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Features of the clinical picture and outcomes in patients from a heart transplantation waiting list with different causes of heart failure

Aim	To identify clinical differences between patients on the heart transplant waiting list (HTWL) in the origin of chronic heart failure (CHF).
Materials and methods	From January 2010 through September 2019, 235 patients (age, 47+13 years (from 10 to 67 years); men, 79% (n=186)) were included in the HTWL. The patients were divided into two groups; group 1 (n=104, 44%) consisted of patients with ischemic heart disease (IHD); group 2 (n=131, 56%) included patients with noncoronarogenic CHF. Clinical and instrumental data and frequency of the mechanical circulatory support (MCS) as a «bridge» to heart transplantation (HT) were retrospectively evaluated.
Results	Group 1 included more male patients than group 2 [97% (n=101) and 82% (n=85), p<0.0001]; patients were older (54±8 and 42±14 years, p=0.0001). On inclusion into the HTWL, the CHF functional class was comparable in the groups, III [III;IV]; there were more patients of the UNOS 2 class in group 1 than in group 2 [75% (n=78) and 57% (n=75), p=0.005]. Patient distribution in UNOS 1B and 1A classes was comparable in the groups: 21% (n=22) and 3% (n=4) in group 1 and 33% (n=43) and 10% (n=13) in group 2. According to echocardiography patients of group 1 compared to group 2 showed a tendency towards higher values of left ventricular ejection fraction (Simpson method) [22 [18;26] % and 19 [15;24] %, p=0.37] and stroke volume [59 [44;72] % and 50 [36;67] %, p=0.07]. Numbers of patients with a cardioverter defibrillator or a cardiac resynchronization device with a defibrillator function were comparable in the groups [35% (n=36) and 34% (n=45)]. Comparison of comorbidities in groups 1 and 2 showed higher incidences of pulmonary hypertension [55% (n=57) and 36% (n=47), p=0.005], obesity [20% (n=21) and 10% (n=13), p=0.03], and type 2 diabetes mellitus [29% (n=30) and 10% (n=13), p=0.0004]. Rates of chronic obstructive lung disease, stroke, chronic kidney disease and other diseases were comparable. Duration of staying on the HTWL was comparable (104 [34; 179] and 108 [37; 229] days). During staying on the HTWL, patients of group 1 less frequently required MCS implantation [3% (n=3) and 28% (n=21), p=0.0009]. HT was performed for 59% patients (n=61) in group 2 and 52% (n=69) patients in group 2. Death rate in the HTWL was lower in group 1 [13% (n=14) and 27% (n=35), p<0.01].
Conclusion	On inclusion into the HTWL, patients with noncoronarogenic CHF had more pronounced CHF manifestations and a more severe UNOS class but fewer comorbidities than patients with CHF of ischemic origin. With a comparable duration of waiting for HT, patients with noncoronarogenic CHD more frequently required MCS implantation and had a higher death rate.

Keywords	Chronic heart failure; ischemic heart disease; noncoronarogenic heart disease; heart transplant waiting list; mechanical circulatory support; heart transplantation
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Introduction

Chronic heart failure (CHF) is the most common cardiovascular disease in adults in developed countries [1]. More than 23 million people worldwide (about 7.9 million in the Russian Federation) have this pathology, and the number is growing rapidly [2].

Coronary artery disease (CAD) is the leading cause of CHF (accounting for more than 70% of cases) in the Framingham Heart Study. Other etiological factors of CHF include other heart diseases. Heart failure (HF) of any origin progresses gradually over time up to the terminal stage. According to the EPOCH-O-CHF population study, the proportion of patients with clinically significant CHF (New York Heart Association [NYHA] functional class [FC] II–IV) is 4.5% (5.5 million people) and the proportion of patients with terminal CHF (FC III–IV) is 2.1% (2.4 million people) [3]. At the same time, mortality among those patients on the heart transplant waiting list (HTWL) who have restrictive cardiomyopathy (RCM)

or congenital heart defects (CHDs) is higher among those who have dilatational cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), or CAD [4].

The objective of our study was to identify clinical differences between patients listed on the HTWL, depending on the origin of CHF.

Material and Methods

HTWL data collected from January 2010 to September 2019 were used. The database included 235 people: mean age 47.4 ± 12.9 (10–67) years old; male patients 79% (n = 186). Patients were divided into two groups (Table 1): Group 1 comprised patients with CAD (n = 104; 44%). Group 2 included patients with non-coronarogenic CHF (n = 131; 56%) with the following causes: DCM (n = 101), HCM (n = 6), chronic rheumatic heart disease (n = 6), CHDs (n = 6), RCM (n = 4), and other disease (arrhythmogenic right ventricular dysplasia [n = 3], non-compact myocardium [n = 4], cardiac sarcoidosis [n = 1]). Group 2 also included six children: 5 girls aged 10–16 and 1 boy aged 16.

The study was conducted under the ethical principles of the Declaration of Helsinki. Clinical examination data, the rate of implantations of mechanical circulatory support (MCS) as a bridge therapy for a heart transplant (HT), and survival of patients on the HTWL were estimated, retrospectively.

The statistical analysis was performed using the STATISTICA 10.0 software (StatSoft Inc., USA). All estimations of the mean were made together with the estimations of the median (Me), the lower and upper quartiles [LQ; UQ], standard deviation (SD), and the minimum and maximum values of the sample. The Lilliefors test (normal distribution of $p > 0.05$) and the symmetry test were used to reliably determine whether the distribution of a variable studied was normal. The results are expressed as the mean values and standard deviations (M ± SD) for the normal distribution or the median and the lower and upper quartiles (Me [LQ; UQ]) for non-normal distribution. If the rate of the variable was less than 10, the median and minimum and maximum values per sample were used. The statistical significance of the findings was $p < 0.05$ calculated using the non-parametric Mann-Whitney test for independent samples and the Wilcoxon test for dependent samples. Correlation analysis was also conducted.

Results

Group 1 included more male patients than Group 2; patients in Group 1 were older. CHF FCs were comparable in both groups when patients were placed on the waiting list, and Group 1 comprised fewer patients of the United Network for Organ Sharing (UNOS) 1B class and more patients of the UNOS 2 class. The distribution of patients in the UNOS 1A class was comparable in both groups. The level of systolic and diastolic blood pressure (BP) was higher in Group 1, and this group included fewer patients with mechanical circulatory support than Group 2.

The degree of tricuspid regurgitation was lower, and pulmonary vascular resistance (PVR) was higher, according to echocardiography, in Group 1 than in Group 2. The number of patients with an implanted cardioverter defibrillator (ICD) or a cardiac resynchronization therapy defibrillator (CRT-D) was comparable in both groups. In our study, more recipients with non-coronarogenic CHF require MCS. When co-morbidities were compared, it turned out that the rates of pulmonary hypertension, obesity, and type 2 diabetes mellitus were higher in Group 1 than Group 2; pulmonary embolism was more common in Group 2. The rates of chronic obstructive pulmonary disease (COPD), cerebrovascular accident (CVA), chronic kidney disease (CKD), and other diseases were comparable. Table 1 summarizes the comparative characteristics of patients listed on the HTWL, depending on the origin of CHF.

Within 9.5 years, HT was performed in 130 patients (96 male patients, 46 ± 14 years old), including 59% (n = 61) of patients from Group 1 and 52% (n = 69) from Group 2. In addition, Group 2 included six patients (two patients on the HTWL with MCS, five female and one male patient) at the aged 10–16 who received an adult donor heart. Analysis of the general transplant population revealed that 70% (91 of 130, $p = 0.002$) of patients were on the HTWL for less than 6 months before they underwent HT. There were no differences in the time of listing on HTWL between the groups. The HTWL mortality was lower in Group 1 versus Group 2.

Discussion

Older age, obesity, and diabetes mellitus are well-known risk factors for CAD and a worse prognosis for such patients [5]. This co-morbidity was expectedly found, in our study, in patients with terminal ischemic CHF. A greater percentage of patients with a history of pulmonary embolism (PE); thus, a higher level of PVR may be due to the presence of additional factors of high- and low-risk PE in patients with ischemic CHF: CAD, myocardial infarction, diabetes mellitus, obesity [6].

More than one-half of patients with terminal CHF die within less than 2 years after the onset of CHF [7]. That is why it is essential to examine patients in a timely manner and put them on the HTWL if indicated. More than one-half of our patients were on HTWL for less than 6 months before receiving HT.

If drug therapy is ineffective in terminal CHF, surgical correction techniques (re-synchronization therapy, implanted cardioverter defibrillators, permanent pacemakers,

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Table 1. Comparative characteristics of patients with CAD and non-coronarogenic CHF

Parameter	Group		
	Group 1 (n = 104)	Group 2 (n = 131)	p
Age, years	56 [51; 59]	43 [31; 53]	< 0.0001
Male, n (%)	101 (97)	85 (82)	0.0001
CHF FC when listed on HTWL, n (%)			
III	78 (75)	84 (64)	0.09
IV	26 (25)	47 (36)	0.09
UNOS when listed on HTWL, n (%)			
Status 1A	4 (3)	14 (10)	0.081
Status 1B	22 (21)	44 (33)	0.041
Status 2	78 (76)	73 (56)	0.003
BMI, kg/m^2	25 [23; 29]	23 [20; 26]	< 0.0001
HR, bpm	80 ± 14	82 ± 15	0.36
sBP, mmHg	108 ± 18	102 ± 16	0.006
dBP, mmHg	70 ± 10	66 ± 9	0.01
LVEF,%	22 [18; 26]	19 [15; 24]	0.37
LVEDD, mm	66 [60; 73]	69 [57; 78]	0.40
LVESD, mm	56 [43; 64]	60 [51; 69]	0.03
LVEDV, mL	249 [205; 301]	248 [181; 331]	0.89
LVESV, mL	167 [133; 224]	184 [106; 270]	0.78
LVSV, mL	59 [44; 72]	50 [36; 67]	0.07
TAPSE, cm	1.3 [1.0; 1.6]	1.3 [1.1; 1.6]	0.26
MR at baseline, grade	2 [2; 3]	2 [2; 3]	0.29
TR at baseline, grade	2 [1; 3]	2 [2; 3]	0.008
VO_2 peak, mL/min/kg	11.1 [9.8; 13.2]	11.3 [10.0; 14.2]	0.63
mPAP at baseline, mmHg	33 [25; 40]	30 [24; 36]	0.15
mPAP after reversion, mmHg	32 [25; 38]	30 [25; 37]	0.68
PVR at baseline, mm Hg	3.6 [2.6; 4.9]	2.9 [2.3; 3.8]	0.0005
PVR after reversion, Wood units	2.9 [1.9; 3.4]	2.6 [2.2; 3.0]	0.15
PP before listing on HTWL, n (%)	4 (4)	15 (11)	0.052
ICD/ICD before listing on HTWL, n (%)	36 (35)	45 (34)	1.0
MCS (EXCOR, ECMO) on HTWL, n (%)	3 (3)	21 (28)	0.0009
Time of listing on HTWL, days	104 [34; 179]	108 [37; 229]	0.71
Number of HTs, n (%)	61 (59)	69 (51)	0.43
Mortality on HTWL, n (%)	14 (13)	35 (27)	0.01
Co-morbidities, n (%)	102 (98)	105 (80)	< 0.0001
Obesity (BMI≥30 kg/m^2), n (%)	21 (20)	13 (10)	0.03
PH, n (%)	57 (55)	47 (36)	0.005
T2DM, n (%)	30 (29)	13 (10)	0.0004
PE, n (%)	22 (21)	46 (35)	0.02
CKD stage IIIa, n (%)	3 (3)	10 (8)	0.15
COPD, n (%)	16 (15)	11 (8)	0.10
CVA, n (%)	15 (14)	15 (11)	0.56

CAD, coronary artery disease; FC III–IV CHF, (New York Heart Association) functional class of chronic heart failure; HTWL, heart transplant waiting list; UNOS, United Network for Organ Sharing: status 1A, 1B, 2; BMI, body mass index; HR, heart rate; sBP, systolic blood pressure; dBP, diastolic blood pressure; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end diastolic dimension; LVESD, left ventricular end systolic dimension; LVEDV, left ventricular end diastolic volume; LVESV, left ventricular end systolic volume; LVSV, left ventricular stroke volume; TAPSE, tricuspid annular plane systolic examination; MR, mitral regurgitation; TR, tricuspid regurgitation; VO2 peak, maximum oxygen uptake; mPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; PP, permanent pacemaker; ICD, implanted cardioverter defibrillator; MCS, mechanical circulatory support (EXCOR/ECMO, extracorporeal membrane oxygenation); PH, pulmonary hypertension; T2DM, type 2 diabetes mellitus; PE, pulmonary embolism; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; M, mean; SD, standard deviation; Me, median; [LQ; UQ], the upper and lower quartiles.

optimizers) are used [8]. MCS (Berlin Heart EXCOR), prosthetic left ventricle (AVK-N), extra-corporeal membrane oxygenation are used as a bridge therapy to HT in order to slow the progression of CHF [9–11]. The retrospective analysis showed that implantable cardioverter defibrillators/cardiac resynchronization therapy defibrillators were implanted in about one-third of patients (34–35%) regardless of the origin of CHF. Long-term MCS using an implantable left ventricular bypass provides stable improvement of organ perfusion, correction of polyorgan dysfunction, regression of initially high pulmonary hypertension, improvement of nutritional status, and an increase in patient motor activity, which contributes to complete functional recovery of a potential recipient before HT [12, 13]. Even though the implantation of MCS reduced mortality, patients in need of MCS had more severe disease and higher risk of complications [13, 14]. According to our findings, the rate of MCS was the highest in recipients with non-coronarogenic CHF, and most of them were able to wait until a new heart was available, thanks to the use of Berlin Heart EXCOR/ECMO/AVK-N. Nevertheless, despite the appearance and spread of new high-tech therapies, HT is the only effective treatment of terminal CHF [1, 14].

Survival rates of patients with CHF originating from DCM, CAD, or HCM are higher than in those with RCM and CHDs [4]. Children form an individual group of patients with non-coronarogenic CHF. However, there are no data on the prevalence of CHF in the child age group. According to the International Society of Heart and Lung Transplantation (ISHLT), DCM and CHDs are the leading causes of CHF in recipients aged 11–17 years old [15, 16]. All six patients (10–16 years old) who were listed in our HTWL ended up receiving HT. They are currently alive, and the follow-up period ranges from 6 months to 8 years.

Moreover, differences in mortality identified in older age and more frequently in male patients with CAD compared to those with non-coronarogenic CAD are characteristic of the following diseases: CAD and DCM [16]. In another study, CAD and co-morbidities were not risk factors of death for patients on the HTWL [17]. Patients with CAD had more co-morbidities in our study. At the same time, recipients with non-coronarogenic CHF who were on the HTWL had more clinically relevant CHF (symptomatic hypotension with systolic dysfunction, need for inotropic support). The rate of MCS implantation and mortality in this group of patients was higher.

Conclusion

When patients with non-coronarogenic CHF were placed on the heart transplant waiting list, they had more pronounced manifestations of chronic heart failure and more severe UNOS class, yet they had fewer co-morbidities than patients with ischemic chronic heart failure. With comparable heart transplant waiting time, patients needed implantation of mechanical circulatory support systems more, and mortality was higher in Group 2.

No conflict of interest is reported.

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