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Assessment of structural and functional changes in recipient's transplanted heart in the long-term postoperative period

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Abstract

Introduction. *Heart transplantation is an effective way of treating patients with end-stage heart failure. Echocardiography allows for the assessment of the transplanted heart functions at all stages of follow-up. The clinical implementation of myocardial deformation imaging by the speckle tracking echocardiography has made it possible to detect subtle changes in myocardial contractility.*

Objective. *To study the structural and functional state of myocardium in recipients in the long term after orthotopic heart transplantation.*

Material and methods. *The study included 13 orthotopic heart transplant recipients (11 men and 2 women) at a mean age of 54.1±9.1 years who* *underwent orthotopic heart transplantation at the N.V. Sklifosovsky Research Institute for Emergency Medicine. The mean follow-up period after orthotopic heart transplantation was 6±0.7 years. All patients underwent transthoracic echocardiography according to the standard protocol, including determination of left ventricular myocardial deformation.*

Results. *The median volume of the left atrium was 60 (53;76) ml, the left ventricular end-diastolic volume was 76 (70;90) ml, and the end-systolic volume was 30 (24;36) ml. The median ejection fraction of the left ventricle in the studied sample was 64 (57;66)%. The median interventricular septum thickness was 12 (11;13) mm, the left ventricular posterior wall thickness was 9 (8;10) mm. At the same time, the left ventricular myocardial mass and the left ventricular myocardial mass index were within the normal range and amounted to 140 (121;155) g and 65 (58;76) g/m*^{2}*, respectively. The right heart chambers were not dilated, as the volume of the right atrium was 41 (40;56) ml, and the right ventricular end-diastolic dimension was 32 (30;33) mm. The right ventricular systolic function was unimpaired: the tricuspid annular plane systolic excursion was 18 (17;19) mm, and the right ventricular fractional area change was 46 (37.5;47.0)%. The calculated systolic pulmonary artery pressure was within the normal range 24 (21;28) mm Hg. The measurements of left ventricle global longitudinal and circumferential strains were -19.6 (-18.6;-21.2)% and -30.9 (-28.8;-32.0) %, respectively. Patients in the study sample showed a decrease in the left ventricular global function index to 25 (24.2;29.6)%. The diastolic dysfunction of a restrictive type was present in 10 patients (76.9%).*

Conclusions. *In the long-term period after heart transplantation, the recipients were found to have a low left ventricular ejection fraction and a diastolic dysfunction of the restrictive type. Considering the normal values of left ventricular myocardial strains, we can assume that after 6* *years post-orthotopic heart transplantation, the recipients have restored the heart adaptive functions, and a favorable outcome has been achieved. However, long-term monitoring is required.*

Keywords: orthotopic heart transplantation, left ventricular myocardial deformation, chronic heart failure

Conflict of interests Authors declare no conflict of interest

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ACR, acute cellular rejection
CAV, cardiac allograft vasculopathy
CHD, coronary heart disease
CHF, chronic heart failure
CHFpEF, chronic heart failure with preserved ejection fraction
CVD, cardiovascular disease
CVE, cardiovascular event
DD, diastolic dysfunction
DF, diastolic function
EchoCG, echocardiography
EDD, end-diastolic dimension
EDV, end-diastolic volume
EF, ejection fraction
ESV, end-systolic volume
FAC, fractional area change
FC, functional class
GCS, global circumferential strain
GFI, global function index
GLS, global longitudinal strain
HF, heart failure
HT, heart transplantation
HTCAD, heart transplant coronary artery disease
IMM, ischemic myocardial mass
LA, left atrium
LV, left ventricle
LVMM, left ventricular myocardial mass

MS, myocardial strain
NYHA, New York Heart Association classification of heart failure
OHT, orthotopic heart transplantation
PWTh, posterior wall thickness
RA, right atrium
HR, hazard ratio
RV, right ventricle
STE, speckle tracking echocardiography
SV, stroke volume
TAPSE, tricuspid annular plane systolic excursion

Introduction

Despite significant progress in treatment strategies for chronic heart failure (CHF), patient prognosis remains poor. In drug-resistant end-stage CHF in patients receiving support with inotropic drugs, after 3, 6, and 12 months of follow-up, the survival rates made 51%, 26%, and 6%, respectively [1]. For these patients, heart transplantation (HT) remains the only treatment option [2–3]. The one-year survival rate after orthotopic heart transplantation (OHT) was 85–90%. Subsequently, every year it began to tend to decrease by an average of 4% [4]. Meantime, alongside with the quality of life improvement and prolonging life expectancy, the cardiac allograft vasculopathy (CAV) and acute cellular rejection (ACR) of the graft may develop in the post-transplant period, which require early diagnosis and treatment.

Surveillance of graft function after OHT typically includes transthoracic echocardiography (EchoCG), endomyocardial biopsy, coronary angiography, and an invasive hemodynamics evaluation with right heart catheterization. EchoCG serves as the main method for monitoring the postoperative course and identifying post-transplant complications, especially with the implementation of myocardial strain (MS) imaging using speckle tracking echocardiography (STE) that help to detect even subtle changes in myocardial contractility [5]. Left ventricular (LV) MS parameters: global longitudinal strain (GLS) and global circumferential strain (GCS) are reliable indicators for predicting myocardial fibrosis. It is known that the MS of both ventricles in recipients is reduced in the early postoperative period and during graft rejection, however, in the long-term follow-up of recipients, these parameters tend to normalize [6]. A cut-off value for LV GLS of 15.5% was a significant predictor of mortality [7]. In a study of GLS by C. Sciaccaluga [8], the layer-specific GLS and endocardial-epicardial gradient, deceleration time of E (DTE) and the ratio E/e', where E is the peak velocity of early diastolic transmitral flow and e' is the peak velocity of early diastolic motion of the lateral portion of the mitral annulus, were the best independent non-invasive cardiac allograft vasculopathy (CAV) predictors.

In addition to the MS assessment, it is also interesting to assess the LV global function index (GFI) in this cohort of patients. Thus, in the study of N. Mewton [9], the endpoints were significantly associated with LV GFI (heart failure, hazard ratio (HR) = 0.64, $p<0.0001$; cardiovascular events, HR=0.79, $p=0.007$; all events, HR=0.79, $p<0.0001$). LV GFI had independent prognostic value in multivariate models for all categories of cardiovascular events (CVEs) and was a powerful predictor of heart failure, cardiovascular events, and death [10].

The assessment of diastolic function (DF) is complex and depends on many factors: tachycardia of the denervated heart, pulmonary venous flow, graft ischemia, or precapillary pulmonary hypertension. Therefore, in the early postoperative period, the DF restrictive pathophysiology has no prognostic value; and in the later period, it has a negative prognostic value and is often associated with inflammation, fibrosis, and CAV [11].

The right heart dysfunction after OHT caused by acute right ventricular failure, leads to complications in 50% of cases, and death in 19% [12]. Therefore, an assessment of right ventricular (RV) function after OHT is of clinical importance. It is known that the RV contraction occurs predominantly in the longitudinal plane, therefore the amplitude of the tricuspid annular plane systolic excursion (TAPSE) can be considered a suitable method for assessing RV systolic function [13]. The risk of cardiovascular disease (CVD) increases with a TAPSE value of less than 24 mm, which is currently recognized as being within the normal range. According to J.K.K. Vishram-Nielsen et al. [14], the RV dysfunction assessed by TAPSE detected in the post-transplant period is significantly associated with increased mortality and vasculopathy. TAPSE value of less than 15 mm represents clinically significant graft dysfunction, requiring monitoring and early pharmacological therapy (diuretics, pulmonary vasodilators). When TAPSE is lower than 15 mm, its each new decrease by 1 mm increases mortality by 22% ($p<0.001$). In HT recipients with TAPSE of 15 mm, 10 mm, and 6 mm, 1-year mortality was 3%, 7%, and 17%, and 5-year mortality was 8%, 20%, and 43%, respectively. Decreased TAPSE was significantly associated with CAV. Thus, a decrease in the TAPSE value indicates the signs of CAV and ACR and is a powerful predictor of survival in patients with OHT.

The objective was to study structural and functional state of recipients' myocardium in the long-term period after orthotopic heart transplantation.

Material and methods

The study included 13 recipients with OHT (11 men and 2 women), the mean age 54.1±9.1 years, who underwent OHT at the clinic of the N.V. Sklifosovsky Research Institute for Emergency Medicine. The mean follow-up period after OHT was 6±0.7 years. OHT was carried out in connection with ischemic, dilated cardiomyopathies, and in iatrogenic conditions (Fig. 1).

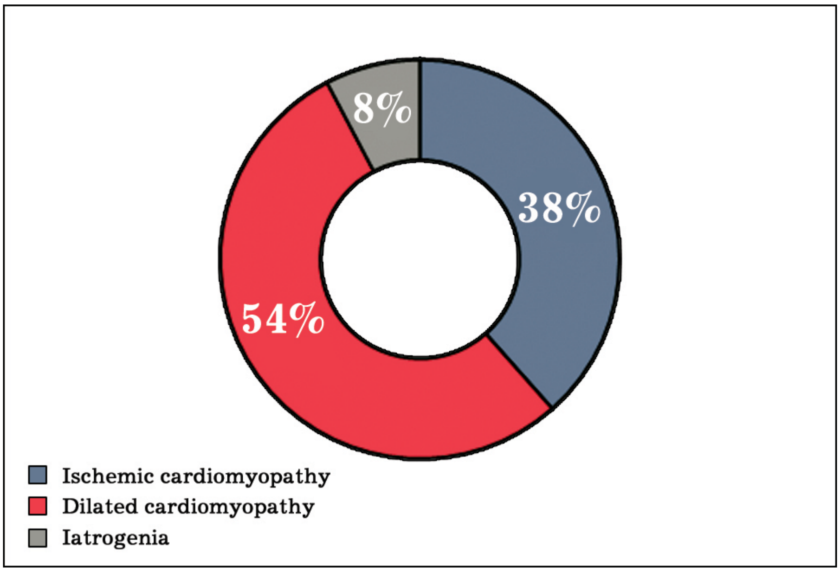

Fig. 1. Causes of orthotopic heart transplantation

During the study, the sample was divided into two groups, with regard to the ACR development: group I consisted of 6 patients who developed ACR during the follow-up period, group II included 7 patients in whom OHT was not accompanied by the ACR development.

Clinical characteristics of patients included in the study are presented in Table 1.

Table 1. Clinical characteristics of patients included in the study

Parameters	Occurrence rate (n=13), %	
	n	%
Arterial hypertension	7	53.84
CHD	4	30.76
Myocardial infarction	1	7.69
CHF	13	100
NYHA FC I	7	53.84
NYHA FC II	5	38.46
NYHA FC III	1	7.69
Post-transplant diabetes mellitus	3	23.07
Ischemic stroke	1	7.69
Chronic kidney disease	2	15.38
Malignant neoplasms	2	15.38
Acute cellular rejection	6	46.15

Notes: CHD, coronary heart disease; FC, functional class; NYHA, New York Heart Association classification of heart failure

At the time of the examination, the recipients had no complains of pain, heart rhythm disturbances or shortness of breath. The mean heart rate was 95.8±10.9 beats/ min, which corresponded to the norm for cardiac allograft recipients; however, due to the development of sick sinus syndrome 5 years after OHT, one recipient was implanted with a dual-chamber pacemaker. Edema of the lower extremities was reported by one recipient. Ten recipients continued working; of these, 6 had work related to physical activity.

All recipients underwent transthoracic EchoCG according to the standard protocol and STE to assess longitudinal and circumferential MS. To assess LV systolic function, the LV GFI was used, calculated using stroke volume (SV), end-diastolic volume (EDV), end-systolic volume (ESV) and left ventricular myocardial mass (LVMM); TAPSE and the RV fractional area change (FAC) were used to assess the RV function.

Statistical processing

Statistical data processing was carried out using the jamovi software, version 2.4.1 for the macOS Sonoma 14.0 operating system. Quantitative data are presented with respect to the nature of the distribution. In a normal distribution, quantitative variables were presented using the mean and standard deviation (m±SD); in the distribution other than normal, the medians and interquartile range were given (Me (Q1;Q3)). The distribution was checked for normality using the Shapiro–Wilk test. Qualitative variables are presented as absolute numbers and percentages (n (%)). Comparison of distributions in the study groups was made using the Mann–Whitney U test. The critical level of statistical significance was taken as 0.05; the differences were considered statistically significant at $p<0.05$.

Results

The results of assessing the structural and functional state of the transplanted heart in the long-term period are presented in Table. 2.

Table 2. Characteristics of the structural and functional state of the transplanted heart

Parameter	Value
LA diameter, mm	40 (37;42)
LA volume, ml	60 (53;76)
LV EDD, cm	4.1 (4.0;4.2)
EDV, ml	76 (70;90)
ESV, ml	30 (24;36)
LV EF, %	64 (57;66)
Interventricular septum thickness, mm	12 (11;13)
LV PWTh, mm	9 (8;10)
LV IMM, g/m^2	65 (58;76)
LVMM, g	140 (121;155)
RA volume, ml	41 (40;56)
RV EDD, mm	32 (30;33)
Pulmonary artery systolic pressure, mm Hg	24 (21;28)
RV FAC, %	46 (37.5;47.0)
GLS, %	-19.6 (-18.6;-21.2)
GCS, %	-30.9 (-28.8;-32.0)
TAPSE, mm	18 (17;19)
LV GFI, %	25 (24.2;29.6)

Notes: IMM, ischemic myocardial mass; EDD, end-diastolic dimension; LA, left atrium; RA, right atrium; PWTh, posterior wall thickness; EF, ejection fraction

As can be seen in Table 2, the volumetric parameters of the heart chambers were within normal range. The median LA volume was 60 (53;76) ml, LV EDV was 76 (70;90) ml, ESV was 30 (24;36) ml. The median LV EF in the study sample was 64 (57;66) %. When assessing the thickness of the LV walls, slight LV hypertrophy was revealed. The median interventricular septum thickness (IVSTh) was 12 (11;13) mm, LV PWTh was 9 (8;10) mm, while the LVMM and LV IMM values were within normal ranges and made 140 (121;155) g and 65 (58;76) g/m^2, respectively. The right heart chambers were not dilated: the RA volume was 41 (40;56) ml, and the RV EDV was 3.2 (3.0;3.3) cm. The systolic function of the RV was not impaired with TAPSE 1.8 (1.7;1.9) cm, the RV FAC was 46 (37.5;47.0) %. The estimated systolic pressure in the pulmonary artery remained within the normal range 24 (21;28) mm Hg.

When assessing LV MS in terms of GLS and GCS values, we found that these parameters remained within normal ranges (Fig. 2).

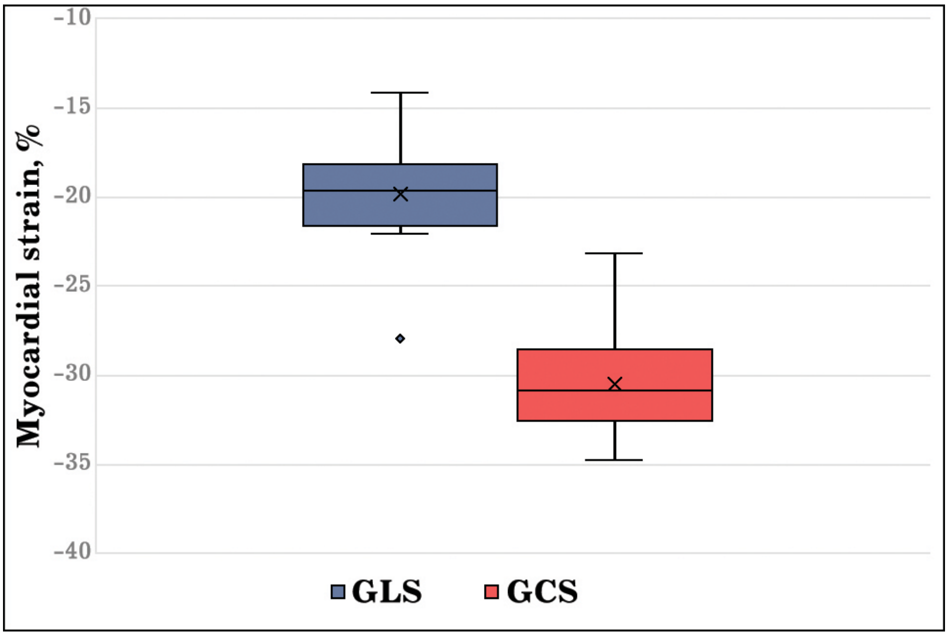

Fig. 2. GLS and GCS values of patients in the study sample

As can be seen in Fig. 2, the LV global longitudinal and circumferential strains were -19.6 (-18.6;-21.2)% and -30.9 (-28.8;-32.0)%, respectively, which corresponded to normal.

In patients in the study sample, there was a decrease in LV GFI to 25 (24.2;29.6) %.

DF in 10 patients (76.9%) was impaired in a restrictive manner.

The results of echocardiography are presented in Table 3.

Table 3. Echocardiography parameters in the study groups

Parameter	Group I (n=6)	Group II (n=7)	p
LA diameter, mm	37 (35.5;40.8)	40 (39.0;46.0)	0.223
LA volume, ml	58.5 (54.0;70.5)	63 (53.5;106)	0.628
LV EDD, cm	4.00 (3.92;4.07)	4.20 (4.05;4.25)	0.220
EDV, ml	80.5 (68.5;91.8)	76 (72.5;86.5)	>0.999
ESV, ml	27 (23.3;32.3)	31 (25.5;37.0)	0.221
LV EF, %	65.5 (64.3;66.0)	60 (56.5;64.5)	0.195
Interventricular septum thickness, mm	12.0 (11.3;12.8)	13 (11.5;13.0)	0.505
PWTh, mm	8.5 (8.0;9.75)	9 (9.0;10.0)	0.658
LV IMM, g/m^2	65.0 (63.5;67.3)	74 (58.0;79.5)	0.720
LVMM, g	130 (122;139)	154 (128;169)	0.224
RA volume, ml	40.5 (40.0;44.0)	43 (35.5;65.5)	>0.999
RV EDD, mm	30 (29.3;31.5)	33 (32.0;33.0)	0.068
Pulmonary artery systolic pressure, mm Hg	26.0 (21.0;31.0)	23.0 (21.0;24.5)	0.519
RV FAC, %	43.5 (37.3;46.8)	46.0 (41.8;49.5)	0.427
GLS, %	-19.5 (-18.9;-21.3)	-20.8 (-18.1;-21.2)	0.943
GCS, %	-32.4 (-29.2;-34.0)	-30.0 (-29.1;-31.2)	0.295
TAPSE, mm	18.5 (17.3;19.8)	18.0 (16.0;19.0)	0.343
LV GFI, %	29.5 (25.9;30.5)	24.4 (22.9;25.8)	0.101

As can be seen in Table 3, the study groups did not differ in terms of thee LA and LV dimensions and volumes. Patients had comparable LV EF 65.5 (64.3;66.0)% versus 60 (56.5;64.5)% (p=0.195). No statistically significant differences between the groups were found in the geometry parameters of the right heart chambers, LV MS, and LV GFI, either.

Discussion

Making the echocardiographic assessment of cardiac chamber functions after OHT appears difficult due to the lack of standardized reference values for individuals undergoing allotransplantation [15]. Cardiac allograft dimensions and functional parameters may differ from those in the general population. According to the study by A. Ingvarsson [6], larger atrial dimensions were observed in recipients when compared with the general population; LV diastolic volume was smaller and its wall thickness enlarged. LV EF was 62±7% ($p<0.01$), the LV global longitudinal strain was -16.5±3.3% ($p<0.0001$), the RV dimensions exceeded the reference values ($p<0.0001$), and its function parameters (TAPSE and FAC) were reduced: TAPSE was 15±4 mm ($p<0.0001$), FAC was 40±8% ($p<0.0001$), and the RV free wall strain was -16.9±4.2% ($p<0.0001$) (all changes shown were statistically significant). The LV EF and LV global longitudinal strain were reduced in patients with ACR. Unless CAV had developed, the LV EF and the regional wall motion (with the exception of the common septal dyskinesia) persisted in most recipients for 10–15 years. Decreased LV systolic function during the first year was a predictor of the allograft rejection or CAV. A decrease in LV EF later (over 5 years) after HT correlated with the CAV progression. LV systolic function was preserved even in later forms of vasculopathy, which makes it an unsuitable echocardiography marker for the early detection of CAD in the transplanted heart. Impaired local contractility may raise suspicion for the presence or progression of CAV, however, these changes can also be observed in ACR [7].

In the present study, cardiac allograft recipients at 6 years after OHT, regardless of the history of ACR and coronary artery disease of the transplanted heart had normal LV EF and LV MS; 7 people among them (70%) were able to work. The median LV EF was 64 (57;66)%. Slight asymmetric LV hypertrophy was revealed: the IVSTh was 1.2 (1.1;1.3) cm, LV PWTh was 0.9 (0.8;1.0) cm with normal values of LVMM and LV IMM showing 140 (121;155) g and 65 (58;76) g/m^2; LA dilatation and diastolic dysfunction (DD) of a restrictive type were observed in 10 patients (76.9%). Meantime, a decrease in LV GFI and DD of a restrictive type indicated myocardial remodeling [16]. This indicator took into account, in addition to the LV contractile function, also myocardial remodeling, which indirectly indicated the risk of unfavorable cardiovascular events in people with still preserved LV EF [17]. It is known that LV GLS and LV early diastolic strain rate are the best predictors of death 6 years after HT. Estimation of LV early diastolic strain rate, which is equivalent to LV DF, is another predictor of primary and secondary endpoints of the CVD and all-cause mortality. In a study by A. Ingvarsson et al. (2021), the assessment of GLS and GCS values was more informative than that of traditional DD parameters such as E/e' [5]. In the present study, 6 years after OHT, the recipients had restrictive DD with normal LV MS values. From a histological point of view, DD is associated with significant destruction of the extracellular matrix due to the presence of edema or fibrosis, which leads to increased myocardial wall stiffness and therefore alters lusitropic properties. In various pathological conditions, they occur before obvious manifestations of the disease, leaving room for preclinical detection. This may also be true for the early detection of graft-related complications, since swelling of cardiomyocytes may be a result of ACR, while fibrosis may be a manifestation of either HTCAD or cavitation. Recent evidence suggests that DF may be associated with microvascular density. DD is a key element of the CAV classification (identified by the presence of visual coronary angiographic stenosis and signs of graft dysfunction, such as decreased LV EF or restrictive filling patterns). DF becomes impaired in patients with severe CAV, which usually leads to restrictive cardiac physiology, and if LV EF declines years after HT, it is necessary to CAV. The development of restrictive dysfunction in recipients with CAV is associated with low 5-year survival [16]. It is known that restrictive DD in the late post-transplantation period has a negative prognostic value [11]; however, taking into account the normal MS values in DD of the restrictive type, we believe that our recipients have a favorable prognosis, but require long-term monitoring of these parameters for an early detection of disorders. However, STE can be used to predict elevated pulmonary capillary wedge pressure. Peak systolic and early diastolic strain rates and the ratio of transmitral early filling velocity to early diastolic strain rate correlate with LV end-diastolic pressure and pulmonary capillary wedge pressure, and also track changes in these parameters well over time, thereby identifying myocardial dysfunction earlier than LV GLS. In the study, R. Chamberlain showed that repeated episodes of ACR can lead to a significant decrease in LV and RV systolic longitudinal strain, with LV GLS varying from -18.1% to -15.3%. Normal MS values for transplanted hearts vary across studies, with LV GLS ranging from -13.4% to -20.0% and RV GLS ranging from -16.9% to -26.9% [17].

According to S. Zheng [18], postoperative survival was higher in transplant recipients when the donor heart had RA/RV dimensions of at least 32 mm. In those who died after HT, the RA/RV dilatation degree at 1 month after surgery was significantly higher than in surviving patients. RV free wall longitudinal strain (3D-RV FWLS) is a strong independent predictor of adverse outcomes and provides additional prognostic value compared with 2D-RV FWLS and conventional echocardiographic parameters in adult patients after HT [19, 20]. Follow-up of 155 recipients for 34 months after HT demonstrated that in 13% of cases, an unfavorable prognosis developed and two- and three-dimensional longitudinal MS rates were low [20]. At 6 years after OHT, no enlargement of the right heart chambers was detected in our patients: thus, the RA volume was 41 (40;56) ml, the RV EDD was 3.2 (3.0;3.3) cm; RV systolic function was unimpaired with TAPSE 1.8 (1.7;1.9) cm, and RV FAC 46 (37.5;47.0)%.

Conclusion

Performing series of echocardiography investigations to assess the function of the left and right heart chambers, and the implementation into practice the assessment of myocardial deformation parameters will allow for earlier non-invasive diagnosis of heart allograft-related complications.

Based of the obtained study results, we have made the following conclusions:

1. In the long-term period (6 years) after orthotopic heart transplantation the recipients show normal values of the left ventricular myocardial global function index 25 (24.2;29.6)%, but meantime, they have a restrictive type of diastolic function impairment , which indicates the risk of adverse cardiovascular events in individuals with still preserved left ventricular ejection fraction.

2. Normal values of left ventricular myocardial global longitudinal and circumferential strains (GLS -19.6 (-18.6;-21.2) % and GCS -30.9 (-28.8;-32.0) %) in the long-term period allow us to assert that after 6 years, the adaptive functions of the heart will be restored in the recipients and they will achieve a favorable outcome, which is confirmed by the absent remodeling of the right heart chambers and the restoration of working capacity in these patient.

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