.8x10^6 [1.0x10^3; 1.9x10^7]##
Lactobacilli		1.6±0.4 x10^8 [2.8x10^5; 3.9x10^9]	2.4±0.9 x10^7 [3.7x10^3; 2.1x10^8]**	9.0±3.4x10^6 [2.9x10^3; 3.8x10^7] ###
Lactose positive Escherichia	Normal gram-negative	1.1±0.3x10^8 [1.2 x10^5; 4.3 x 10^8]	6.3±4.9x10^6 [0.0; 1.1x10^8]**	9.2±3.2x10^5 [2.9x10^3; 3.8 x 10^7] ###

Lactose negative Escherichia	Gram-negative conditional pathogen microflora	$2.0\pm0.9x10^4$ [10; $1.0x10^5$]	$7.0\pm2.9x10^6$ [$3.4x10^2$; $6.2x10^7$]*	$8.1\pm3.7x10^7$ [$1.2x10^4$; $4.2x10^8$] #
Enterobacteria		$5.3\pm2.0x10^3$ [0; $3.3x10^4$]	$7.6\pm3.1x10^5$ [$7.0x10^2$; $6.1x10^6$]*	$6.9\pm3.2x10^6$ [$3.3x10^3$; $4.4x10^7$] #
Staphylococcus (s. aurius)	Gram-positive conditional pathogen microflora	$6.0\pm2.4x10^3$ [$1.7x10^2$; $3.6x10^4$]	$5.1\pm1.8x10^5$ [$1.7x10^2$; $4.1x10^6$]**	$2.2\pm0.5x10^5$ [$1.8x10^3$; $5.6x10^5$] ###
Fungi (c. albicans)		$4.1\pm1.6x10^3$ [$1.0x10^2$; $2.5x10^4$]	$3.1\pm1.2x10^4$ [$1.1x10^2$; $2.2x10^5$]*	$5.0\pm1.7x10^4$ [$1.0x10^3$; $2.5x10^5$] ##

Note: * - significance of difference between CHF II FC patients and reference values: * - $p<0.05$; ** - $p<0.01$; *** - $p<0.001$; # - significance of difference between CHF III FC patients and reference values: # - $p<0.05$; ## - $p<0.01$; ### - $p<0.001$.

In II and III FC of CHF patients with intermediate LVEF numbers of Bifidobacteria, Lactobacilli and Lactose positive Escherichia decreased respectively from 4.8 x 10^8 to 2.1 x 10^7 ($p<0.01$) and 4.6 x 10^6 ($p<0.01$); from 1.6 x 10^8 to 2.9 x 10^7 ($p<0.01$) and 8.1 x 10^6 ($p<0.001$); from 1.1 x 10^8 to 1.6 x 10^7 ($p>0.05$) and 8.3 x 10^5 ($p<0.001$) CFU/g compared to reference values. On the contrary, it was found that numbers of Lactose negative Escherichia, Enterobacteria, Staphylococcus and Fungi increased respectively from 2.0 x 10^4 to 4.4 x 10^6 and 6.4 x 10^6 ($p<0.05$); from 5.3 x 10^3 to 5.3 x 10^5 and 4.4 x 10^6 ($p<0.05$); from 6.0 x 10^3 to 2.9 x 10^5 ($p<0.05$) and 3.0 x 10^5 ($p<0.05$); and from 4.1 x 10^3 to 2.8 x 10^4 ($p<0.05$) and 3.7 x 10^4 ($p<0.01$) CFU/g (Table 4).

Table 4

Qualitative and quantitative description of intestinal microbiota in CHF patients with intermediate LVEF

Name of microflora	**Group of microflora**	**Reference indicator, n=20**	**CHF II FC, n=22**	**CHF III FC, n=19**
		CFU/g		
Bifidobacteria	Normal gram-positive	$4.8\pm1.6x10^8$ [$1.2x10^5$; $1.8x10^9$]	$2.1\pm0.9\ x10^7$ [$3.1x10^3$; $1.3x10^8$]**	$4.6\pm1.6x10^6$ [$1.3x10^3$; $1.9x10^7$] ##
Lactobacilli		$1.6\pm0.4\ x10^8$ [$2.8x10^5$; $3.9x10^9$]	$2.9\pm0.9x10^7$ [$2.7x10^3$; $1.4x10^8$]**	$8.1\pm3.0x10^6$ [$3.1x10^3$; $3.8x10^7$] ###
Lactose positive Escherichia	Normal gram-negative	$1.1\pm0.3x10^8$ [$1.2x10^5$; $4.3x10^8$]	$1.6\pm1.0\ x10^7$ [0.0; 1.4x 10^8]*	$8.3\pm2.7x10^5$ [0.0; 3.5 $x10^6$]###

Lactose negative Escherichia	Gram-negative conditional pathogen microflora	$2.0\pm0.9x10^4$ [10; $1.0x10^5$]	$4.4\pm2.0 \times 10^6$ [$3.2x10^2$; $4.1x10^7$]*	$6.4\pm3.0 \times 10^6$ [$1.2x10^4$; $4.5x10^7$] #
Enterobacteria		$5.3\pm2.0x10^3$ [0; $3.3x10^4$]	$5.3\pm2.5x10^5$ [$7.0x10^2$; $5.2x10^6$]*	$4.4\pm1.9x10^6$ [$3.6x10^3$; $4.8x10^7$] #
Staphylococcus (s. aurius)	Gram-positive conditional pathogen microflora	$6.0\pm2.4x10^3$ [$1.7x10^2$; $3.6x10^4$]	$3.9\pm1.9x10^5$ [$2.3x10^2$; $3.2x10^6$]*	$3.0\pm1.3x10^5$ [$1.8x10^3$; $4.7x10^6$] #
Fungi (c. albicans)		$4.1\pm1.6x10^3$ [$1.0x10^2$; $2.5x10^4$]	$2.8\pm1.1x10^4$ [$1.1x10^2$; $2.1x10^5$]*	$3.7\pm1.3x10^4$ [$1.2x10^3$; $2.2x10^5$] ##

Note: * - significance of difference between CHF II FC patients and reference values: * - $p<0.05$; ** - $p<0.01$; *** - $p<0.001$; # - significance of difference between CHF III FC patients and reference values: # - $p<0.05$; ## - $p<0.01$; ### - $p<0.001$.

In II and III FC of CHF patients with preserved LVEF numbers of Bifidobacteria, Lactobacilli and Lactose positive Escherichia decreased respectively from 4.8×10^8 to 3.3×10^7 ($p<0.01$) and 2.0×10^7 ($p<0.01$); from 1.6×10^8 to 6.3×10^7 ($p<0.05$) and 3.6×10^7 ($p<0.01$); from 1.1×10^8 to 2.4×10^7 ($p>0.01$) and 1.2×10^5 ($p<0.01$) CFU/g compared to reference values. On the contrary, it was found that numbers of Lactose negative Escherichia, Enterobacteria, Staphylococcus and Fungi increased respectively from 2.0×10^4 to 3.9×10^6 and 2.5×10^6 ($p<0.05$); from 5.3×10^3 to 2.7×10^5 and 3.2×10^5 ($p<0.05$); from 6.0×10^3 to 3.5×10^5 ($p<0.05$) and 3.2×10^5 ($p<0.01$); and from 4.1×10^3 to 1.2×10^4 ($p<0.01$) and 2.7×10^4 ($p<0.05$) CFU/g (Table 5).

Table 5

Qualitative and quantitative description of intestinal microbiota in CHF patients with preserved LVEF

Name of microflora	**Group of microflora**	**Reference indicator, n=20**	**CHF II FC, n=22**	**CHF III FC, n=19**
		CFU/g		
Bifidobacteria	Normal gram-positive	$4.8\pm1.6x10^8$ [$1.2x10^5$; $1.8x10^9$]	$3.3\pm1.1x10^7$ [$1.9x10^3$; $1.7x10^8$]**	$2.0\pm0.9x10^7$ [$1.1x10^3$; $1.8x10^8$] ##
Lactobacilli		$1.6\pm0.4 \times10^8$ [$2.8x10^5$; $3.9x10^9$]	$6.3\pm2.2x10^7$ [$3.7x10^3$; $3.2x10^8$]*	$3.6\pm1.8x10^7$ [$3.6x10^3$; $4.1x10^8$] ##
Lactose positive Escherichia	Normal gram-negative	$1.1\pm0.3x10^8$ [1.2×10^5; 4.3×10^8]	$2.4\pm1.0x10^7$ [0.0; $1.2x10^8$]**	$1.2\pm0.7x10^7$ [0.0; $1.4x10^8$] ##

Lactose negative Escherichia	Gram-negative conditional pathogen microflora	$2.0\pm0.9x10^4$ [10; $1.0x10^5$]	$3.9\pm1.9x10^6$ [$2.3x10^2$; $6.2x10^7$]*	$2.5\pm1.1x10^6$ [$2.8x10^2$; $3.9x10^7$] #
Enterobacteria		$5.3\pm2.0x10^3$ [0; $3.3x10^4$]	$2.7\pm1.3x10^5$ [$1.0x10^2$; $5.5x10^5$]*	$3.2\pm1.2x10^5$ [$4.0x10^2$; $4.8x10^6$] #
Staphylococcus (s. aurius)	Gram-positive conditional pathogen microflora	$6.0\pm2.4x10^3$ [$1.7x10^2$; $3.6x10^4$]	$3.5\pm1.4x10^5$ [$1.1x10^2$; $3.0x10^6$]*	$3.2\pm1.1x10^5$ [$1.8x10^2$; $4.1x10^6$] ##
Fungi (c. albicans)		$4.1\pm1.6x10^3$ [$1.0x10^2$; $2.5x10^4$]	$1.2\pm0.2x10^4$ [$1.0x10^2$; $1.0x10^5$]**	$2.7\pm1.1x10^4$ [$1.4x10^2$; $2.x10^5$] #

Note: * - significance of difference between CHF II FC patients and reference values: * - p<0.05; ** - p<0.01; *** - p<0.001; # - significance of difference between CHF III FC patients and reference values: # - p<0.05; ## - p<0.01; ### - p<0.001.

During the study, changes of varios degrees was obseved in gut microbiota of patients involved in tha study. Among patients of the 1st group, 1 (2.4%) had normal biocenosis, 14 had (34.1%) I degree dysbiosis, 19 had (46.3%) II degree dysbiosis, and 7 (17.1%) had III degree dysbiosis. In the 2nd and 3rd group normal biocenosis was found respectively in 2 (5.2%) and 6 (13.6%) patients, I degree dysbiosis in 14 (36.8%) and 18 (40.9%), II degree dysbiosis in 17 (44.7%) and 17 (38.6%), III degree dysbiosis in 5 (13.2%) and 3 (6.8%) patients (Figure 1).

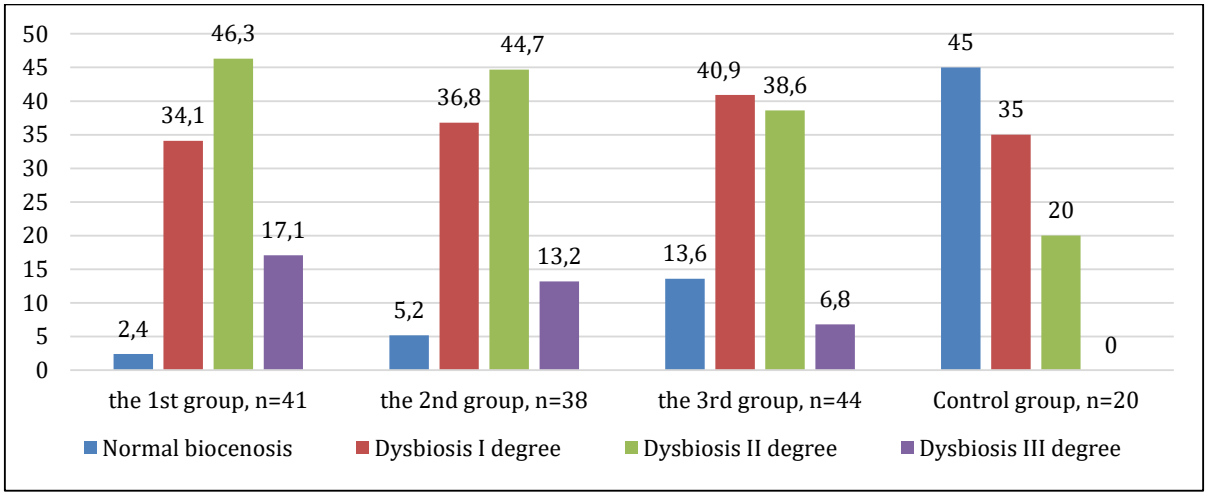

Figure 1. Disorders of intestinal microbiota in patients with chronic heart failure and in the control group,%.

In the 1st group patients of our study pathological changes in gut microbiota was more prominent compared to the 2nd and 3rd group patients. In the formen group normal biocenosi was observed less frequently (respectively 5.2 and 13.6 vs 2.4%, p<0.05), while II and III degree dysbiosis was found more often compared

to other groups (respectively 44.7 and 38.6 vs 46.3%; 13.2 and 6.8 vs 17.1%, p<0.05). Moreover, there was also an increase in intestinal dysbiosis and it coincided with an increase in FC. It was characterised by decrease in normal obligate microflora, and increase in facultative anaerobic microflora, especially gram-negative microorganisms – lactose negative form of Escherichia coli, enterobacteria, staphylococci and fungi. (Table 6)

Table 6

Changes in the intestinal microbiota and the degree of endotoxinemia in different hemodynamic phenotypes of chronic heart failure

Condition of microbiota	Control group, n=20	1st group		2nd group		3rd group	
		II FC n=22	III FC n=19	II FC n=18	III FC n=20	II FC n=21	III FC n=23
Normal-biocenosis,(%)	9 (45.0)	1 (4.6)	0	2 (11.1)	0	4 (19.0)	2 (8.7)
Dysbiosis I degree, (%)	7 (35.0)	9 (40.9)	5 (26.3)	8 (44.4)	6 (30.0)	9 (42.8)	9 (39.1)
Dysbiosis II degree, (%)	4 (20.0)	9 (40.9)	10 (52.6)	6 (33.3)	11 (55.0)	7 (33.4)	10 (43.5)
Dysbiosis III degree, (%)	0	3 (13.6)	4 (21.1)	2 (11.1)	3 (15.0)	1 (4.8)	2 (8.7)
Endotoxin, EU/ml	0.13 [0.07;0.21]	3.0* [0.9; 3.9]	3.6 [2.5; 4.5] * ###	1.9* [0.8; 2.8]	2.5* [1.1; 3.1] ###	1.5* [0.6; 1.9]	1.7* [0.7; 2.4] ≠

Note: * - significance of difference between II - III FC CHF patients and reference values, p<0.001; ≠ - significance of difference between II FC and III FC of CHF, p<0.05; ## - p<0.01; ### - p<0.001; # - significance of difference between the groups, p<0.01; ## - p<0.001; ### - p<0.000.

In the patients of the 1st group II and III degrees of dysbiosis was found respectively 3.5 - 29.5 percent more frequently compared to the 2nd and the 3rd groups. In II and III FC patients of this group statistically significant increase in levels of endotoxin compared to reference values (respectively 0.13 vs 3.04 and 3.6 (p<0.001) EU/ml) was found. Results of this groups were respectively 1.6 and 1.4 (p<0.001); and 2.0 and 2.1 (p<0.001) times higher compared to the 2nd and 3rd group patients. Moreover, endotoxin levels corresponded to the disease gravity. Namely, it was 18.4% higher in III FC of CHF patients with with decreased LVEF compared to II FC (3.04 ± 0.1 vs 3.6 ± 0.1. p<0.001).

In II and III FC patients of the 2nd group endotoxin levels in serum increased compared to reference values (respectively 1.9 and 2.5 vs 0.13 EU/ml; p<0.000). Endotoxin vales of this groups were respectively 1.3 (p<0.01) ва 1.5 (p<0.001)

times higher compared to CHF patients with preserved LVEF. It was also found that the amount of endotoxin in this group also coincided with the aggravation of the disease FC (increase from 1.9 ± 0.1 to 2.5 ± 0.1 EU/ml, p<0.001).

In II and III FC patients of the 3rd group endotoxin levels in serum increased compared to reference values (respectively 1.5 and 1.7 vs 0.13 EU/ml; p<0.000). In this group too it was also found that the amount of endotoxin in this group also coincided with the increase of the disease FC (increase from 1.5 ± 0.08 to 1.7 ± 0.1 EU/ml; p<0.05).

The serum endotoxin levels of all three groups of patients were higher than the reference values, which was more pronounced in CHF patients with decreased LVEF, and the level of endotoxinemia was consistent with the severity of the disease. When the correlation of the level of endotoxinemia with the disruption of the intestinal microbiota in the patients involved in the study, the following was found (Table 7).

Table 7

Correlation between the level of endotoxinemia and intestinal dysbiosis in patients with chronic heart failure

Microorganisms CFU/g	**CHF with reduced LVEF**		**CHF with intermediate LVEF**		**CHF with preserved LVEF**	
	II FC n=22	**III FC n=19**	**II FC n=18**	**III FC n=20**	**II FC n=21**	**III FC n=23**
Bifidobacteria	r= - 0.84 p<0.001	r= - 0.86 p<0.001	r= - 0.71 p<0.001	r= - 0.68 p<0.001	r= - 0.92 p<0.001	r= - 0.64 p<0.01
Lactobacilli	r= - 0.83 p<0.001	r= - 0.87 p<0.001	r= - 0.83 p<0.001	r= - 0.47 p<0.05	r= - 0.89 p<0.001	r= - 0.58 p<0.01
Lactose positive Escherichia	r= - 0.77 p<0.001	r= - 0.85 p<0.001	r= - 0.60 p<0.01	r= - 0.45 p<0.05	r= - 0.90 p<0.001	r= - 0.56 p<0.01
Lactose negative Escherichia	r= 0.51 p<0.02	r= 0.70 p<0.001	r= 0.49 p<0.05	r= 0.38 p = insig.	r= 0.30 p = insig.	r= 0.39 p = insig.
Enterobacteria	r= 0.52 p<0.02	r= 0.66 p<0.01	r= 0.49 p<0.05	r= 0.37 p = insig.	r= 0.25 p = insig.	r= 0.41 p<0.05
Staphylococcus	r=0.51 p<0.02	r=0.64 p<0.01	r=0.48 p<0.05	r=0.19 p = insig.	r=0.26 p = insig.	r=0.42 p<0.05
Fungi	r= 0.55 p<0.01	r= 0.72 p<0.001	r= 0.58 p<0.02	r= 0.44 p<0.05	r= 0.46 p<0.05	r= 0.51 p<0.02

Note: degree of correlation (according to Chaddock's scale): r< 0.3 – very weak, 0.3<r<0.5 - weak, 0.5<r< 0.7 – moderate, 0.7<r<0.9 – strong, 0.9<r<1.0 – very strong. insig. – correlation is statistically insignificant.

A reliable correlation between endotoxinemia and the degree of intestinal dysbiosis was found in all groups of patients monitored. In particular, negative moderate and strong correlations were noted between a decrease in normal intestinal anaerobic microorganisms, such as bifidobacteria, lactobacilli and lactosapositive escherichia on one hand and endotoxinemia on the other. At the same time, in CHF patients with decreased LVEF, strong negative correlation between endotoxinemia and obligate anaerobic microgranisms - bifidobacteria, lactobacilli and lactose positive escherichia in patients with II and III FC was observed (respectively r = - 0.84; r = -0.83; r = -0.77. = - 0.86; r = -0.87; r = -0.85. p <0.001). In this group, moderately positive correlation was found between intestinal microorganisms that are considered conditionally pathogenic – lactose negative escherichia, enterococci, staphylococci and fungi on one hand and the level of endoxinemia (respectively r = 0.51; r = 0.52; r = 0.51. p <0.02 and r = 0.55. p <0.01, r = 0.70, p <0.001; r = 0.66; r = 0.66. p <0.01 and r = 0.72. p <0.001).

In CHF patients with intermediate LVEF in both II and III FC, correspondingly strong and moderately negative correlation was found between endotoxinemia and bifidobacteria (r = -0.71 and r = -0.68, p <0.001). Between endotxinemia and lactobacilli correlation was respectively, strong and weak negative (r = -0.83, p <0.001 and r = -0.47. p <0.05) and between endotxinemia and lactose-positive escherichia moderately and weak negative (r = - 0.60; p <0.01 and r = -0.45. p <0.05). Weak and moderately positive correlation was fond (r = 0.49; r = 0.49; r = 0.48. p <0.05 and r = 0.58. p <0.02, respectively) between lactosanegative escherichia, enterococci, staphylococci, and fungi with level of endoxinemia in II FC of CHF patients in this group. In III FC of the disease, the only reliable correlation was between level of endoxinemia and fungi and it was weak positive (r = 0.44. p <0.05).

In CHF patients with preserved LVEF of both II and III FC, between endotoxinemia on one hand and bifidobacteria, lactobacilli and lactose positive escherichia on the other respectively strong (r = -0.92; r = -0.89 and r = -0.90; p <0.001) and moderately (r = -0.60; r = -0.58 and r = -0.56. p <0.01) negative correlation was found. In CHF patients of this group, there was moderately positive correlation between the level of endoxinemia and lactose negative escherichia, enterococci, and staphylococci (r = 0.46. R <0.05). Correlation between endotoxinemia and enterococci as well as staphylococci was weak positive, while with fungi it was moderately positive (r = 0.51. r <0.05).

Discussion. Patients with CHF have pathological changes not only in the cardiovascular system, but also in a number of target organs, especially the

gastrointestinal tract. Studies have shown changes of the composition of the normal intestinal microflora in CHF, with a decrease in obligate anaerobic microorganisms, an increase in gram-negative microflora [5, 6]. This in turn leads to increased production of endotoxins by gram-negative bacteria in the gut. They initially trigger a local inflammatory process in the intestine. In this case, the bacteria and their breakdown products are phagocytosed by macrophages in the intestinal wall and cells of the reticuloendothelial system. Activated macrophages enter the local lymph nodes, where they pass into the circulating blood along with broken down bacterial products, leading to activation of the immune system and cytokinemia [11]. Activation of the immune system under the influence of BLPS in CHF is carried out by immunocompetent cells CD14 and TLR-4 (Toll like receptor - 4) receptors expressed by cardiomyocytes, and a systemic inflammatory process occurs in the body [12, 19, 20, 21]. A study by S. Mag and co-authors (2015) found that BLPS may have a direct effect on myocardial remodeling in CHF. This study is based on the fact that BLPS has a direct or indirect effect on intracardiac Ca (2+) homeostasis and leads to the development of myocardial hypertrophy [17]. BLPS leads to the synthesis of excess collagen in the extracellular matrix due to the activation of fibroblasts in the heart. Moreover, BLPS induces apoptosis of cardiomyocytess by activating the endoplasmic reticulum and stimulating the actin A-follistatin system [13]. In all three groups of patients involved in our study, cardiac remodeling rates differed sharply. Spherical dilatation and eccentric hypertrophy was found in CHF patients with decreased LVEF. Interventricular septum thickening, which is a symptom of left ventricular hypertrophy and an increase in the thickness of the posterior wall of the left ventricle and the relative thickness of the left ventricle, ie in most cases concentric hypertrophy was found in most cases of the preserved hemodynamic phenotype of the disease. Cardiac remodeling in CHF with intermediate LVEF was found to be between decreased and preserved hemodynamic phenotypes of the disease.

Indeed, the difference in cardiac remodeling in the patients involved in the study was reflected in changes in the composition of the intestinal microbiota depending on different hemodynamic phenotypes of CHF, disease stage, and FC. The study found conditional pathogenic fungi of the genus Candida and bacteria Campylobacter, Shigella, Yersinia in the feces of the majority of patients with severe CHF [18]. In the research by E. Егорова and co-authors it was noted that the levels of dysbiosis, cytokinemia and endotoxinemia are related to the severity of patients with CHF [4, 5, 7]. Investigation of intestinal microbiota in all groups of patients of our study showed a statistically significant decrease in the normative anaerobic microorganisms - bifidobacteria, lactobacilli and lactosapositive

Escherichia coli (p <0.000), and increase of conditional pathogenic microorganisms, in particular, gram-negative microflora, lactobacilli, lactobacilli, lactose. (p <0.000). It was also found that the degree of intestinal dysbiosis in all patients was consistent with the severity of the disease. The marked development of intestinal dysbiosis in the decreased hemodynamic phenotype of CHF is due to a sharp decrease in the inotropic properties of the heart with systemic arterial hypoxemia, venous stasis and edema, and in the preserved LVEF phenotype of the disease with impaired cardiac diastole and systemic neurohormonal activation. The intermediate hemodynamic phenotype of the disease occupied the intermediate state in regart to the low and preserved phenotypes of CHF.

A study by Г. Арутюнов and co-authors (2005) noted that serum endotoxin levels in severe (III-IV) FC of CHF were in the upper limit of normal values, twice as high as in healthy volunteers in the control group [2]. Е. Егорова and co-authors (2012) found that serum endotoxin levels in patients with stage IIA and B of CHF were respectively 1.5 and 2 times higher, than in stage I of the disease. It has also been suggested that some authors suggest that BLPS levels higher than 0.51 EU/ml in patients with CHF indicate small circulatory stagnation in 90% of cases [16]. Another study found that serum endotoxin levels in patients with MI were three times higher than in healthy people of the same age [1]. The connectedness of clinical and functional status and endotoxinemia in patients with CHF has been noted by a number of authors [4, 5, 15]. Hypoxia and acidosis in enterocytes, impaired sodium and hydrogen metabolism, increased fluid and sodium retention in the intestinal wall, decreased intestinal pH and permeability events associated with inflammation are directly related to the severity of CHF [19]. Some authors have suggested that bacterial translocation in CHF leads to endotoxinemia. A number of scientific papers published under the direction of Г. Арутюнов have shown that in patients with CHF, the microbiota is disturbed due to the increase of gram-negative flora in the colon, and fibrosis in the small intestine. It has been noted that these changes are related to the amount of C reactive protein (CRP) in the blood serum and the degree of swelling of the intestinal mucosa [2, 3]. The level of serum endotoxinemia in the patients involved in our study was 3.5-29.5% higher in patients with group dysbiosis II-III than in groups 2 and 3, respectively, and the endotoxin level was 3.04 and 3.6 EU/ml, respectively. It was statistically significant increase relative to the indicators (p <0.000). It was also found that the amount of endotoxin in this group was 1.4 - 1.6 (p <0.000) and 2.0 - 2.1 (p <0.000) times higher than in patients of groups 2 and 3, respectively. Moreover, in all three groups, the amount of endotoxin in the serum was found to be consistent with the severity of the disease (p <0.001). Also, in patients with CHF, moderate and strong

negative correlation (p <0.001) was found between endotoxinemia and bifidobacteria, lactobacilli and lactose positive escherichia. The correlation between endotxinemia and lactose negative escherichia, enterococci, staphylococci and fungi in decreased hemodynamic phenotype of the disease was moderately positive (r=0.66. p<0.01 ва r=0.72. p<0.001), it was weak and moderately positive in the intermediate and preserved hemodynamic phenotypes of the disease (respectively r = 0.48. p <0.05; r = 0.58 p <0.02; and r=0.46. p<0.05; r= 0.51. p<0.05).

This means that patients with CHF undergo a number of changes not only in the cardiovascular system, but also in the colon. Different hemodynamic phenotypes of CHF differ in the composition of the intestinal microbiota, the decreased LVEF hemodynamic phenotype has a high degree of dysbiosis compared to intermediate and preserved phenotypes, with a decrease in normal anaerobic microflora and conditional pathogens, especially gram-negative in all three groups. It has also been found that the degree of disruption of the intestinal microbiota is consistent with an increase in FC of CHF. This can lead to an increase in the level of endotoxinemia in the serum, leading to the activation of immune inflammatory processes. Indeed, for the adequate treatment of various hemodynamic phenotypes of CHF, it is advisable to periodically monitor the level of intestinal microbiota and dysbiosis and endotoxinemia.

REFERENCES

1. Anixovskaya I.A. Dinamika konsentrasii endotoksina v sivorotke krovi u bol'nix s ostrim neoslojnyonnim Q-infarktom miokarda // Patologicheskaya fiziologiya i eksperimental'naya terapiya. - 2015. - T. 59, № 3. - S. 55 - 61.

2. Arutyunov, G.P. Xronicheskaya serdechnaya nedostatochnost': strukturnie i mikrobiologicheskie izmeneniya v tolstoy kishke / G.P. Arutyunov, L.I. Kafarskaya, N.A. Savelov [i dr.] // Terapevticheskiy arxiv. – 2007. – T. 79., № 2. – S. 31–37.

3. Dolenc J. Pulmonary hypertension in patients with advanced heart failure is associated with increased levels of interleukin-6 / J. Dolenc, M. Šebeštjen, B. Vrtovec [et al.] // Biomarkers. – 2014. – Vol. 19, № 5. – P. 385–390.

4. Egorova Ye.N. Dinamika faktorov sistemnogo vospaleniya i aminoterminal'nogo mozgovogo natriyureticheskogo propeptida pri lechenii xronicheskoy serdechnoy nedostatochnosti / Ye.N. Yegorova, M.I. Kuz'mina, V.V. Mazur [i dr.] // Terapevticheskiy arxiv. – 2011. – № 1. – S. 56–59.

5. Egorova Ye.N. Mikrobiosenoz i aktivnost' vospalitel'nogo prosessa tolstoy kishki u bol'nix xronicheskoy serdechnoy nedostatochnost'yu / Ye.N.

Yegorova, M.I. Kuz'mina, V.V. Mazur [i dr.] // Klinicheskaya medisina. – 2012. – T. 90, № 7. – S. 46–48.

6. Egorova Ye.N. Sistemnoe vospalenie v patogeneze xronicheskoy serdechnoy nedostatochnosti / Ye.N. Yegorova, M.N. Kalinkin, Ye.S. Mazur // Tverskoy medisinskiy jurnal – 2013. – № 1 – S. 2-9.

7. Evdokimova A.G. Optimizasiya lecheniya bol'nix xronicheskoy serdechnoy nedostatochnost'yu ishemicheskogo geneza v sochetanii s alkogol'noy bolezn'yu pecheni / A.G. Yevdokimova, A.E. Radzevich, A.V. Tomova [i dr.] // Antibiotiki i ximioterapiya. – 2011. – T. 56, № 5–6. – S. 64–68.

8. Gadaev A.G., Ernazarov M.M., Kurbonov A.K., Turakulov R.I. Surunkali yurak yetishmovchiligi kechishida immun yallig‘lanish jarayoni xamda ichak mikrobiosenozining ahamiyati // Toshkent tibbiyot akademiyasi axborotnomasi. – 2019, №2. - S.13 – 17.

9. Galeev Yu.M. Metodi yadernoy medisini v izluchenii patogeneza bakterial'noy translokasii abdominal'nogo proisxojdeniya: avtoref. dis. … d- ra med. nauk: 14.01.13 / – Tomsk, 2011. – 51 s.

10. Grinevich V.B. Vklad kishechnoy mikrobioti v patogenez insulinorezistentnosti (obzor literaturi) / V.B. Grinevich, O.N. Tkacheva, L.V. Yegshatyan [i dr.] // Profilakticheskaya medisina. – 2015. – T. 18, № 1. – S. 54–58.

11. Koshman Y.E. Connective tissue growth factor regulates cardiac function and tissue remodeling in a mouse model of dilated cardiomyopathy / Y.E. Koshman, M.D. Sternlicht, T. Kim [et al.] // J. Mol. Cell. Cardiol. – 2015. – № 89. – P. 214–222.

12. Liao P. H. Heat-killed Lactobacillus Reuteri GMNL-263 prevents epididymal fat accumulation and cardiac injury in high-calorie diet-fed rats / P.-H. Liao, W.-W. Kuo, D. J.-Y. Hsieh [et al.] // Int. J. Med. Sci. – 2016. – Vol. 13, № 8. – P. 569– 577.

13. Maghsood F. Dual Effects of Cell Free Supernatants from Lactobacillus acidophilus and Lactobacillus rhamnosus GG in regulation of MMP-9 by Up-Regulating TIMP-1 and Down-Regulating CD147 in PMA-differentiated THP-1 Cells / F. Maghsood, A. Mirshafiey, M.M. Farahani [et al.] // Cell. J. – 2018. – Vol. 19, № 4. – P. 559–568.

14. Mareev V.Yu., Fomin I.V., Ageev F.T. i dr. Klinicheskie rekomendasii OSSN – RKO - RNMOT. Serdechnaya nedostatochnost': xronicheskaya (XSN) i ostraya dekompensirovannaya (ODSN). Diagnostika, profilaktika i lechenie // Kardiologiya. - 2018. - Tom - 58. (№6). - S. 8 - 158.

15. Paleev F.N. Immunopatogenez serdechnoy nedostatochnosti u pasientov s infeksionno-immunnim miokarditom / F.N. Paleev, N.P. Sanina, A.I. Makarkov [i dr.] // Rossiyskiy kardiologicheskiy jurnal. – 2016. – № 1 (129). – S. 32–40.

16. Pan'kova M.N. Ingibitorniy effekt interleykina-1β na sokratitel'nuyu deyatel'nost' gladkix mishs kapsuli limfaticheskix uzlov / Pan'kova M.N., Lobov G.I. // Regionarnoe krovoobrashenie i mikrosirkulyasiya. – 2013. – T. 12. – № 3 (47). – S. 53–56.

17. Pasini E. Pathogenic gut flora in patients with chronic heart failure / E. Pasini, R. Aquilani, C. Testa [et al.] // JACC Heart. Fail. – 2016. – Vol. 4, № 3. – P. 220–227.

18. Sandek A. Intestinal blood flow in patients with chronic heart failure: a link with bacterial growth, gastrointestinal symptoms, and cachexia / A. Sandek, A. Swidsinski, W. Schroedl [et al.] // J. Am. Coll. Cardiol. – 2014 – Vol. 64, № 11. – P. 1092–1102.

19. Tang W.H. We are not alone: understanding the contributions of intestinal microbial communities and the congested gut in heart failure / W.H. Tang // JACC Heart Fail. – 2016. – Vol. 4, № 3. – P. 228–229.

20. Tereshenko S.N. Diagnosticheskaya znachimost' immunologicheskix markerov u bol'nix vospalitel'noy kardiomiopatiey / S.N. Tereshenko, A.A. Skvorsov, A.Yu. Shedrina [i dr.] // Rossiyskiy kardiologicheskiy jurnal. – 2017. – № 2. – S. 22–29.

21. Tkachenko Ye.I. Trofologicheskie aspekti noosferogeneza. K 90-letiyu so dnya rojdeniya A.M. Ugoleva / Ye.I. Tkachenko, S.I. Sitkin, L.S. Oreshko, O.I. Medvedeva // Eksperimental'naya i klinicheskaya gastroenterologiya. – 2016. – T. 2, № 126. – S. 4–13.Antonov I.B. Matrix metalloproteinases MMP-1 and MMP-9 and their inhibitor TIMP-1 as markers of dilated cardiomyopathy in patients of different age / I.B. Antonov, K.L. Kozlov, E.M. Pal'tseva [et al.] // Bull. Exp. Biol. Med. – 2018. – Vol. 164, № 4. – P. 550–553.

22. Verbiskaya V.S. Disfunksiya slizistoy obolochki tonkoy kishki v posttravmaticheskom periode ushiba serdsa / V.S. Verbiskaya, O.V. Korpacheva, T.P. Xramix // Politravma. – 2011. – №3. – S. 84–88.