MYOCARDIAL REMODELING AND LIVER TRANSPLANTATION: THE RESULTS OF PROSPECTIVE SINGLE-CENTER STUDY

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Objective: to determine structural and functional characteristics of the heart in patients with chronic terminal hepatopathy in need of transplantation and their dynamics in liver transplant recipients in the postoperative period.
Materials and Methods. A single-center prospective cohort study was carried out. The observation period of patients with CTH was 5.4±3.29 years. Structural and hemodynamic parameters of the heart were measured by the method of echocardiography M-, B-modal and colored Doppler mode manufactured by General Electrics (USA) following the standard procedure.
Results. The liver transplant recipients showed an enlargement of the left heart chambers and an increase in the myocardium mass index of the left ventricle (111.4±4.54 g/m^2 и 128.9±32.04 g/m^2 respectively, p<0.05), decrease in the diameter of the inferior vena cava (24.3±3.17 mm and 17.2±3.46 mm respectively, p<0.05) and of the right atrium volume index (62.3±11.76 ml/m^2 and 26.4±4.23 ml/m^2 respectively, p<0.01) in the long-term postoperative period in comparison with the initial examination results at the stage of putting them on the waiting list. Application of the method of 2D-Speckle Tracking Imaging enabled us to reveal reliable reduction of the global systolic longitudinal deformation of the right ventricle in the liver transplant recipients in comparison with the general population patients with metabolic syndrome (-17.6±1.48 % and -23.4±1.07 % respectively, p<0.01) and chronic ischemic heart disease (-16.4±1.61 % and -22.1±1.54 % respectively, p<0.01). The proportion of liver transplant recipients who showed a diastolic dysfunction of the left ventricle appeared to be higher in the study group than in the general population (70.7 % and 57.5 % respectively, p<0.05). The proportion of patients with the normal geometry of the left ventricle was lower among the liver transplant recipients in the long-term postoperative period in comparison with the patients from the general population with metabolic syndrome (22.1 % and 45.0 % respectively, p<0.01) and chronic ischemic heart disease (19.5 % and 40.0 % respectively, p<0.01).
Conclusions. The results of the study provide evidence of the reverse development of cirrhotic cardiomyopathy manifestations and appearance of the signs of left ventricular remodeling after the orthotopic liver transplantation. The number of liver transplant recipients with metabolic syndrome, ischemic heart disease and diagnosed diastolic dysfunction of the left ventricle appeared to be higher in the study group than in the general population (70.7 % and 57.5 % respectively, p<0.05). Liver transplant recipients revealed the prevalence of disadaptive forms in the structure of remodeling: eccentric hypertrophy of the left ventricle (p<0.01), concentric remodeling (p<0.01) and dilatation hypertrophy of the left ventricle (p<0.01) in the long-term postoperative period in comparison with the patients from the general population.

Introduction

Cardiovascular risk factors in liver transplant recipients can be divided into three main groups: traditional risk factors, associated with liver failure, risk factors due to transplantation and risk factors connected with immunosuppressive therapy. There is no age limit for liver transplant recipients, but patients over 65 years of age need a multidisciplinary assessment in order to exclude concomitant diseases, which in turn may become an obstacle to perform the organ-replacing operation. Currently, orthotopic liver transplantation (OLT) is successfully performed in people over 65 years who are at a high risk of cardiovascular complications [1]. The tendency towards the age increase in candidates for liver transplantation is associated both with demographic changes, that is, with the aging society and with a change in the epidemiology of the liver damage.

Currently, liven (LC) is known to be associated with numerous disorders of the cardiovascular system in addition to systemic microcirculation disorders. The nature and severity of these changes do not depend on the etiology of LC. Cardiovascular complications in LC and portal hypertension are part of multiorgan syndrome.

The type of cardiac dysfunction which is characterized by inhibition of contractile reactivity to stress and/or changes in diastolic relaxation with typical electrophysiological manifestations without any other cardiac pathology in patients with LC is commonly defined as cirrhotic cardiomyopathy (Monreal, 2005) [2, 3].

Patients with cirrhotic cardiomyopathy (CCM) belong to a high perioperative risk group in the liver transplantation. CCM is a cause of death in 7–15 % of the total mortality rate in case of OLT. Left ventricular failure has

been shown to result in high intraoperative mortality and in most cases it is a contraindication for liver transplantation [4–6].

In patients with liver cirrhosis the prevalence of CCM has not been studied. The lack of these data indicates low awareness of practitioners about the changes in the cardiovascular system in case of liver cirrhosis; moreover, there are no clear criteria to diagnose this pathology. Unfortunately, the extensive polymorphism of cardiodepressive effects in LC does not make it possible to identify the leading pathogenetic mechanism of CCM development; it requires clarification and continuation of research in this area.

Clinical manifestations of CCM are nominally divided into the following categories: systolic myocardial dysfunction, diastolic myocardial dysfunction, electrophysiological changes, structural and morphological changes, biochemical changes.

Physical activity is the most studied factor capable of manifesting the existing disorder of the contractile response of the myocardium to physiological stress in LC. Recent studies revealed a disorder in the adequate response of the cardiovascular system in liver cirrhosis to various physiological and pharmacological stimuli [7].

Another important manifestation of CCM is diastolic myocardial dysfunction present to some extent in the majority of cirrhosis patients. In addition, in patients with intense ascites, the degree of diastolic dysfunction is higher than in patients without it [8, 9]. This was due to the fact that ascites can lead to pressure on the diaphragm and an increase in intrathoracic pressure, preventing the diastolic relaxation of the myocardium.

Structural or histological changes in the heart are found in most LC patients [10–12]. An echocardiographic examination reveals left ventricular (LV) hypertrophy with thickening of the interventricular septum developing as a result of hemodynamic overload and activation of the neuro-endocrine system. At the same time, the size of the right ventricle can be enlarged, reduced or not changed [13].

In CCM serious histological changes are also observed: subendocardial and myocardial edema, segmental fibrosis, myocardial hypertrophy, exudation, vacuolization of nuclei and pigmentation. Autopsy of the cardiac tissue in LC patients revealed histological changes in 32 % of cases [14, 15].

The specific treatment of CCM is currently not developed. Liver transplantation has proven its ability to reduce systolic and diastolic myocardial dysfunctions, prolongation of the QT interval; as a result, this method of treating LC complications is considered to be effective. However, there is always a risk of a sharp deterioration in the course of CCM, its transition from the latent form to the stage of marked clinical manifestations of heart failure after the liver transplantation [16, 17].

Although cirrhotic cardiomyopathy often decreases after liver transplantation, myocardial dysfunction can lead to cardiovascular complications during transplantation and in the early postoperative period.

The presence of cirrhotic cardiomyopathy in a patient affects the outcome of liver transplantation, increasing mortality in case of cardiovascular complications; therefore, timely diagnosis of myocardial dysfunction is important at the stage of examination of a candidate for liver transplantation. A sharp increase in preload during liver reperfusion causes hemodynamic stress. Under conditions of previous cardiomyopathy, pulmonary hypertension and low mean arterial pressure, an increase in preload may cause the development of a reperfusion syndrome and lead to cardiovascular complications in the intraoperative and early postoperative periods, including cardiac arrest (47.9 % of deaths from cardiovascular complications), stroke (12.5 %), acute heart failure (12.3 %) [5, 6].

The mechanisms of development of vasodilation and impaired contractility of cardiomyocytes in liver cirrhosis have been studied in numerous experimental models. Hyperproduction of nitric oxide and endocannabinoids, as well as activation of the intracellular pathways of the signal through cannabinoid receptors contribute to the development of vasodilation [15]. Various pathophysiological and biochemical changes impair the systolic function of the myocardium, affecting heart rate control, contractility of cardiomyocytes, conductivity and repolarization of the myocardium. These mechanisms include reduced sensitivity of β-adrenergic receptors, reduced content of G-proteins, activation of cannabinoid receptors-1, increased inhibitory effects of hemoxygenase, carbon monoxide, nitric oxid and tumor necrosis factor-α [18].

A distinctive feature of cirrhotic cardiomyopathy is an impairment of the myocardial systolic function, despite the normal ejection fraction and an increase in cardiac output per unit of time, which is manifested in response to physical exertion, pharmacological effects or changes in circulating blood volume and preload. In the absence of cirrhotic cardiomyopathy, an increase in exercise causes a proportional increase in cardiac output. In patients with cirrhosis of the liver, especially in case of its decompensation, there is no increase in cardiac output during exercise tolerance test [12].

Along with systolic dysfunction, cirrhotic cardiomyopathy is characterized by the development of diastolic dysfunction. The severity of diastolic dysfunction has been found to correlate with the class of cirrhosis on the Childe-Pugh scale and an indicator of the severity scale for patients with liver diseases MELD, as well as the incidence of hepatorenal syndrome. The survival of patients with diastolic dysfunction is lower than that of other patients with cirrhosis of the liver, respectively [9]. However, 6–12 months after orthotopic liver transplantation the normal diastolic function of the myocardium and the systolic response to stress are restored on their own [5, 19].

After liver transplantation cirrhotic cardiomyopathy and hyperdynamic syndrome decrease, as a rule, but in clinical practice hemodynamic normalization does not always occur. According to some authors increased cardiac output remains up to two years after orthotopic liver transplantation, according to others – the hyperdynamic syndrome and diastolic dysfunction disappear immediately [19]. M. Soresi et al. state that changes in hemodynamics in the portal vein system occurring during liver cirrhosis and leading to disturbances in the cardiovascular system as a whole gradually decrease within 12 months after transplantation [20]. M. Torregrosa et al. provide evidence

that within 6–12 months after transplantation myocardial hypertrophy and diastolic dysfunction decrease and the systolic response to exercise becomes normal [19].

The dynamic difficulties of observing this category of patients on the waiting list are due to the fact that prior to performing liver transplantation cirrhotic cardiomyopathy may not be manifested clinically, but if hemodynamics changes during the operation acute decompensated heart failure may develop. During the long-term arterial vasodilation and decentralization of blood flow, the cardiovascular system adapts to reduced preload. The preload is even more reduced intraoperatively and then it increases very sharply at the stage of reperfusion of the liver transplant. This hemodynamic stress may lead to rhythm disturbances, acute heart failure, myocardial infarction, especially in the presence of initial high pressure occlusion of pulmonary capillaries and/or low mean arterial pressure. Adequate anesthesia, fluid balance control, volume monitoring are extremely important to prevent cardiovascular complications during liver transplantation [21].

The development of the reperfusion syndrome during liver transplantation is associated with an increase in the incidence of perioperative complications, impaired renal function and decreased survival of the recipients. Reperfusion syndrome is characterized by a decrease in mean arterial pressure by 30 % for at least 1 minute within 5 minutes after reperfusion. At the same time, decreased heart rate, cardiac output, peripheral vascular resistance and increased pressure occlusion of pulmonary capillaries, pressure in the pulmonary artery and central venous pressure are observed [5, 22, 23]. The mechanism underlying this condition is multicomponent and complex, it includes acidosis, hyperkalemia, hypothermia, hypocalcemia. When the inferior vena cava is clamped in the ahepatic phase, products of ischemia (lactate, hydroxide ions, carbon dioxide) are accumulated in the tissues of the extremities and in the abdominal cavity. At the time of reperfusion these molecules enter the systemic circulation causing acidosis. The ingestion of a significant amount of cold perfusate having a low pH into the abdominal cavity and bloodstream sharply lowers the temperature and aggravates the existing metabolic acidosis. In addition, the perfusate contains a large amount of potassium ions, that is, it leads to hyperkalemia, which causes bradycardia and cardiac arrest. Impaired renal function, preceding or developing intraoperatively, aggravates acidosis and hyperkalemia. The release of pro-inflammatory cytokines from ischemic graft cells during reperfusion contributes to the development of hypotension. Thus, severe bradycardia, arterial hypotension, decreased cardiac output increase the risk of developing effective blood circulation arrest. The incidence of cardiac arrest during reperfusion varies from 1 to 5.5 % [4, 24, 25].

Decreased peripheral vascular resistance, manifested by arterial hypotension, can also be characterized by vasoplegia, that is, lack of vascular response to catecholamines. The manifestations of reperfusion syndrome include a pathological decrease in cardiac output with an increase in high pressure occlusion of pulmonary capillaries, which can be observed in 22 % of patients [23, 24]. According to Z.D. Xu et al. diastolic dysfunction which is one of the components of the cirrhotic cardiomyopathy syndrome is an independent risk factor for the reperfusion syndrom [25].

Until recently infectious complications were considered to be the main cause of death for the recipients of liver transplants in the early postoperative period (up to the 30th postoperative day). In 2014 the results of the study of causes of death based on the analysis of data of 54697 liver transplants were published. Despite the exclusion of contraindications on the part of the cardiovascular system during examination of patients with cirrhosis of the liver while including them on the waiting list (ischemic heart disease, heart failure, rhythm disorders and conduction disturbances, alcoholic cardiomyopathy) cardiovascular complications turned out to cause 40.2 % of deaths before the 30th postoperative day. This was followed by infections (27.9 %) and graft dysfunction (12.2 %). The authors explain such a high proportion of cardiovascular mortality by increased age of patients on the waiting list, increased number of recipients with decompensated liver cirrhosis and a high MELD. Risk factors for death from cardiovascular diseases up to the 30th postoperative day were the age of the recipient, a high MELD score, hospitalization the day before the liver transplantation, stay in the intensive care unit and the need for artificial respiration before surgery. In addition, the donor's body mass index and the time of cold ischemia were higher in the group of deceased recipients. Multifactor analysis showed a significant relationship between cardiovascular mortality after transplantation and high MELD, as well as the development of acute renal failure [26, 27].

Heart failure after liver transplantation may develop in about 10 % of cases. Systolic (ejection fraction <50 %) heart failure is more commonly (7 %) diagnosed than diastolic or combined one. Currently, there is no generally accepted examination method to determine the risk for the development of these complications. The relationship between the myocardial diastolic dysfunction in the preoperative period, the level of the brain natriuretic peptide and the incidence of heart failure in the early postoperative period has been found [28, 29].

Thus, cardiovascular dysfunction generally results from combined neurohumoral and hemodynamic disorders in LC. Therefore, CCM is considered as an integral part of multiorgan syndrome, which affects the survival and quality of patients' life. Still, many aspects in the development of CCM remain elusive, which means that the treatment regimen of this category of patients is far from perfect. All this dictates the need to continue research aimed at understanding complex mechanisms underlying cardiovascular disorders in liver pathology and structural and functional changes of the heart in patients with CCM after liver transplantation.

The aim of the study is to determine structural and functional characteristics of the heart in patients with chronic terminal hepatopathy (CTH) who are in need of transplantation and evaluate their dynamics in liver transplant recipients in the postoperative period.

Materials and methods

A single-center prospective cohort study was carried out, one part of which was evaluation of the dynamics of

structural and functional heart characteristics in patients with chronic terminal hepatopathy (CTH) and in recipients of the donor organ transplant. According to the study design the study group was formed by the liver transplant recipients (n=150). The opportunity to participate in the study was given to patients with chronic terminal liver diseases who signed an informed consent when they were included on the waiting list and met the criteria of inclusion developed on the basis of the aim and objectives of the study. The control group consisted of the patients with CTH from the waiting list who did not receive a liver transplant during the observation period (n=100).

Patients were assigned to the study and control groups on the basis of the following inclusion criteria: a signed informed consent for participation in the study; the presence of an irreversible liver disease with an unfavorable prognosis for life; the presence of chronic liver disease significantly reducing the patient's quality of life and ability to work; progressive liver disease with a shorter life expectancy than in case of liver transplantation.

Non-inclusion criteria: the presence of relative or absolute contraindications for transplantation in patients with chronic liver disease indicated in the clinical protocol of liver transplantation, approved by the Decree of the Ministry of Health of the Republic of Belarus of January 5, 2010 No. 6 (Appendix 6) and amended by the Decree of the Ministry of Health of the Republic of Belarus of 28.12.2012 No. 1540; ischemic damage of the donor liver in the process of organ procurement and preservation; the presence of coronary heart disease at the stage of including the patient on the waiting list; detection of stenosing atherosclerosis in other vascular beds besides the coronary one; the presence of diabetes mellitus type 1 or 2.

Exclusion criteria from the study: development of acute or chronic rejection which required a change in the basic immunosuppressive therapy, the patient's refusal to participate further in the study, death of the patient from a cause that is not the major and/or additional outcome of the study.

The follow-up period for patients with CTH was 5.4 ±3.29 years. Physical examination of patients which included questioning, taking a detailed case history, clinical examination, laboratory and instrumental studies were carried out when including patients on the waiting list (visit 0: day 0±7 days), at the stage of orthotopic liver transplantation (visit 1: day 1±1 day), at the end of the early postoperative period (visit 2: day 30±0 days), in the late postoperative period at 1 year (visit 3: day 365±30 days) and 5 years (visit 4: 5 years ±30 days) after the orthotopic liver transplantation.

Two comparison groups were formed from patients who matched transplant recipients by age, sex and traditional cardiovascular risk factors and who had metabolic syndrome (comparison group I), chronic ischemic heart (IHD) disease and metabolic syndrome (MC,comparison group II).

The mean age of liver transplant recipients was 41.8 ±7.29 years, in the subgroup of recipients with coronary heart disease and metabolic syndrome – 46.45±3.12 years. The age composition was as follows: 20–29 years old – 4.4 % (n=11), 30–39 years old –19.2 % (n=48), 40–49 years old – 43.2 % (n= 08), 50–59 years old – 28.4 % (n=71), 60 years and over – 4.8 % (n=12).

The comparison group I had the following age composition: 20–29 years – 5 %, 30–39 years – 20 %, 40–49 years – 40 %, 50–59 years – 30 %, 60 years and over – 5 %. The age composition of the comparison group II: 30–39 years – 5 %, 40–49 years – 15 %, 50–59 years – 65 %, 60 years and over – 15 %.

All examined organ transplant recipients had no coronary heart disease at the time of inclusion in the study. The risk factors for coronary heart disease in the study group were: smoking – in 9.6 %; family history of early cardiovascular diseases (in females over 65 years, in males under 55 years) – in 40.4 %; abdominal obesity (waist circumference ≥80 cm in females, ≥94 cm in males) – in 64.7 %. A history of arterial hypertension was detected in 53.2 % of patients with CTH, and the duration of arterial hypertension was 2.81 (2; 3.93) years. A combination of two or more cardiovascular risk factors at the time of inclusion on the waiting list was found in 60.0 % of the examined liver transplant recipients.

Structural and hemodynamic parameters of the heart were examined by M-, B-mode echocardiography and color Doppler mode in liver transplant recipients (the study group) and in patients with chronic terminal liver diseases from the control group during visits 0 (using tissue Doppler imaging), visit 2, visit 3 and visit 4 (using tissue Doppler imaging), in the comparison groups I and II – once during the inclusion of patients in the study. The study was conducted using the device «Vivid-7» manufactured by General Electrics (USA) according to the standard method using an ultrasonic sensor with a scanning frequency of 3.5 MHz. The permissible measurement error in the M-mode is 2 %, in the B-mode – 5 %, in the Doppler mode – 4–10 %. All formulas for calculating volumes and indices were integrated into the software package of the echocardiograph, immediately after the calculation the measurement results were presented on the monitor of the device and recorded in an individual patient's card.

The following structural and functional parameters were determined: size of the left atrium (LA), diameter of the aortic (Ao) root, amplitude of aortic valve (AV) opening, anteroposterior size of the right ventricle (APSRV), thickness of the anterior wall of the right ventricle (AWRV), end diastolic (EDP) and systolic (ESP) dimensions of LV, end diastolic (EDV) and systolic (ESV) volumes of LV, stroke volume (SV) of LV, thickness of the posterior wall of LV (PWLV) and thickness of the interventricular septum (IVS) in diastole, LV ejection fraction (EF) in M-(Teichgolz) and B-modes (Simpson).

Blood flow velocity indicators in the aortic, mitral, tricuspid and pulmonary valves and tricuspid insufficiency development speed were determined. Using pulse-wave Doppler transmitral flow indices were calculated: speed parameters of E, A peaks and their ratio (E/A), DT (time of early delay of mitral blood flow), IVRT (isovolumetric relaxation time of the left ventricle).

To assess the diastolic function, spectral tissue Doppler indices were used: systolic and diastolic velocities (Em, Am, Em/Am, E/Em) of the mitral valve movement from the accessible compartments (septal, lateral, anterior-septal, lower lateral, inferior and anterior). Septal Em ≥8 cm/s and lateral Em ≥10 cm/s were considered as reference

values. The recording of tissue Doppler examination contained speed indicators for at least one second. Deformation analysis was performed using tissue Doppler and QLAB StrainQuantification.

To detect the impairment of diastolic function the values of four indicators were used: the speed of movement of the mitral valve ring Em (septal Em <7 cm/sec and lateral Em <10 cm/sec), the ratio of E velocity of the mitral flow to the average E/Em_{av} velocity of the mitral ring (>14), the left atrium volume index (>34 ml/m^2), the maximum speed of tricuspid regurgitation (>2.8 m/s).

To assess the LV remodeling process, the LV myocardium mass index (LVMMI, g/ml) and the index of the relative LV wall thickness in diastole (IRWT) were determined. LVMMI was calculated as the ratio of the LV myocardium mass (LVMM) to the surface area of the body. The LVMM was calculated by the equation of R.Devereux and N. Reicheck:

$$LVMM = 0.8 \times 1.04 \times [(EDP+TIVSd+TPWLVd)^3 - EDP^3] + 0.6.$$

where EDP – end diastolic size of the LV, TIVSd – thickness of the interventricular septum in diastole, TPWLVd – thickness of the posterior wall of LV in diastole.

The surface area of the body (SAB) was calculated from the expression:

$$SAB = 0.007184 \cdot h^{0.725} \cdot m^{0.425},$$

where m – body weight, kg, h – height, cm.

According to the ASE updated guidelines for measuring heart chambers in the M-mode the upper limit in females was LVMMI > 95 g/m^2 and > 115 g/m^2 in males.

The index of the relative wall thickness (IRWT) of LV in diastole was calculated by the equation:

$$IRWT=(TIVSd+TPWLVd)/EDP.$$

The index of the final diastolic volume of the left ventricle was calculated by the equation:

$$LV\ EDV\ index = LV\ EDV/SAB.$$

The combination of the LVMMI index (vertical axis), LV EDV (horizontal axis) and IRWT enabled us to reveal the type of left ventricular remodeling. The classical description of the geometry of the left ventricle used in the analysis of findings of the examined patients is presented in Table 1.

For additional evaluation of the functional state of the right ventricle, echocardiography was performed using 2D-Speckle Tracking Imaging. In the four-chamber apical position, the global systolic longitudinal deformation of the free wall of the right ventricle (Strain) was determined offline. The global longitudinal systolic deformity of the right ventricle was considered normal at values of –18.9±2.5 % taking into account the type of equipment and software.

Data processing was carried out using statistical packages Statistica (version 8.0) and Excel. For samples with normal distribution methods of variation statistics and parameter criteria were used. The data were presented as: mean value (M), non-sampling error (m). Comparison of two independent groups based on quantitative characteristics was carried out using t-Student criterion. The significance of variations within the same group was estimated using the non-parametric Friedman and Wilcoxon criteria for dependent variables with the introduction of the Bonferroni correction with false discovery rate (FDR). The central tendencies and variances of quantitative characteristics that did not have normal distribution were described by the median (Me) and interquartile range (25th and 75th percentile). Differences in the groups were considered reliable with a probability of an accurate prognosis of 95.5 % ($p<0.05$). In case of multiple comparisons the critical level of p significance was calculated using the FDR method. The comparison of groups based on qualitative characteristics was performed using the analysis of the occurrence rate of the characteristics. Assessment of the difference between independent samples by the occurrence rate of the characteristic based on Fisher's exact test, χ^2 test (Pearson method, maximum likelihood method) was performed.

Results and discussion

Analyzing the results of the echocardiographic examination in liver transplant recipients in the late postoperative period compared with the initial examination results during the visit 0 we established expansion of the aorta in the ascending part, enlargement of the left heart chambers sizes, LVMMI and IRWT, decrease in the diameter of the inferior vena cava and the right atrium volume index (Table 2). Positive dynamics of the size of the right atrium and inferior vena cava was first noted 12 months after OLT and remained during five years of follow-up of the study group recipients.

In the patients of the control group who did not receive a liver transplant during the observation period we revealed increased size of both atria, the right ventricle with decreased systolic excursion of the tricuspid valve ring, enlarged diameter of the inferior vena cava and increased peak velocity of tricuspid regurgitation, as well as reduced ratio of the velocity of transtricuspid flow in the phase of early diastole to the flow rate in the right atrium systole phase (Table 2) at the end of the five-year study period compared with the initial examination results during visit 0, which, in addition to aggravation in the severity of symptoms of hepatic insufficiency provided evidence of progressive cirrhotic cardiomyopathy and the right ventricle failure in these patients.

Table 1 – Criteria for determining the geometry of the left ventricle according to measurements made in the M-mode

Left ventricular geometry	LV EDV index, ml/m^2	LVMMI, g/m^2	IRWT
Normal	≤75	≤115 g/m^2 (males) ≤95 g/m^2 (females)	0.32–0.42
Physiological hypertrophy	>75	>115 g/m^2 (males) >95 g/m^2 (females)	0.32–0.42
Concentric hypertrophy	≤75	>115 g/m^2 (males) >95 g/m^2 (females)	>0.42
Eccentric hypertrophy	>75	>115 g/m^2 (males) >95 g/m^2 (females)	<0.32
Dilatation hypertrophy	>75	>115 g/m^2 (males) >95 g/m^2 (females)	0.32–0.42
Mixed hypertrophy	>75	>115 g/m^2 (males) >95 g/m^2 (females)	>0.42
Concentric remodeling	≤75	≤115 g/m^2 (males) ≤95 g/m^2 (females)	>0.42
Eccentric remodeling	>75	≤115 g/m^2 (males) ≤95 g/m^2 (females)	<0.32

Table 2 – Dynamics of changes in echocardiography data of patients with chronic terminal liver diseases, M±m

Characteristics	Study group n=150 Visit 0	Control group n=100 Visit 0	P*	Study group n=128 Visit 2	Control group n=96 Visit 2	P*	Study group n=117 Visit 3	Control group n=50 Visit 3	P*	Study group n=92 Visit 4	Control group n=40 Visit 4	P*
The size of the ascending aorta, mm	28.2 ±4.12	27.1 ±2.34	0.33	30.3 ±4.63	29.8 ±2.61	0.42	33.1 ±2.65	28.4 ±1.34	<0.01	36.4 ±3.19●	29.7 ±3.42	<0.01
LA size in M-mode, mm	32.7 ±3.48	34.7 ±4.32	0.32	38.9 ±4.96	36.4 ±2.12	0.11	36.9 ±3.23	38.7 ±6.24	0.24	41.7 ±3.46●●	40.2 ±3.21■	0.09
LA volume, ml	39.9 ±15.94	42.1 ±4.53	0.43	46.7 ±13.41	44.2 ±5.18	0.34	45.9 ±3.24	49.3 ±10.62	0.12	65.19 ±7.23●●	50.8 ±12.43■	<0.05
LA volume index, ml/m²	32.1 ±4.56	32.4 ±3.23	0.98	33.2 ±5.18	34.6 ±4.21	0.64	34.1 ±2.34	35.8 ±6.44	0.12	38.54 ±6.73●	32.7 ±9.24■	<0.05
TIVSd, mm	9.1 ±1.32	10.2 ±1.54	0.16	9.4 ±2.16	10.1 ±3.01	0.09	11.2 ±3.14	10.8 ±2.31		15.3 ±3.19●●	10.2 ±1.54	<0.05
TPWd, mm	7.8 ±1.34	7.3 ±1.02	0.64	8.1 ±1.56	7.6 ±2.18	0.66	12.4 ±3.51●	7.4 ±1.19	<0.05	14.2 ±2.19●●	7.5 ±2.19	<0.01
E / Amv	0.94 ±0.03	0.89 ±0.05	0.12	0.96 ±0.04	0.89 ±0.03	0.08	0.82 ±0.04●	0.84 ±0.03	0.74	0.84 ±0.06	0.87 ±0.04	0.33
RA volume index, ml / m²	62.3 ±11.76	65.8 ±14.42	0.87	64.4 ±9.19	66.3 ±12.37	0.84	28.2 ±5.34●●	72.1 ±14.28	<0.01	26.4 ±4.23●●	79.6 ±11.38■	<0.01
RV size, parasternal section, mm	28.4 ±4.32	29.1 ±5.11	0.94	30.6 ±3.31	31.4 ±4.19	0.67	28.1 ±4.56	32.8 ±5.24	0.43	27.9 ±3.18	36.5 ±4.11■	<0.05
TAPSE, mm	17.4 ±4.26	16.8 ±3.11	0.45	18.6 ±3.52	16.4 ±4.23	0.09	19.1 ±2.48	14.3 ±2.34	<0.01	19.6 ±3.72	12.7 ±3.18■	<0.01
E/Atv	0.87 ±0.04	0.84 ±0.06	0.32	0.86 ±0.03	0.84 ±0.04	0.33	0.92 ±0.06	0.86 ±0.08	0.09	1.34 ±0.06●	0.82 ±0.07	<0.01
Inferior vena cava, mm	24.3 ±3.17	26.1 ±4.52	0.07	21.8 ±3.46	24.7 ±3.44	0.38	18.5 ±2.76●	28.2 ±4.43	<0.05	17.2 ±3.46●	34.3 ±6.32■■	<0.01
Peak velocity of tricuspid regurgitation, cm/s	227.4 ±32.18	236.7 ±11.43	0.23	242.6 ±39.32	251.3 ±41.38	0.44	231.4 ±19.48	259.1 ±38.14	0.06	217.5 ±31.18	268.5 ±38.54■	<0.05
Estimated systolic pressure in PA, mHg	29.6 ±3.16	32.4 ±5.28	0.34	28.9 ±4.39	32.6 ±8.19	0.39	30.1 ±4.26	34.8 ±7.14	0.19	26.1 ±4.34	39.5 ±14.08	<0.05
EDP, cm	5.1 ±0.17	5.3 ±0.18	0.21	5.2 ±0.14	5.4 ±0.17	0.26	5.3 ±0.21	5.4 ±0.19	0.67	5.3 ±0.29	5.6 ±0.27	0.43
EDV index, ml/m²	72.2 ±3.19	74.8 ±9.26	0.48	73.8 ±4.56	74.6 ±12.42	0.36	74.6 ±5.23	75.9 ±11.16	0.66	83.1 ±3.18●	76.1 ±8.34	0.21
ESP, cm	3.1 ±0.07	3.3 ±0.09	0.09	3.4 ±0.21	3.2 ±0.11	0.07	3.3 ±0.11	3.4 ±0.08	0.84	3.2 ±0.25	3.3 ±0.29	0.54
EF, %	66.3 ±5.98	61.5 ±4.27	0.34	62.5 ±9.34	61.8 ±11.32	0.43	62.4 ±7.19	61.8 ±11.32	0.73	64.6 ±5.46	61.3 ±14.19	0.44
LVMMI, g/m²	111.4 ±4.54	112.9 ±5.13	0.33	116.2 ±3.84	114.7 ±4.38	0.38	116.8 ±24.31	110.9 ±14.18	0.63	128.9 ±32.04●	114.6 ±9.24	0.32
IRWT	0.35 ±0.01	0.32 ±0.02	0.65	0.36 ±0.04	0.33 ±0.03	0.44	0.43 ±0.11	0.39 ±0.04	0.24	0.48 ±0.12●	0.37 ±0.08	0.07

*Note: * – reliability of differences in intergroup comparison of indicators, ● – reliability of differences in intragroup comparison with baseline values (visit 0) of liver transplant recipients with p <0.05, ●● – with p <0.01, ■ – reliability of differences in intragroup comparison with baseline values (visit 0) of patients of the control group at p <0.05, ■■ at p <0.01.*

2. LA – left atrium (the volume was calculated by the «area-length» algorithm in the four-chamber position); TIVSd – thickness of the interventricular septum in diastole; TPWd – thickness of the posterior wall of the left ventricle in diastole; E/A_{mv} – ratio of the transmitral flow rate in the early diastole phase (E peak) to the flow rate in the left atrial systole phase (peak A); RA – right atrium; RV – right ventricle; TAPSE – tricuspid annular plane systolic excursion; E/A_{tv} – the ratio of transtricuspid flow rate in the early diastole phase (E peak) to the flow rate in the right atrial systole phase (peak A); PA – pulmonary artery; EDP – the end diastolic size of the left ventricle; ESP – the end systolic size of the left ventricle; EF – left ventricular ejection fraction; LVMMI is left ventricle myocardial mass index; IRWT is index of the relative wall thickness of the left ventricle.

Intergroup comparative analysis of echocardiographic parameters showed that recipients of liver transplants compared with patients of the control group had a large left atrium size (65.19±7.23 ml and 50.8±12.43 ml respectively, p<0.05) and left ventricle wall thickness (TIVSd 15.3±3.19 mm and 10.2±1.54 mm, respectively, p<0.05; TPWd 14.2 ±2.19 and 7.5±2.19, respectively, p<0.01) five years after OLT. However, the size of the right heart, the diameter of the inferior vena cava, the peak velocity of tricuspid regurgitation, the estimated systolic pressure in the pulmonary artery in patients after OLT were lower than in the control group (Table 2).

The proportion of patients with valvular regurgitation (without taking into account the severity) among liver transplant recipients examined in the late postoperative period is presented in Table 3. The proportion of subjects with mitral regurgitation among asymptomatic liver transplant recipients who had verified coronary heart disease exceeded the corresponding number in the comparison group II (p <0.05).

When analyzing the diastolic myocardial function in liver transplant recipients with coronary heart disease and/or metabolic syndrome compared with patients from the general population included in the comparison groups, a decrease in the flow rate of the early filling period (E peak) and the E/A transmitral blood flow ratio, as well as an increase in the delay time of the early transmitral diastolic flow (DT) and left ventricle isovolumetric relaxation time (IVRT) were found (Table 4). Despite the absence of changes in transtricuspid flow rates during Doppler study, the use of 2D-Speckle Tracking Imaging revealed a significant decrease in global systolic longitudinal deformation of the right ventricle in liver transplant recipients in the late postoperative period compared with patients of the general population with MS and/or CHD who were included in the comparison group I (-17.6±1.48 % and -23.4±1.07 %, respectively, p<0.01) and the comparison group II (-16.4 ±1.61 % and -22.1±1.54 %, respectively, p<0.01), which is evidence of persisting right ventricular myocardial subendocardial fibers dysfunction after OLT.

The proportion of liver transplant recipients with metabolic syndrome and ischemic heart disease who had diagnostic criteria for left ventricular diastolic dysfunction was higher in the study group than in the general population (Figure 1).

The use of spectral tissue Doppler in examining liver transplant recipients in the late postoperative period enabled us to reveal increased proportion of patients with left ventricular diastolic dysfunction among patients with ischemic heart disease compared with patients in the general population. The incidence of identifying patients with impaired diastolic function of the left ventricle when using new diagnostic criteria was higher in the study group compared with the use of such a characteristic as E/A_{mv}: 70.7 % and 46.3 %, respectively.

In accordance with the consensus adopted by the International Forum on Heart Remodeling myocardial remodeling can be defined as a change in genome expression, molecular, cellular, and interstitial changes which are manifested by the transformation of the size, shape and function of the left ventricle after its damage. LV remodeling is often considered as a completely non-specific process independent of the nature of the underlying disease or cluster of diseases. Such an approach which contradicts the theory of multimodal myocardial reaction, largely depending on the nature and time of the initiating factor, and modern concepts about the types of LV remodeling and the division of the latter into adaptive and maladaptive forms has become the subject of justified criticism.

The geometrical model of the left ventricle was determined in the study groups by a combination of the LVMMI (vertical axis), LV EDV index (horizontal axis) and IRWT measured in M-mode. A description of the types of remodeling and their incidence in liver transplant recipients with metabolic syndrome and/or ischemic heart disease in the late postoperative period (visit 4) is presented in Table 5.

In the study group of liver transplant recipients compared with patients with MS and/or CHD of the general population, a smaller proportion of individuals with normal left ventricular geometry was detected in the late postoperative period. Maladaptive forms prevailed in the remodeling structure: the proportion of liver transplant recipients with MS who have a prognostically unfavorable form of LV myocardial remodeling was 50.4 % vs 25.0 % in the comparison group I (p<0.01), in liver transplant recipients with coronary heart disease – 58.5 % vs 37.5 % in comparison group II (p<0.05). The structure of maladaptive disorders of the geometric model in liver transplant recipients with metabolic syndrome more frequently revealed eccentric left ventricular hypertrophy and concentric remodeling (p<0.01), with ischemic heart disease – eccentric and dilated (p<0.01) LV hypertrophy (Figure 2).

Conclusion

Liver transplants recipients showed an increase in the size of the left heart chambers (left atrium volume 39.9 ±15.94 ml and 65.19±7.23 ml, respectively p<0.01; EDV

Table 3 – Distribution of patients with valvular regurgitation,% (abs.)

Characteristics	Liver transplant recipients (MS) n=109	Liver transplant recipients (MS+CHD) n=41	Comparison group I n=40	Comparison group II n=40
Aortic valve	22.9 % (25)	46.3 % (19)	22.5 % (9)	40.0 % (16)
Pulmonary valve	11.0 % (12)	4.9 % (2)	10.0 % (4)	7.5 % (3)
Mitral valve	47.7 % (52)	70.7 % (29) *	47.5 % (19)	47.5 % (19)
Tricuspid valve	48.6 % (53)	24.4 % (10)	42.5 % (17)	35.0 % (14)

*Note: * – significance of difference compared with the characteristics of comparison group II at p <0.05.*

Table 4 – Echocardiographic indicators of LV and RV diastolic function, MS (25–75 %)

Characteristics	Liver transplant recipients (MS) n=109	Liver transplant recipients (MS +CHD) n=41	Comparison group I n=40	Comparison group II n=40
E_{mv}, cm/s	53 (45; 67)*	52 (45; 54)●	65 (50; 70)	62 (49; 68)
A_{mv}, cm/s	60 (56; 68)	62 (48 ;69)	56 (47; 63)	60 (50; 65)
E/A_{mv}	0.85 (0.74; 1.2)**	0.83 (0.72; 1.2)●	1.15 (0.89; 1.38)	1.0 (0.75; 1.17)
DT, ms	164 (98; 279)	221 (119; 308)●	156 (96; 265)	154 (90; 270)
IVRT, ms	112 (84; 152)	154 (90; 326) ●	104 (75; 148)	108 (70; 165)
E_{tv}, cm/s	50 (41; 60)	56 (45; 70)	55.5 (45; 62)	60 (42; 70)
A_{tv}, cm/s	50 (43; 58)	49 (42; 68)	49.5 (43; 60)	49 (40; 70)
E/A_{tv}	0.97 (0.8; 1.22)	1.14 (0.82; 1.34)	1.09 (0.86; 1.33)	1.17 (0.82; 1.33)
RV global strain, %	-17.6±1.48**	-16.4±1.61●●	-23.4±1.07	-22.1±1.54
Characteristic, % (abs.)				
Decrease in the speed of movement of the mitral valve ring (Em)	62.4 % (68)	70.7 % (29)●	60.0 % (24)	57.5 % (23)
Ratio of E velocity of the mitral flow to the mean velocity of the mitral ring (E/Em_{av}) > 14	47.7 % (52)	46.3 % (19)●	47.5 % (19)	30.0 % (12)
Left atrium volume index (LAVI)> 34 ml/ m²	39.4 % (43)	53.6 % (22)●	42.5 % (17)	22.5 % (9)
Peak tricuspid regurgitation rate (CTP)> 280 cm / sec	34.9 % (38)	41.5 % (17)●●	35.0 % (14)	17.5 % (7)
E/A_{mv} < 1	41.3 % (45)	46.3 % (19)	55.0 % (22)	52.5 % (21)

*Note: * – significance of difference in intergroup comparison with the comparison group I indicators of liver transplant recipients with MS at p <0.05, ** – at p <0.01, ● – significance of difference in intergroup comparison with comparison group II of liver transplant recipients with CHD and MS at p <0.05, ●● with p <0.01.*
2. E – transmitral flow rate in the early diastole phase; A_{mv} – transmitral flow rate in the left atrial systole phase; E/A_{mv} – ratio of the transmitral flow rate in the early diastole phase (E peak) to the flow rate in the left atrial systole phase (peak A); DT is the delay time of the early transmitral diastolic flow; IVRT is the time of isovolumetric relaxation of the left ventricle; E_{tv} – transstricuspid flow rate in the early diastole phase; A_{tv} – transstricuspid flow rate in the systole phase of the right atrium; E/A_{tv} – the ratio of transtricuspid flow rate in the early diastole phase (E peak) to the flow rate in the right atrial systole phase (peak A).

index 72.2±3.19 ml/m² and 83.1±3.18 ml/m², respectively, p<0.05), LVMMI (111.4±4.54 g/m² and 128.9±32.04 g/m², respectively, p<0.05) and IRWT (0.35±0.01 and 0.48±0.12, respectively, p<0.05), decrease in the diameter of the inferior vena cava (24.3±3.17 mm and 17.2±3.46 mm, respectively, p<0.05) and of the right atrial volume index (62.3±11.76 ml/m² and 26.4±4.23 ml/m², respectively, p<0.01) in the late postoperative period compared with the initial results of the examination at the stage of their inclusion on the waiting list, which indicates the reverse development of manifestations of cirrhotic cardiomyopathy and the appearance of signs of left ventricular remodeling after orthotopic liver transplantation. Positive dynamics of the size of the right atrium and inferior vena cava were first observed 12 months after the operation and remained during five follow-up years of the study group recipients.

Among the patients of the control group who did not receive a liver transplant during the observation period an increase in the size of both atria was observed at the end of the five-year period of participation in the study compared with the initial results of the examination (left atrium volume was 42.1±4.53 ml and 50.8±12,43 ml, respectively, p<0.05, the volume index of the right atrium 65.8 ±14.42 ml/m² and 79.6±11.38 ml/m², respectively, p<0.05), of the right ventricle (29.1±5.11 mm and 36.5 ±4.11 mm, respectively, p<0.05) with a decrease in the systolic excursion of the tricuspid valve ring (16.8±3.11 mm and 12.7±3.18 mm, respectively, p<0.05), the diameter of the inferior vena cava (26.1±4.52 and 34.3±6.32 mm, respectively, p <0.01) and the peak speed of tricuspid regurgitation (236,7±11.43 cm/s and 268.5±38.54 cm/s, respectively, p<0.05), which, in addition to exacerbating the

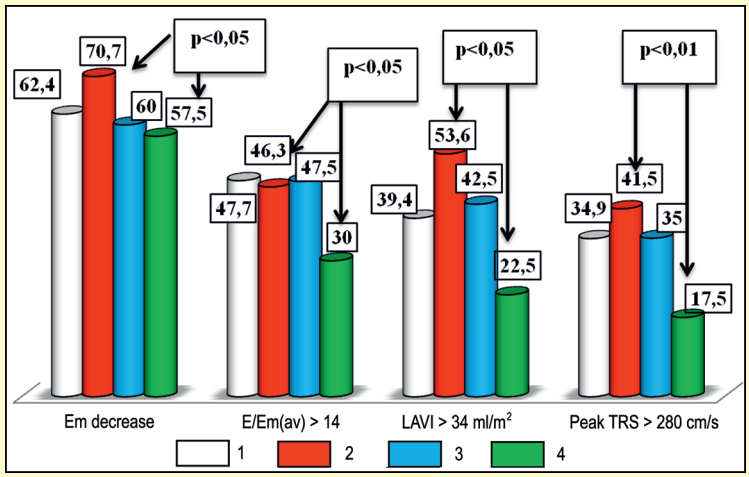

Figure 1 – The incidence of detection of left ventricular diastolic dysfunction signs in liver transplants recipients of the study group and the general population patients. 1 – Liver transplant recipients (MS), 2 – Liver transplant recipients (MS+CHD), 3 – Comparison group I, 4 – Comparison group II.

Table 5 – Incidence of various types of left ventricular remodeling in liver transplant recipients in the late postoperative period

Characteristics	Liver transplant recipients (MS) n=109	Liver transplant recipients (MS +CHD) n=41	Comparison group I n=40	Comparison group II n=40
Percentage of individuals with normal LV geometry	22.1 % (24)**	19.5 % (8)●●	45.0 % (18)	40.0 % (16)
Percentage of individuals with physiological LV hypertrophy	17.4 % (19)	4.9 % (2)	17.5 % (7)	5.0 % (2)
Percentage of individuals with concentric LV hypertrophy	10.1 % (11)	17.1 % (7)	12.5 % (5)	17.5 % (7)
Percentage of individuals with eccentric LV hypertrophy	15.6 % (17)	24.4 % (10)	20.0 % (8)	20.0 % (8)
Percentage of individuals with dilated LV hypertrophy	5.5 % (6)*	21.9 % (9)●●	0 % (0)	2.5 % (1)
Proportion of individuals with mixed LV hypertrophy	7.3 % (8)*	0 % (0)	0 % (0)	0 % (0)
Percentage of individuals with concentric LV remodeling	13.8 % (15)*	2.4 % (1)●●	5.0 % (2)	12.5 % (5)
Percentage of individuals with eccentric LV remodeling	8.2 % (9)*	9.8 % (4)●●	0 % (0)	2.5 % (1)

*Note: * – significance of difference in intergroup comparison with the comparison group I indicators of liver transplant recipients with MS at p <0.05, ** – at p <0.01, ●– significance of difference in intergroup comparison with comparison group II of liver transplant recipients with CHD and MS at p<0.05, ●● with p<0.01.*

severity of manifestations of liver failure provided evidence of progressive cirrhotic cardiomyopathy and right ventricular failure in this category of patients.

When analyzing the diastolic function of the myocardium in liver transplant recipients with coronary heart disease and/or metabolic syndrome compared with patients from the general population, a decrease in the

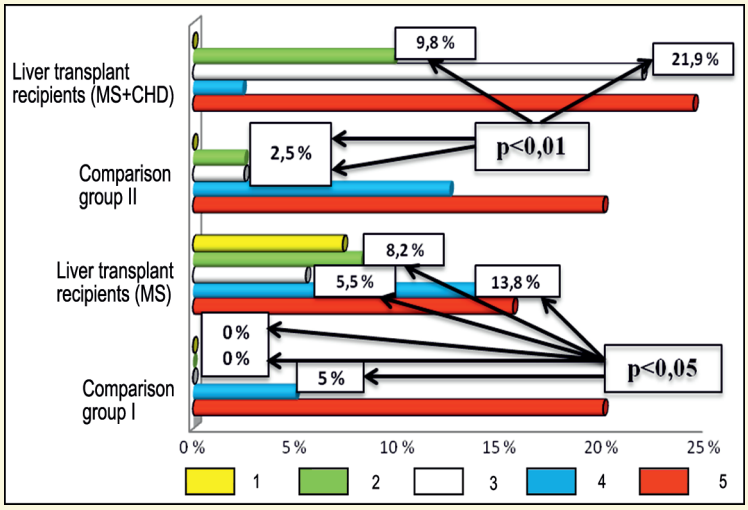

Figure 2 – The incidence of maladaptive forms of left ventricular remodeling in liver transplant recipients in the late postoperative period. 1 – Mixed LV hypertrophy, 2 – Eccentric LV remodeling, 3 – Dilatation LV hypertrophy, 4 – Concentric LV remodeling, 5 – Eccentric LV hypertrophy.

flow rate of the early filling period and the E/A ratio of transmitral blood flow, an increase in the delay time of the early transmitral diastolic flow and isovolumetric relaxation of the left ventricle were established. The use of the 2D Speckle Tracking Imaging method revealed a significant decrease in global systolic longitudinal deformation of the right ventricle compared with the general population patients with MS (-17.6±1.48 % and -23.4±1.07 %, respectively, p<0,01) and CHD (-16.4±1.61 % and -22.1±1.54 %, respectively, p<0.01), which indicates preserved dysfunction of the right ventricular subendocardial myocardial fibers after orthotopic liver transplantation. The proportion of liver transplant recipients with metabolic syndrome and coronary heart disease who had diagnostic criteria for left ventricular diastolic dysfunction was higher in the studied group than in the general population (70.7 % and 57.5 %, respectively, p<0.05).

Among the recipients of liver transplants compared with patients from the general population with MS (22.1 % and 45.0 %, respectively, p<0.01) and CHD (19.5 % and 40.0 %, respectively, p<0.01) a smaller proportion of individuals with normal left ventricular geometry was detected in the late postoperative period. Maladaptive forms prevailed in the remodeling structure: the proportion of liver transplant recipients with MS who have a prognostically unfavorable form of LV myocardial remodeling was 50.4 % vs 25.0 % in comparison group I (p<0.01), with hepatic transplant recipients coronary heart disease – 58.5 % vs 37.5 % in comparison group II (p<0.05). The structure of maladaptive disorders of the geometric model in liver transplant recipients with metabolic syndrome more frequently revealed eccentric left ventricular hypertrophy and concentric remodeling (p<0.01), with ischemic heart disease – eccentric and dilated (p<0.01) left ventricular hypertrophy.

Conflict of interests. *The authors declare that there is no conflict of interests that could affect the results of the study or their interpretation.*

References

[1] D'Amico G., Garcia-Tsao G., Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. *J Hepatol*, 2016, vol. 44, № 1, pp. 217–231.

[2] Al Hamoudi W., Lee S.S. Cirrhotic cardiomyopathy. *Ann Hepatol*, 2005, vol. 5, № 3, pp. 132–139.

[3] Gaskari S.A., Honar H., Lee S.S. Therapy insight: Cirrhotic cardiomyopathy. *Nat Clin Pract Gastroenterol Hepatol*, 2006, vol. 3, № 6, pp. 329–337.

[4] Liu H., Lee S.S. What happens to cirrhotic cardiomyopathy after liver transplantation? *Hepatology*, 2015, vol. 42, № 5, pp. 1203–1205.

[5] Myers R.P., Lee S.S. Cirrhotic cardiomyopathy and liver transplantation. *Liver Transpl*, 2010, vol. 6, Suppl. 1, pp. 44–52.

[6] Therapondos G., Flapan A.D., Plevris J.N., Hayes P.C. Cardiac morbidity and mortality related to orthotopic liver transplantation. *Liver Transpl*, 2004, vol. 10, № 12, pp. 1441–1453.

[7] Moller S., Henriksen J.H. Cardiovascular dysfunction in cirrhosis: pathophysiological evidence of a cirrhotic cardiomyopathy. *Scand J Gastroenterol*, 2001, vol. 36, pp. 785–794.

[8] Kim M.Y., Baik S.K. Cirrhotic cardiomyopathy. *Korean J Hepatol*, 2007, vol. 13, № 1, pp. P. 20–26.

[9] Cazzaniga M., Salerno F., Pagnozzi G., Dionigi E., Visentin S., Cirello I., Meregaglia D., Nicolini A. Diastolic dysfunction is associated with poor survival in patients with cirrhosis with transjugular intrahepatic portosystemic shunt. *Gut*, 2007, vol. 56, № 6, pp. 869–875.

[10] Moller S., Henriksen J.H. Cardiovascular complications of cirrhosis. *Gut*, 2008, vol. 57, № 2, pp. 268–278.

[11] Liu H., Gaskari S.A., Lee S.S. Cardiac and vascular changes in cirrhosis: pathogenic mechanisms. *World J Gastroenterol*, 2006, vol. 12, № 6, pp. 837–842.

[12] Lee S.S. Cardiac dysfunction in spontaneous bacterial peritonitis: a manifestation of cirrhotic cardiomyopathy? *Hepatology*, 2003, vol. 38, № 5, pp. 1089–1091.

[13] Ruiz-del-Arbol L., Monescillo A., Arocena C., Valer P., Ginès P., Moreira V., Milicua J.M., Jiménez W., Arroyo V. Circulatory function and hepatorenal syndrome in cirrhosis. *Hepatology*, 2005, vol. 42, pp. 439–447.

[14] Pozzi M., Grassi G., Ratti L., Favini G., Dell'Oro R., Redaelli E., Calchera I., Boari G., Mancia G. Cardiac, neuroadrenergic, and portal hemodynamic effects of prolonged aldosterone blockade in postviral child A cirrhosis. *Am J Gastroenterol*, 2005, vol. 100, № 5, pp. 1110–1116.

[15] Pacher P., Batkai S., Kunos G. Cirrhotic cardiomyopathy: an endocannabinoid connection? *Br J Pharmacol*, 2005, vol. 146, № 3, pp. 313–314.

[16] Rabie R., Cazzaniga M., Salerno F., Wong F. The effect of cirrhotic cardiomyopathy on the pos-TIPS outcome of patients treated for complications of portal hypertension. *Hepatology*, 2006, vol. 44, Ssuppl. 1, pp. 444A.

[17] Trevisani F., Merli M., Savelli F., Valeriano V., Zambruni A., Riggio O., Caraceni P., Domenicali M., Bernardi M. QT interval in patients with noncirrhotic portal hypertension and in cirrhotic patients treated with transjugular intrahepatic portosystemic shunt. *J Hepatol*, 2003, vol. 38, № 4, pp. 461–467.

[18] Ford W.R., Honan S.A., White R., Hiley C.R. Evidence of a novel site mediating anandamide induced negative inotropic and coronary vasodila-tator responses in rat isolated hearts. *Br J Pharmacol*, 2002, vol. 135, № 5, pp. 1191–1198.

[19] Torregrosa M., Aguadé S., Dos L., Segura R., Gónzalez A., Evangelista A., Castell J., Margarit C., Esteban R., Guardia J., Genescà J. Cardiac alterations reversibility after liver transplantation. *J Hepatol*, 2005, vol. 42, № 1, pp. 68–74.

[20] Acosta F., De La Morena G., Villegas M., Sansano T., Reche M., Beltran R., Roques V., Contreras R.F., Robles R., Bueno F.S., Ramirez P., Parrilla P. Evaluation of cardiac function before and after liver transplantation. *Transplant Proc*, 1999, vol. 31, № 6, pp. 2369–2370.

[21] Al-Hamoudi W., Alqahtani S., Tandon P., Ma M., Lee S.S. Hemodynamics in the immediate post-transplantation period in alcoholic and viral cirrhosis. *World J Gastroenterol*, 2010, vol. 16, № 5, pp. 608–612.

[22] Carey E.J., Douglas D.D. Effects of orthotopic liver transplantation in patients with end-stage liver disease. *Dig Dis Sci*, 2005, vol. 50, № 2, pp. 320–323.

[23] Ruiz-del-Arbol L., Monescillo A., Arocena C., Valer P., Ginés P., Moreira V., Milicua J.M., Jiménez W., Arroyo V. Circulatory function and hepatorenal syndrome in cirrhosis. *Hepatology,* 2005, vol. 42, № 2, pp. 439–447.

[24] Pateron D., Beyne P., Laperche T., Logeard D., Lefilliatre P., Sogni P., Moreau R., Langlet P., Elman A., Bernuau J., Valla D., Erlinger S., Lebrec D. Elevated circulating cardiac troponin I in patients with cirrhosis. *Hepatology*, 1999, vol. 29, № 3, pp. 640–643.

[25] Pozzi M., Carugo S., Boari G., Pecci V., de Ceglia S., Maggiolini S., Bolla G.B., Roffi L., Failla M., Grassi G., Giannattasio C., Mancia G. Evidence of functional and structural cardiac abnormalities in cirrhotic patients with and without ascites. *Hepatology*, 1997, vol. 26, № 5, pp. 1131–1137.

[26] Nasraway S.A., Klein R.D., Spanier T.B. et al. Hemodynamic correlates of outcome in patients undergoing orthotopic liver transplantation: evidence for early postoperative myocardial depression. *Chest*, 1995, vol. 107, № 1, pp. 218–224.

[27] Ocel J.J., Edwards W.D., Tazelaar H.D., Petrovic L.M., Edwards B.S., Kamath P.S. Heart and liver disease in 32 patients undergoing biopsy of both organs, with implications for heart or liver transplantation. *Mayo Clin Proc*, 2004, vol. 79, № 4, pp. 492–450.

[28] Silver M.A., Maisel A., Yancy C.W., McCullough P.A., Burnett J.C. Jr, Francis G.S., Mehra M.R., Peacock W.F. 4th, Fonarow G., Gibler W.B., Morrow D.A., Hollander J. BNP Consensus Panel. BNP Consensus Panel 2014: a clinical approach for the diagnostic, prognostic, screening, treatment monitoring, and therapeutic roles of natriuretic peptides in cardiovascular diseases. *Congest Heart Fail*, 2004, vol. 10, Suppl. 3, pp. 1–30.

[29] Grigorenko E.A., Mitkovskaya N.P., Rummo O.O., Kalachik O.V. Strukturno-funkzional'nye izmeneniya kardiovaskulyarnoy sistemy, lipidnye i gemostaziologicheskie narusheniya posle transplantazii pecheni i pochek [Structural and functional changes of cardiovascular system, lipid and emostaziological violations after kidney and liver transplantation]. *Medizinskiy zhurnal*, 2013, № 1, pp. 67–70.

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