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Dynamics of heart failure markers and cardiac reverse remodeling in patients receiving cardiac contractility modulation therapy

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Aim. To assess the clinical course and cardiac reverse remodeling in patients with heart failure (HF) with reduced ejection fraction (HFrEF) receiving cardiac contractility modulation (CCM) therapy.

Material and methods. Fifty-five patients (mean age, 53±11 years, 46 males) with NYHA class II-III HFrEF (ischemic etiology in 73% of patients), sinus rhythm, QRS<130 ms or QRS<150 ms of non-LBBB morphology receiving optimal medical therapy were enrolled into the study. CCM devices were implanted to all patients between October 2016 and September 2017. We assessed the following parameters: hospitalizations and mortality due to decompensated HF; changes in HF class, NTproBNP concentration, peak oxygen consumption, six-minute walk test, left ventricular end-systolic and end-diastolic volumes and ejection fraction (EF), atrial and ventricular arrhythmias. A comparative analysis of the studied parameters was carried out depending on the pacing with one and two ventricular leads, on LVEF value (≥25% and <25%) and HF etiology.

Results. CCM therapy was associated with a decrease in HF class ($p<0,00004001$), HF-related hospitalization rate ($p<0,0001001$), blood NTproBNP concentration ($p\leq 0,018$), an increase in peak oxygen consumption during the first year ($p<0,006011$), as well as a decrease in LV volumes and a LVEF increase ($p<0,0001001$). The direction of these changes did not depend on the number of ventricular leads and LVEF. The presence of ischemic cardiomyopathy and old myocardial infarction did not affect the disease prognosis, but was associated with a lower change in LV volumes and NTproBNP during 24 months of CCM therapy. LVEF values were significantly higher in the group of patients with

HFrEF not associated with coronary artery disease after 12 and 24 months of follow-up.

Conclusion. In the group of patients with class II-III HFrEF, CCM therapy in most patients was associated with improved clinical and hemodynamic status, increased exercise tolerance, decreased HF-related hospitalization rate, positive echocardiographic and NTproBNP changes.

Key words: cardiac contractility modulation, heart failure, reduced ejection fraction.

Relationships and Activities: none.

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Received: 27.07.2020

Revision Received: 14.09.2020

Accepted: 19.09.2020



For citation: Vander M. A., Lyasnikova E. A., Belyakova L. A., Trukshina M. A., Galenko V. L., Kim I. M., Lelyavina T. A., Abramov M. L., Lyubimtseva T. A., Sitnikova M. Yu., Lebedev D. S., Mikhaylov E. N. Dynamics of heart failure markers and cardiac reverse remodeling in patients receiving cardiac contractility modulation therapy. *Russian Journal of Cardiology*. 2021;26(1):4035. (In Russ.) doi:10.15829/1560-4071-2021-4035

Cardiac contractility modulation is a new treatment method for patients with moderate and severe chronic heart failure (CHF) with a low left ventricular ejection fraction (EF), narrow QRS <130 ms or QRS <150 ms of the type of non-specific intraventricular block, which are not indicated for cardiac resynchronization therapy, and the CHF symptoms persist and/or progress, despite taking optimal drug therapy. The principle of cardiac contractility modulation (CCM) is to stimulate the interventricular septum (IVS) with pulses of high amplitude and duration during the absolute refractory period. These impulses do not cause electrical activation of the myocardium, do not affect the heart rate, but increase the strength and duration of the action potential of cardiomyocytes, which contributes to the improvement of myocardium contractile function and the reverse remodeling in long-term period. In recent decades, the CCM influence on the clinical CHF course and LV myocardial remodeling has been of considerable interest [1]. However, there is currently insufficient data on the positive CCM effect, published randomized studies [2, 3] include a limited follow-up period, and despite receiving approval from the US Food and Drug Administration (FDA), CCM is not included in the recommendations for the treatment of patients with HFrEF.

Goal of the study: to evaluate the clinical course dynamics and the possibility of inversion of myocardial remodeling in patients with HFrEF associated with CCM.

Material and methods

In the period from October 2016 to September 2017, within the framework of the CCM clinical testing for the treatment of CHF at the Federal State Budgetary Institution “Almazov National Medical Research Centre” of the Ministry of Health of Russia, 55 patients were implanted with CCM devices (50 Optimizer Generation IV and 5 Optimizer Smart, Impulse Dynamics, Germany), endocardial electrodes for active fixation St. Jude Medical Tendril STS 2088TC.

The conditions for participation in the project, the criteria for clinical testing enrollment and exclusion were described in detail in the previous publication [4]. The main criteria for enrollment in the protocol were: HFrEF of functional class (FC) II and III (NYHA), sinus rhythm, QRS <130 ms or QRS <150 ms in the presence of non-specific intraventricular block, optimal and stable CHF drug therapy for at least 3 months.

Method of CCM system implantation. Implantation of CCM devices was carried out in the X-ray operating room; incision was performed in the right subclavian region under local anesthesia with an

anesthetic solution; puncture of subclavian vein and/or venesection of the brachiocephalic vein, electrode insertion: atrial electrode was placed in the area of right atrial auricle, ventricular electrodes (VEs) — in basal and median parts of IVS at a distance of >2 cm from each other. In animal studies, it has been shown that stimulation of basal and median IVS parts is preferred [5], which is associated with the location of β 1-adrenoreceptors in these zones [6], the stimulation of which leads to the activation of slow calcium channels and the launch of calcium-mediated intracellular mechanisms that lead to improved myocardial contractility. In 15 patients, VEs were implanted in the middle and basal parts of IVF, in 33 in the middle part, and only in 7 patients with ischemic HFrEF, one of the VEs was implanted in the lower third of the IVF, which was associated with a large area of post-infarction scar changes and the inability to achieve optimal parameters of stimulation and sensitivity. The external analyzer was used to test the electrodes resistance, the sensitivity to atrial and ventricular signals, and the stimulation thresholds. With satisfactory test results, the electrodes were connected to corresponding ports of stimulating device, and the patient's sensations during the application of CCM stimuli were evaluated. Separately, a bed for the electrodes and the device under subcutaneous adipose tissue was formed. The wound was sutured in layers.

Follow-up. After devices implantation, all patients were monitored by a case manager of patients with implanted electronic devices and specialists in heart failure (HF) treatment. Scheduled visits to the clinic were conducted every 3 months during the first year and every 6 months during the second year of follow-up. During each visit, the clinical status was assessed: patients were examined and current therapy was corrected, CHF FC was determined, a 6-minute walk test (6MWT), electrocardiography (ECG), daily ECG monitoring, monitoring of CCM work and setting up were carried out. The concentration of N-terminal pro B type natriuretic peptide (NT-proBNP) in blood serum was assessed every 6 months for one and a half years, and a cardiorespiratory test was performed for one year (tradmil, Ohusop Rgo model, Jaeger, Germany). Echocardiography (EchoCG) according to the standard method by one operator on the device VIVID 9 (GE, USA), was performed for 2 years. For each patient, the number of hospitalizations for 6 months was assessed before implantation; the average number of hospitalizations for each control point was calculated over the previous 6-month time interval.

The initial clinical characteristics of the patients are presented in Table 1.

The study assessed the dynamics of the following indicators: CHF FC, NT-proBNP, peak oxygen

Table 1

Clinical characteristics of patients

General data	
Gender (men), n (%)	46 (84%)
Age, years, M \pm SD	53 \pm 11
Resting heart rate, beats/min, M \pm SD	62 \pm 9
Underlying disease	
CHD, proportion of patients with PICS, n (%)	40 (73%), 37 (92,5%)
Myocardial revascularization, n (%)	30 (55%)
Dilated cardiomyopathy, n (%)	15 (27%)
ICD, n (%)	12 (22%)
Paroxysmal atrial fibrillation, n (%)	8 (14%)
Diabetes mellitus, n (%)	8 (14%)
Hospitalizations	
Number of patients hospitalized for 6 months before implantation, n (%)	38 (69%)
Number of hospitalizations for 6 months before implantation, Me [Q1; Q3]	1 [0; 1]
Minimum/maximum number of hospitalizations	0-4
Examination data	
Functional class of CHF (NYHA), Me [Q1; Q3]	2 [2; 3]
6MWT, m, M \pm SD	383 \pm 98
VO ₂ peak, ml/kg/min, M \pm SD	16,2 \pm 5
LV EF, %, M \pm SD	26 \pm 6
LV EDV, ml, M \pm SD	257 \pm 58
LV ESV, ml, M \pm SD	187 \pm 54
Width of QRS complex, MS, M \pm SD	112 \pm 16
Laboratory data	
NT-proBNP, pg/ml, Me [Q1; Q3]	1094 [569; 1749]
Drug therapy	
β -AB, n (%)	55 (100%)
ACE inhibitors/ARA, n (%)	52 (96%)
Mineralocorticoid receptor antagonists, n (%)	51 (93%)
Diuretics: loop, n (%)	53 (96%)
Amiodarone, n (%)	7 (13%)

Notes: the data is presented: 1) n — absolute number of patients (%); 2) Me [Q1; Q3] — median and quartiles; 3) M \pm SD — mean \pm standard deviation.

Abbreviations: AIIIRA — angiotensin II receptor blocker, CHD — coronary heart disease, ACE inhibitors — angiotensin-converting enzyme inhibitors, ICD — implanted cardioverter defibrillators, EDV — end-diastolic volume, CSR — end-systolic volume, LV — left ventricle, PICS — postinfarction cardiosclerosis, 6MWT — 6-minute walk test, EF — ejection fraction, CHF — chronic heart failure, ECG — electrocardiography, EchoCG — echocardiography, β -AB — β -adrenergic blocker, NT-proBNP — N-terminal pro brain natriuretic peptide.

consumption (peakVO₂), walking distance during 6MWT, end-systolic and end-diastolic LV (ESV and EDV, respectively) volumes, LV EF measured by the Simpson method, atrial and ventricular arrhythmias according to the results of daily ECG monitoring and statistics of implanted cardioverter defibrillators (ICD), hospitalizations and deaths due to CHF decompensation, cases of heart transplantation.

Statistical data processing. Statistical analysis was carried out using the software pack IBM SPSS 23 and STATISTICA 10. The categorical indicators are represented by the frequencies and percentages of the total number of observations. Quantitative indicators were checked for normality using the Kolmogorov-Smirnov test. The data is described as the mean value \pm standard deviation (M \pm SD) in case of normal distribution; the median of 25% and

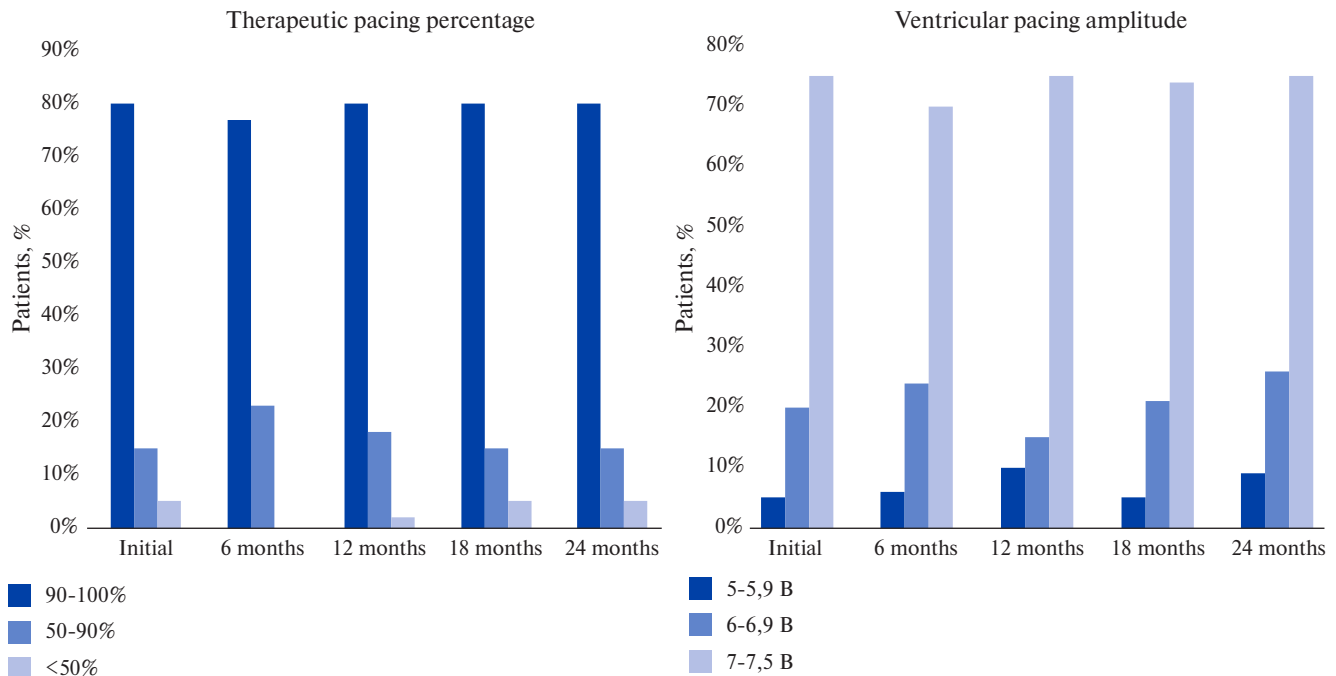


Figure 1. The percentage of therapeutic stimulation (left panel) and the amplitude of ventricular stimulation (right panel) in patients with implanted CCM devices.

75% quartiles in case of abnormal distribution; the minimum and maximum values. The Wilcoxon's test (2 time points) and the Friedman's test (3 or more time points) were used to assess the dynamics of indicators with distribution other than normal. The CHF FC indicators and the number of hospitalizations due to CHF decompensation had an abnormal distribution, but due to the fact that their median values did not change from 6-24 months of follow-up, graphs were plotted using the mean values to visually display the indicator dynamics. The variance analysis for dependent samples ANOVA Repeated was used to analyze the quantitative repeat indicators with normal distribution. At $p < 0,05$, the differences were considered significant.

The study was carried out in accordance with the Good Clinical Practice standards and the principles of the Helsinki Declaration. The study protocol was approved by the Ethics Committees of all participating clinical centers. All participants received written informed consent before enrollment.

Results

There were no intraoperative complications. In the early postoperative period, one patient was found to have suppuration of the CCM bed and its reimplantation was performed for 6 days.

The survival rate for the 2-year follow-up period was 80% (44 patients): 2 cases of sudden cardiac death (SCD) and 1 fatal case due to CHF decompensation during the first year of follow-up; 2 cases

of SCD and 4 fatal cases due to CHF decompensation, 1 heart transplant, 1 fatal case due to cancer progression after device implantation during the second year of follow-up. Detailed data on the outcomes were presented earlier [4].

Electrophysiological parameters of stimulation. CCM devices were programmed immediately after implantation, before patients were discharged for 3-4 days, every 3 months for 1 year, and every 6 months for 2 years of follow-up. The necessary recommendations were followed during programming: achieving the maximum percentage of therapeutic stimulation ($>90\%$) and setting the maximum tolerable amplitude of ventricular stimulation (7-7,5 V for both VEs). The recommended amplitude and duration of ventricular stimulation in CCM are 5-7,5 V and 5,14 ms, respectively. In cases of insufficient therapeutic stimulation ($<90\%$), the device operating time increased from 7 to 9-10 hours per day. As a result, the majority of patients within 2 years achieved and maintained the required percentage of therapeutic stimulation during the day ($>90\%$) and established the maximum tolerable amplitude of ventricular stimulation (7-7,5 V for both VEs) (Figure 1).

3 months after implantation, unpredictable adverse events were detected in the form of stimulation of the CCM bed associated with violation of VEs isolation. Within 2 years, 48% of patients had to disconnect a single VE [4]. After VEs disconnection, the maximum stimulation amplitude was

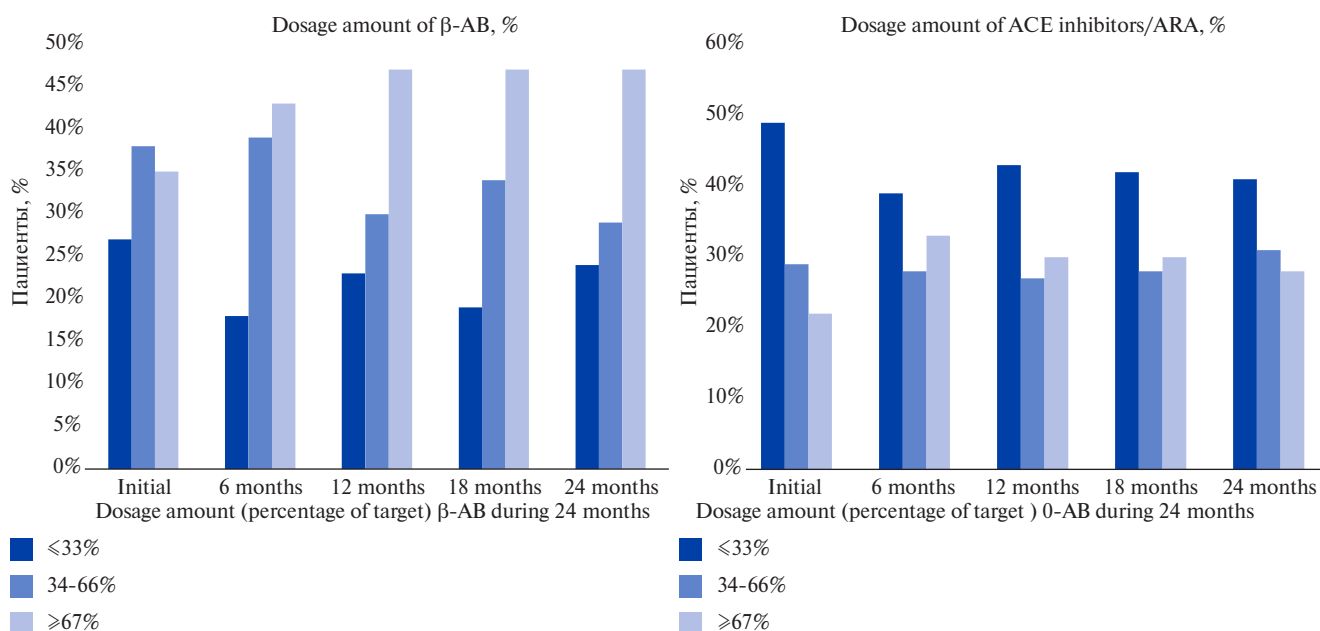


Figure 2. Dosage amount (percentage of recommended target) of β-AB (left panel), ACE inhibitors/ARA (right panel) during 24 months of follow-up.

Abbreviations: AIIIRA — angiotensin II receptor blocker, ACE inhibitors — angiotensin-converting enzyme inhibitors, β-AB — β-adrenergic blocker.

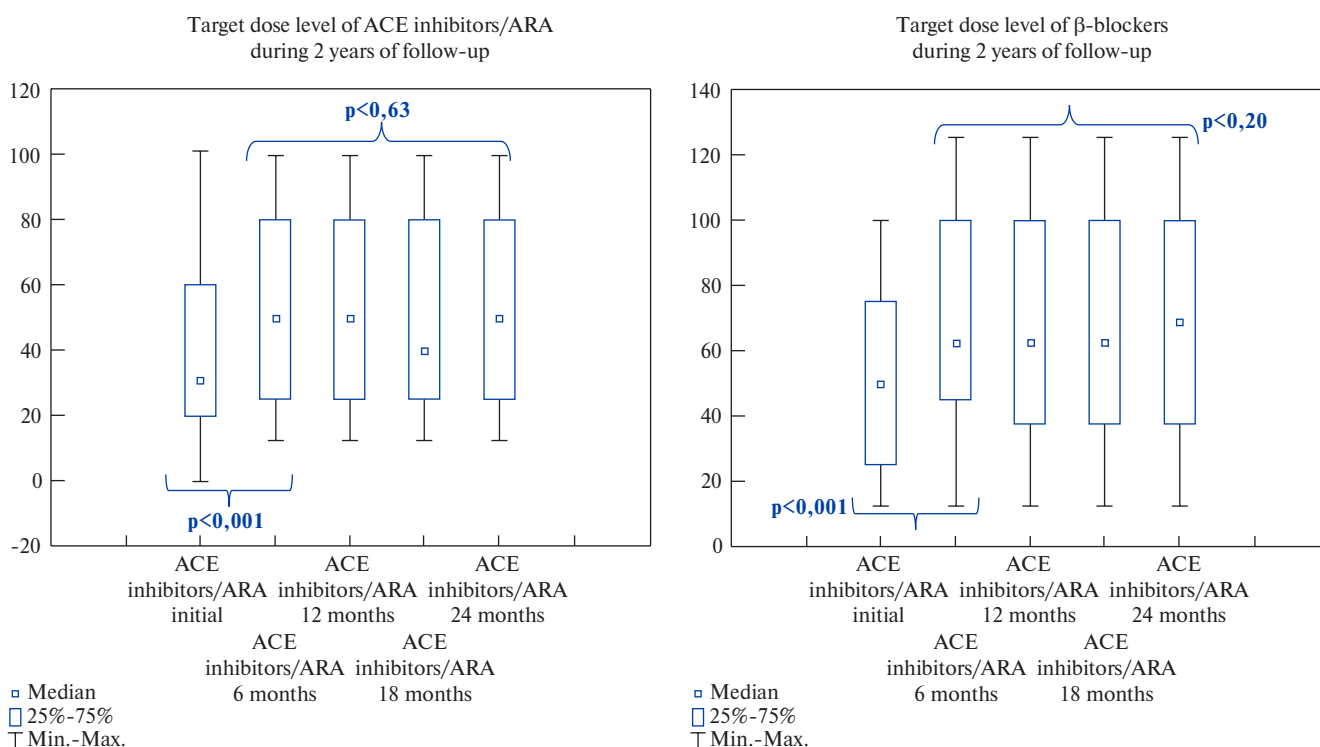


Figure 3. Dynamics of the dose of ACE inhibitors/ARA (left panel) and β-AB (right panel) during 24 months of follow-up.

Abbreviations: AIIIRA — angiotensin II receptor blocker, ACE inhibitors — angiotensin-converting enzyme inhibitors, β-AB — β-adrenergic blocker.

set from a single VE and the stimulation duration was increased to 9-10 hours per day. CCM system audit and replacement of both VEs was carried out in 10 patients over 2 years. In all patients, the audit

revealed violations of VEs insulation in several places and carbonisation in the area of insulation defects.

To assess the effect of disconnecting one VE on the studied parameters, patients were divided into

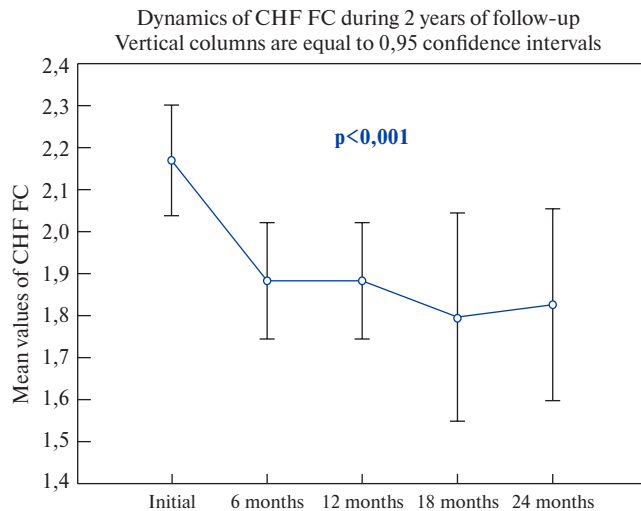


Figure 4. Dynamics of mean values of CHF FC during 2 years of follow-up.

Abbreviations: CI — confidence interval, FC — functional class, CHF — chronic heart failure.

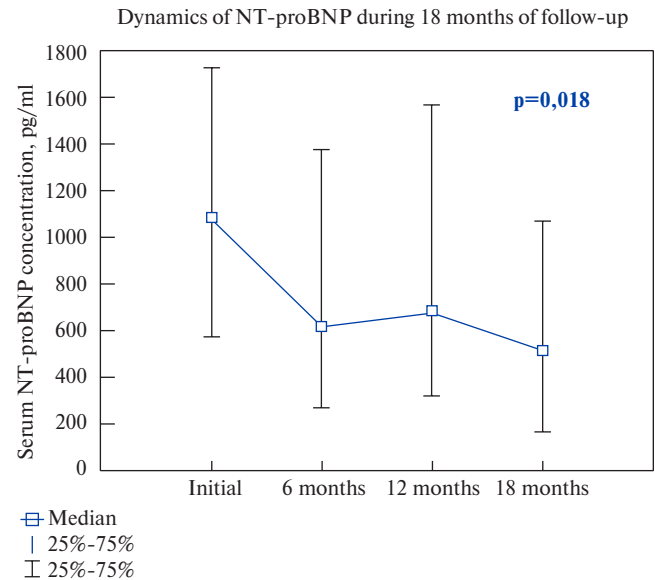


Figure 5. Dynamics of NT-proBNP during 18 months of follow-up.

Abbreviation: NT-proBNP — N-terminal pro brain natriuretic peptide.

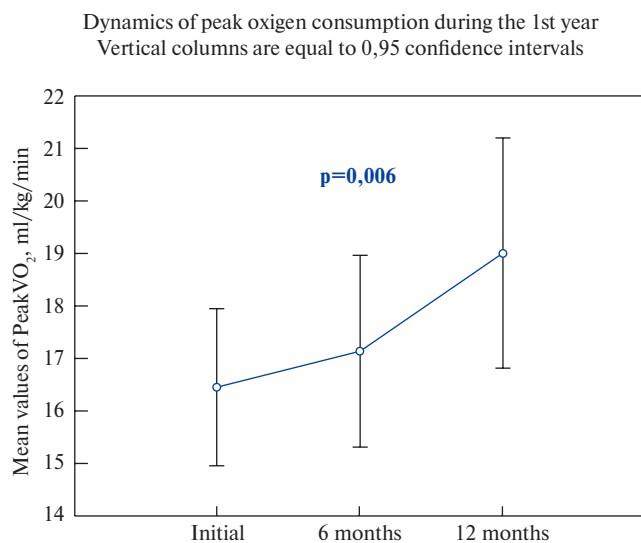


Figure 6. The dynamics of peakVO₂ during 1 year.

Abbreviations: CI — confidence interval, peakVO₂ — peak oxygen consumption.

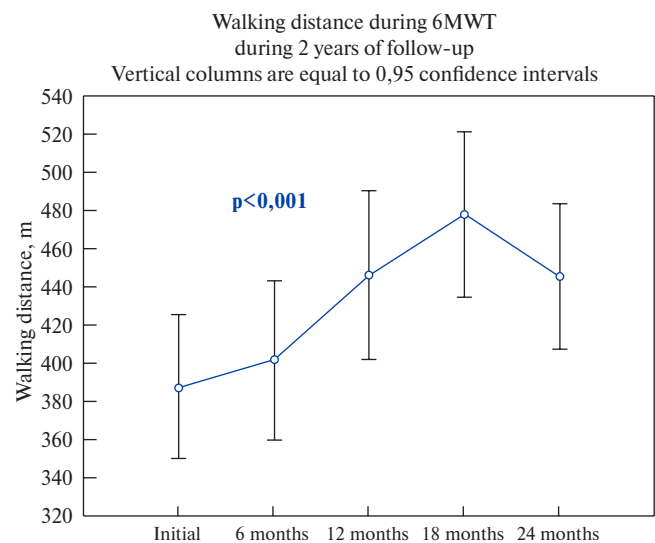


Figure 7. Dynamics of the 6MWT distance during 2 years of observation.

Abbreviations: CI — confidence interval, 6MWT — 6-minute walk test.

groups with one and two operating VEs. The first year of follow-up and 2 years of follow-up were analyzed separately; the patients were divided into those who did not have insulation violations during the entire follow-up period, and those who had 1 electrode disconnected or both VEs replaced.

Analysis of HFrEF drug therapy. The dosage amount (percentage of recommended target) of β -adrenergic blockers (β -AB) and angiotensin-converting enzyme inhibitors (ACE inhibitors)/angio-

tensin I receptor blocker (AIRA) and dose titration of these drugs are shown in Figure 2.

The analysis of drug therapy showed a significant increase in the dose of ACE inhibitors and ARA during the first 6 months ($p<0,001$) after CCM implantation and the lack of drug dose dynamics during further follow-up ($p<0,63$). β -AB doses were also significantly increased in the first 6 months after implantation ($p<0,0001$) and did not change during the subsequent follow-up period

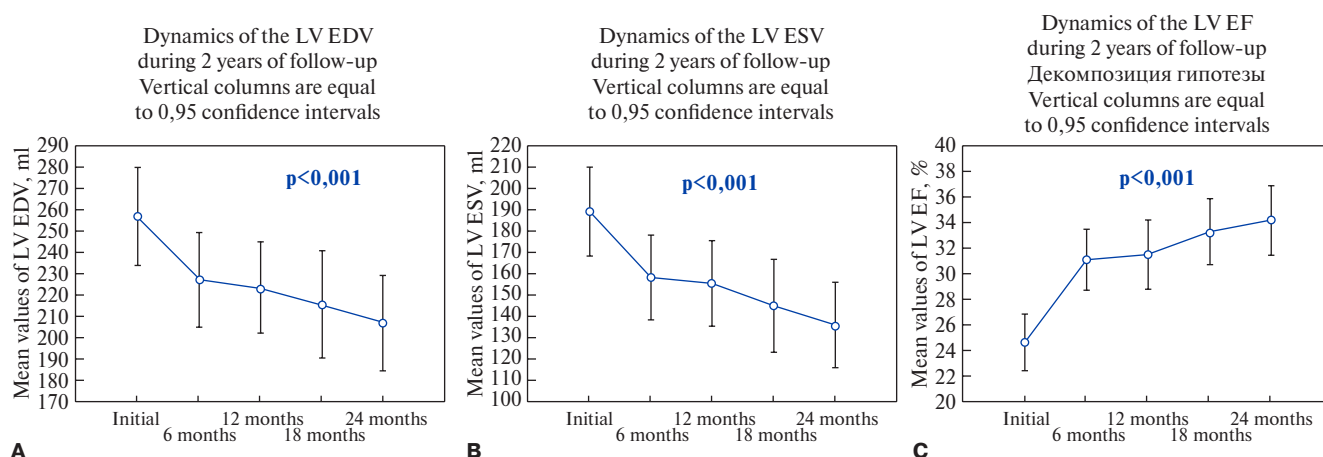


Figure 8. Dynamics of LV EDV (A), LV ESV (B), and LV EF (C) during 2 years of follow-up.

Abbreviations: CI — confidence interval, LV EDV — left ventricular end-diastolic volume, LV ESV — left ventricular end-systolic volume, LV EF — left ventricular ejection fraction.

Table 2

Dynamics of studied parameters in patients with stimulation of one and two VEs

Period	Without electrodes disconnection	Electrodes disconnection
Functional class of CHF, Me [Q1, Q3]		
Initial	2 [2; 3]	2 [2; 2]
12 months	2 [2; 2]	2 [2; 2]
24 months	2 [2; 2]	2 [1; 2]
NT-proBNP concentration, pg/ml, Me [Q1, Q3]		
Initial	1137 [542; 1749]	1066 [728; 1452]
12 months	446 [317; 1326]	748 [438; 1571]
18 months	551 [268; 1653]	478 [136; 800]
VO ₂ peak, ml/kg/min, M±SD		
Initial	16,9 [12,4; 18,2]	16,5 [13,4; 21,4]
12 months	17,2 [14,6; 22,9]	20,7 [15,9; 24,3]
End-diastolic volume, ml, M±SD		
Initial	264±19	253±14
12 months	239±17	215±13
24 months	223±18	198±14
End-systolic volume, ml, M±SD		
Initial	193±17	188±13
12 months	167±16	150±12
24 months	153±16	127±12
Ejection fraction, %, M±SD		
Initial	23±2	25±1
12 months	31±2	32±2
24 months	31±2	36±2
Number of hospitalizations due to CHF decompensation, Me [Q1, Q3]		
Initial	1 [0; 1]	1 [0; 2]
12 months	0 [0; 0]	0 [0; 0]
24 months	0 [0; 0]	0 [0; 0]

Note: Me [Q1, Q3] — median, 25% and 75% quartiles, M±SD — the mean±standard deviation. For all parameters in subgroups comparison $p>0,05$.

Abbreviations: CHF — chronic heart failure, NT-proBNP — N-terminal pro brain natriuretic peptide.

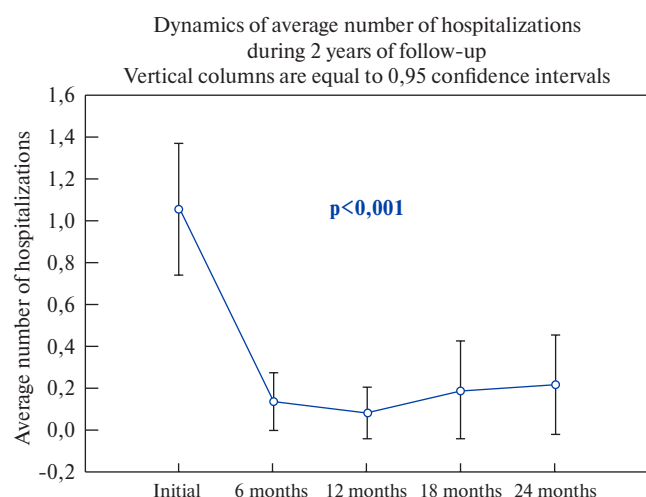


Figure 9. Dynamics of hospitalizations due to CHF decompensation during 2 years of follow-up.

Abbreviation: CI — confidence interval.

($p<0,20$). The dynamics of drug doses is shown in Figure 3.

The loop diuretic dose in 15 patients (27%) during 24 months of follow-up decreased by 25-50%.

Dynamics of studied indicators

CHF FC. Within 2 years, there was a significant decrease in CHF FC ($p<0,001$, $n=44$). Pronounced dynamics were observed after 6 months compared to the initial values of FC, $p<0,001$ ($n=53$), 12 months ($p<0,001$, $n=51$), 18 months ($p=0,003$, $n=49$), 24 months ($p<0,001$, $n=44$). No significant dynamics of CHF FC from 6 to 24 months of follow-up was revealed, $p=0,43$ (Figure 4).

A decrease in CHF FC within 2 years was observed in 15 patients (27%), an increase in CHF FC was observed in 6 patients (11%), of which 3 patients had a decrease in CHF FC within 1 year and an increase in CHF FC with pronounced CHF

Table 3**Differences in NT-proBNP levels in patients with and without CHD anamnesis (Mann-Whitney test)**

Value	n	n	NT-proBNP	NT-proBNP	p-value
	no CHD	CHD	no CHD	CHD	
NT-proBNP initial	15	40	1029 [316; 1446]	1049 [686,5; 1908]	p=0,712
NT-proBNP 6 months	13	35	278 [117; 543]	916 [396; 2222]	p=0,008
NT-proBNP 12 months	14	36	299,0 [93,9; 689]	845,8 [442; 1804,5]	p=0,006
NT-proBNP 18 months	7	13	136,2 [59; 268]	793 [478; 1318]	p=0,007
Dynamics of NT-proBNP over 12 months, p-value (Friedman test)			p=0,02	p=0,01	

Abbreviations: CHD — ischaemic heart disease, NT-proBNP — concentration of N-terminal pro brain natriuretic peptide.

Table 4**Differences in peakVO₂ levels in patients with and without CHD anamnesis (Mann-Whitney test)**

Value, Me [Q1; Q3]	n	n	PeakVO ₂ , ml/kg/min	PeakVO ₂ , ml/kg/min	p-value
	no CHD	CHD	no CHD	CHD	
PeakVO ₂ original	15	39	20,8 [13,0; 21,8]	16,0 [12,4; 18,2]	p=0,007
PeakVO ₂ 6 months	12	31	21,2 [14,5; 23,8]	16,2 [12,3; 19,1]	p=0,05
PeakVO ₂ 12 months	15	37	18,1 [15,9; 28,2]	17,3 [14,5; 22,5]	p=0,24
Dynamics of peakVO ₂ for 1 year, p-value (Friedman criterion)			p=0,56	p=0,03	

Abbreviations: CHD — coronary heart disease, peakVO₂ — peak oxygen consumption.

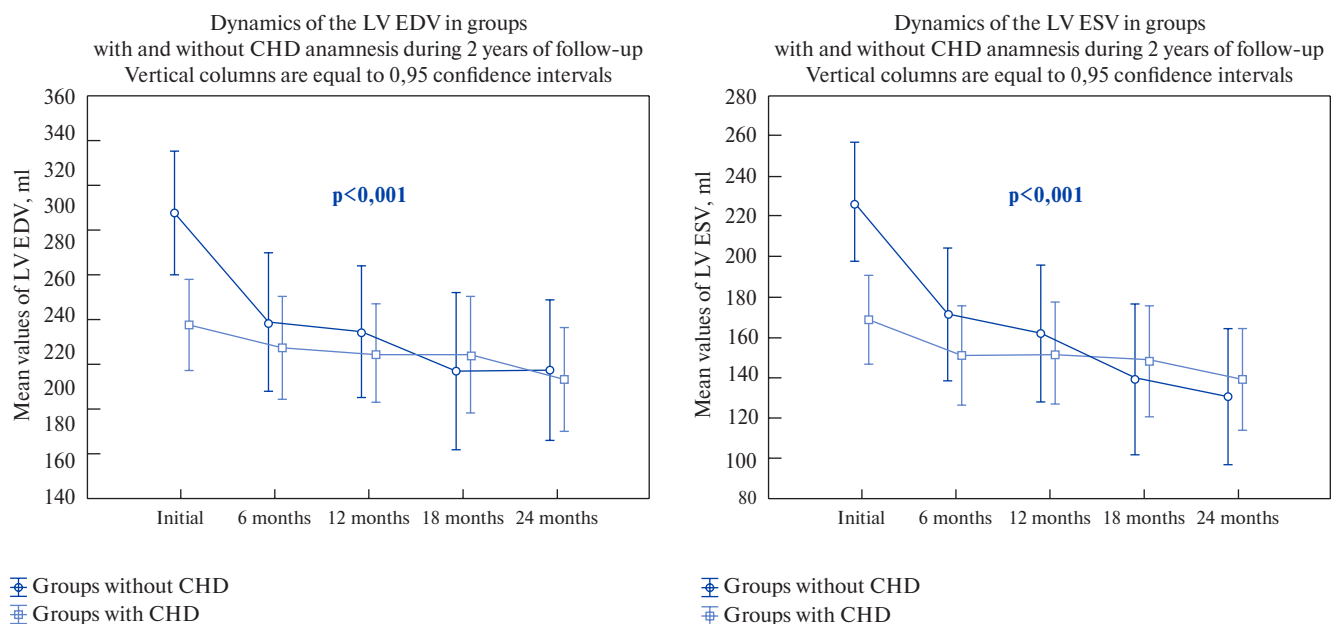


Figure 10. Dynamics of the LV EDV and LV ESV for 2 years in the group with CHD and without CHD.

Abbreviations: CI — confidence interval, CHD — coronary heart disease, LV EDV — left ventricle end-diastolic volume, LV ESV — left ventricle end-systolic volume.

decompensation up to fatal case by the end of 2 years of follow-up. 3 patients (5%) had an increase in FC by the end of the 1st year and a decrease in FC in the second year of follow-up. FC did not change in 31 (56%) patients.

Concentration of NT-proBNP in the blood. The level of NT-proBNP was studied in the first 18 months of follow-up. There was a positive trend over the entire follow-up period, p=0,018, n=20 (Figure 5). A decrease in the NT-proBNP level

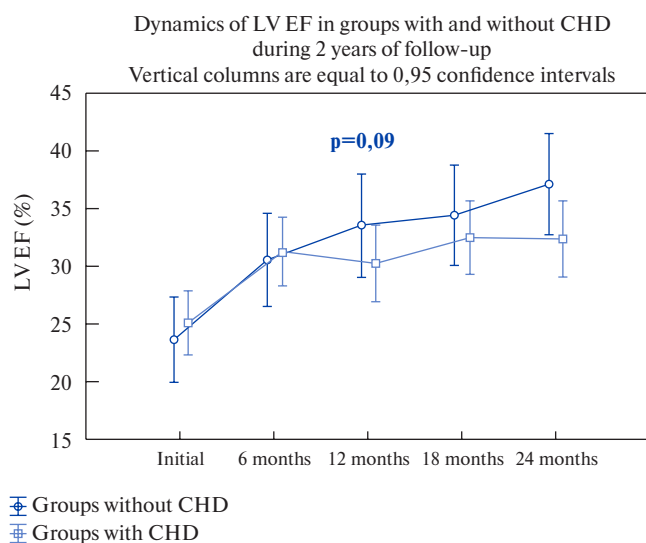


Figure 11. Dynamics of LV EF in groups with and without CHD during 2 years of follow-up.

Abbreviations: CI — confidence interval, CHD — coronary heart disease, LV EF — left ventricular ejection fraction.

compared to the initial value was observed after 6 months ($p < 0,001$, $n = 48$), 12 months ($p = 0,018$, $n = 50$) and 18 months ($p = 0,027$, $n = 20$).

A decrease in the NT-proBNP level within 1 year was observed in 30 (55%) patients, an increase — in 11 (20%) patients, without changes — in 13 (24%). After 18 months after CCM device implantation, the NT-proBNP level was studied in 20 patients. The decrease in NT-proBNP compared to the initial value was in 14 (70%), the increase — in 5 (25%), without changes in 1 (5%) patient.

PeakVO₂. The PeakVO₂ value increased during the first year by an average of $21 \pm 31\%$ in 35 (64%) patients, $p = 0,006$. The peakVO₂ dynamics at three time points is shown in Figure 6.

6MWT. The 6MWT analysis on average for the group showed a positive trend one year later ($p < 0,001$, $n = 35$) and 2 years later ($p < 0,001$, $n = 34$) after CCM implantation. Individual indicators, compared with the initial, improved in 27 patients by 12 months, and in 29 patients by 24 months. The 6MWT dynamics is shown in Figure 7.

EchoCG data. 6 months after the CCM device implantation, a 10% decrease in LV ESV compared to the initial was detected in 27 of 55 patients (49,1%), 12 months later — in 22 of 52 patients (42%), 24 months later — in 29 of 44 patients (66%). An increase in LV EF by more than 10% compared to the initial was detected in 26 of 54 patients (48%) after 6 months, in 25 of 52 (48%) — after 12 months and in 34 of 44 patients (77%) — 24 months after CCM implantation.

The dynamics of mean values of these indicators is shown in the figures (Figure 8 A, B, C).

Hospitalizations due to CHF decompensation. The number of hospitalizations due to CHF decompensation, compared with the indicator for 6 months before surgery decreased by 6 months after CCM device implantation ($p < 0,0001$), this effect persisted for 2 years of follow-up (Figure 9).

Dynamics analysis of the studied parameters in patients with one and two VEs. The dynamics of all the studied parameters did not differ in the groups of patients with and without disconnecting one of the VEs at all control points, $p > 0,05$ (Table 2).

Dynamics of the studied parameters depending on HFrEF etiology. Dynamics of CHF FC in groups of patients with coronary heart disease (CHD) (92,5% of patients with post-infarction cardiosclerosis (PIC)) and without CHD did not differ during the first year, 2 [2; 2] and 2 [1; 2], respectively, $p = 0,22$, and the second year of follow-up, 2 [2; 2] and 2 [1; 2], respectively, $p = 0,25$. There were also no differences in the dynamics of number of hospitalizations due to CHF decompensation (minimum-maximum number of hospitalizations 0-1 and 0-3 during the first and second years, respectively, for patients without CHD, 0-2 and 0-3 during the first and second years, respectively, for patients with CHD), $p > 0,05$ at all-time points.

The dynamics analysis of the NT-proBNP level in the groups with CHD and without CHD showed that the initial NT-proBNP level did not differ in both groups (Table 3). However, at 6, 12, and 18 months after implantation, the NT-proBNP level was significantly higher in patients with CHD (Table 3). There was a significant positive dynamic of the indicator within each group during 1 year of follow-up (Table 3).

The peakVO₂ values was at baseline and 6 months after CCM implantation was lower in the group of patients with CHD (Table 4).

The EchoCG parameters dynamics of LV EDV and LV ESV differed in the groups of patients with ischemic and non-coronary cardiomyopathy during 1 year and 2 years of follow-up, $p = 0,036$ and $p = 0,0003$ for LV EDV and $p = 0,007$ and $p < 0,001$ for LV ESV, respectively, due to the initial values of LV EDV and LV ESV (Figure 10). When excluding the starting point, the dynamics in the two groups was not significant, $p = 0,39$ for LV EDV and $p = 0,25$ for LV ESV. The decrease in volume parameters was more expressed in the group of patients with non-coronary cardiomyopathy.

The analysis of LV EF absolute values showed significant differences in the two groups at 12 and 24 months after CCM therapy, $p = 0,03$ and $p = 0,01$, respectively. However, the indicator dynamics in

Table 5

Differences in NT-proBNP index in groups with baseline of LV EF $\geq 25\%$ and LV EF $\leq 25\%$ during 18 months of follow-up (Mann-Whitney test)

Value	n	n	NT-proBNP	NT-proBNP	p-value
	EF $\geq 25\%$	EF $< 25\%$	EF $\geq 25\%$	EF $< 25\%$	
NT-proBNP исходно	29	26	866 [511; 1094]	1300 [1137; 1777]	p=0,006
NT-proBNP 6 мес.	25	23	547 [205; 942]	936 [416; 2230]	p=0,07
NT-proBNP 12 мес.	27	23	533,4 [221,9; 849]	1099 [374,9; 2152]	p=0,06
NT-proBNP 18 мес.	10	10	763 [190,1; 1318]	407,3 [136,2; 823,5]	p=0,5
Dynamics of NT-proBNP over 12 months, p-value (Friedman test)			p=0,07	p=0,005	

Abbreviations: EF — ejection fraction, NT-proBNP — N-terminal pro brain natriuretic peptide.

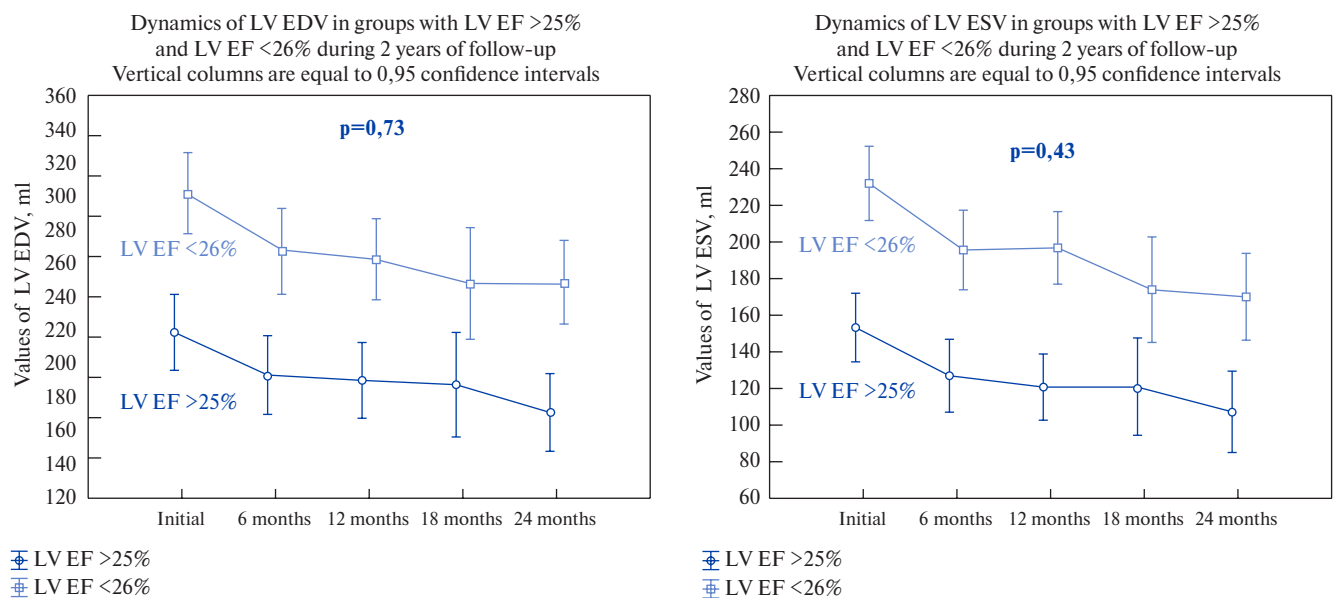


Figure 12. Dynamics of LV EDV and LV ESV in groups with initial value of LV EF $>$ and $< 25\%$ during 2 years of follow-up.

Abbreviations: CI — confidence interval, LV EDV — left ventricular end-diastolic volume, LV ESV — left ventricular end-systolic volume, LV EF — left ventricular ejection fraction.

both groups did not differ significantly, $p=0,09$ (Figure 11).

Dynamics of studied parameters in patients in the groups with the initial value of LV EF $\geq 25\%$ and LV EF $< 25\%$. The dynamics of CHF FC, the number of hospitalizations due to CHF decompensation, and peak VO_2 did not differ in the LV EF groups $\geq 25\%$ and LV EF $< 25\%$ during 2 years of follow-up.

The absolute NT-proBNP values were initially higher in the group with LV EF $< 25\%$. At further follow-up, there were no significant differences in NT-proBNP in the groups (Table 5).

The analysis of EchoCG parameters revealed regular significant differences in LV volumes in the groups with LV EF $\geq 25\%$ and LV EF $< 25\%$. With that, the volume dynamics in both groups was identical (Figure 12).

Cardiac arrhythmias analysis and indications for ICD implantation. In accordance with the European Recommendations of 2016 and the recommendations of the All-Russian Scientific Society of Arrhythmologists, 2017, the presence of HFrEF with LV EF $\leq 35\%$ in the absence of reversible causes is an indication for the SCC primary prevention [7, 8]. Prior to the CCM device implantation, 11 (22%) patients had ICD for the primary SCC prevention. The remaining patients were scheduled for ICD implantation after CCM implantation. During the 1 and 2 years of follow-up, ICDs were implanted in 21 (38%) and 3 (4%) patients, respectively. There were no ICD triggers with regards to paroxysmal ventricular arrhythmias. 2 patients refused ICD implantation, and two died suddenly during the first 6 months before ICD implantation. Within 2 years, 10 patients

(18%) were removed from the ICD waiting list due to achievement of LV EF >35% (LV EF was 38% in 2 patients and >40% — in 8 patients), of which 1 patient died suddenly at the age of 18 months (his initial LV EF was 35%, and at the 12-month visit it reached 43%).

Cessation of CCM therapy occurred in one patient after 18 months after device implantation due to transition of atrial fibrillation to a permanent form. Electro-pulse therapy with sinus rhythm withholding for no more than 1 month was carried out twice. Arrhythmia catheter ablation was not carried out due to the predicted low efficiency.

Discussion

Our study shows a clear positive trend of current HFrEF associated with CCM within a two-year follow-up period: reduction of CHF FC hospitalizations because of CHF decompensation, decrease the concentration of NT-proBNP in the blood, an increase in peakVO₂ in the first year of follow-up as well as the decrease and increase in LV EF volumes.

Violations of the VEs isolation were detected in half of the patients during the follow-up, which required the disconnection of one VE. Subjectively, when VEs disconnecting, patients noted a feeling unwell, a decrease in tolerance to physical activity, discomfort with the appearance of muscle stimulation and inconvenience due to the need for additional visits to the clinic. However, the dynamics of objective indicators and EchoCG parameters for 2 years did not differ in the groups with one and two VEs. Our data correlate with Röger S, et al. [9], who compared 2 groups of patients with one and two VEs (23 and 25 patients in each group, respectively) and assessed peakVO₂, CHF FC, quality of life, and also did not receive any differences. The obtained results may be important in the future when optimizing CCM devices. The currently recommended parameters of stimulation, as well as the need for implantation of two VEs, are based on data obtained in the study on CCM therapy in animal models [10].

The curation feature of the studied group of patients had involvement of a HF cardiologist expert that provided their management in accordance with the current recommendations from the patients formation position and the dose selection of modern drugs [8, 11]. A significant increase in the dose of β -AB and ACE inhibitors/ARA was observed during the first 6 months, then the doses of these drugs did not significantly change. It should be noted that 27% of patients managed to reduce the dose of loop diuretics by 25-50%, which confirms a significant improvement in their status. There were no changes in drug doses of the main groups for CHF treatment in the period from 6-24 months of the follow-up,

while the positive dynamics of HF severity, the improvement of laboratory and echocardiographic parameters continued, makes it highly likely that we were dealing not only with the drug therapy contribution, but also CCM to the positive dynamics of the patients' status.

When analyzing the studied parameters, depending on CHF etiology, it was shown that patients with ischemic HFrEF had significantly higher NT-proBNP values after 6, 12 and 18 months, and lower peakVO₂ values at baseline and 6 months after CCM implantation. The positive dynamics of EchoCG parameters was observed in both groups, but the curve of LV volume reduction was significantly more expressed in the group of patients with non-coronogenic HFrEF. Initially, higher values of LV EDV and ESV in this group significantly decreased in the first 6 months after implantation, with a further decrease by the end of the 2-year follow-up, while patients with ischemic HFrEF had initially lower values of LV volumes, and the volume dynamics curve was flatter. LV EF significantly increased in both groups within 2 years, but its absolute values were significantly higher in the group of patients with HFrEF of non-coronary etiology after 12 and 24 months of follow-up. It is important to note that despite the differences in the clinical response to CCM in patients with CHF of different etiologies, the presence of CHD, PIX did not have a significant negative effect on CHF outcomes (mortality and hospitalization due to CHF decompensation) [4].

Randomized clinical studies (HF-FIX-5, HF-FIX-5 subgroup with LV EF 25-45%, HF-FIX-5C) showed a better response to CCM in patients with LV EF 25-45% [2, 3]. In 2019, an analysis of the economic CCM applicability in patients with HFrEF [12] was conducted, that showed the advantage of implanting CCM devices in this group compared to traditional drug therapy. However, extension study is needed to confirm this data. The cohort of patients presented in the study did not include persons with LV EF >35%. All patients were divided into groups with LV EF \geq 25% and <25%. There were no significant differences in the number of hospitalizations due to CHF decompensation, the dynamics of CHF FC, peakVO₂, and NT-proBNP. The dynamics of echocardiographic parameters did not differ in the groups. Lower values of LV volumes were observed in patients with LV EF more than 25%. There were no differences in the HFrEF course outcomes with LVEF value of more or less than 25% for 2 years [4].

The experience obtained in the study showed the need to implant ICDs in patients before implanting CCM devices, as required by national and European recommendations [7, 8]. In 18% of patients, during a two-year follow-up period, LV EF ranged from

35-40%, which turned out to be an obstacle to ICD implantation, resulting in SCC. The encouraging results of the CCM use in the majority of HFrEF patients with sinus rhythm should stimulate the search for predictors of a positive response to this type of electrophysiological treatment, which will help to personalize the electrotherapy type when choosing tactics to improve the prognosis.

Study limitations. The presented data were obtained in the course of follow-up study, which was conducted within the protocol of clinical testing of the Ministry of Health of the Russian Federation 2016-19-16 and did not have a control group. The sample of patients included mainly men, which did not allow to assess the gender characteristics of the CCM use.

Conclusion

In the group of patients with HFrEF of FC II-III, the CCM use in most patients was associated

with improvement or stabilization of clinical and hemodynamic state, increase in exercise tolerance, decrease in number of hospitalizations due to HF decompensation, positive dynamics of functional and geometric parameters of LV and marker of myocardial NT-proBNP stress.

The positive trend of changes in the indicators of CHF severity markers and prognosis was not affected by disease causation, but the presence of CHD, PICS was associated with a lower dynamics of the volume EchoCG parameters of reverse myocardial remodeling and NT-proBNP associated with CCM.

When using CCM, an individual approach to the implantation technique, the choice of consumables and constant dynamic monitoring with the participation of a cardiologist-a specialist in heart failure is required.

Relationships and Activities: none.

References

1. Mando R, Goel A, Habash F, et al. Outcomes of Cardiac Contractility Modulation: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. *Cardiovascular Therapeutics*. 2019;21:1-10. doi:10.1155/2019/9769724.
2. Kadish A, Nademanee K, Volosin K, et al. A randomized controlled trial evaluating the safety and efficacy of cardiac contractility modulation in advanced heart failure. *Am Heart J*. 2011;161:329-37. doi:10.1016/j.ahj.2010.10.025.
3. Abraham WT, Kuck KH, Goldsmith RL, et al. A randomized controlled trial to evaluate the safety and efficacy of cardiac contractility modulation. *JACC Heart Fail*. 2018;6:874-83. doi:10.1016/j.jchf.2018.04.010.
4. Vander MA, Lyasnikova EA, Belyakova LA, et al. Two-year outcome analysis of patients with chronic heart failure with reduced ejection fraction receiving cardiac contractility modulation therapy. *Russ J Cardiol*. 2020;25(7):3853. (In Russ.) doi:10.15829/1560-4071-2020-3853.
5. Winter J, Brack KE, Ng GA. The acute inotropic effects of cardiac contractility modulation (CCM) are associated with action potential duration shortening and mediated by β 1-adrenoceptor signalling. *J Mol Cell Cardiol*. 2011;51:252-62. doi:10.1016/j.yjmcc.2011.04.010.
6. Habecker BA, Anderson ME, Birren SJ, et al. Molecular and cellular neurocardiology: development, and cellular and molecular adaptations to heart disease. *J Physiol*. 2016;594.14:3853-75. doi:10.1113/jp271840.
7. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *European Heart Journal*. 2016;37:2129-200. doi:10.1093/eurheartj/ehw128.
8. Mareev VY, Fomin IV, Ageev FT, et al. Russian Heart Failure Society, Russian Society of Cardiology. Russian Scientific Medical Society of Internal Medicine Guidelines for Heart failure: chronic (CHF) and acute decompensated (ADHF). Diagnosis, prevention and treatment. *Kardiologiya*. 2018;58:8-158. (In Russ.) doi:10.18087/cardio.2475.
9. Röger S, Said S, Kloppe A, et al. Cardiac contractility modulation in heart failure patients: Randomized comparison of signal delivery through one vs. two ventricular leads. *J Cardiol*. 2017;69:326-32. doi:10.1016/j.jjcc.2016.06.015.
10. Lyon AR, Samara MA, Feldman DS, et al. Cardiac contractility modulation therapy in advanced systolic heart failure. *Nat Rev Cardiol*. 2013;10:584-98. doi:10.1038/nrcardio.2013.114.
11. Sitnikova MY, Lyasnikova EA, Yurchenko AV, et al. Results of 3 years work of the Russian hospital register of chronic heart failure (RUSSIAN hoSpital Heart Failure Registry — RUS-HFR): relationship between management and outcomes in patients with chronic heart failure. *Kardiologiya*. 2018;58:9-19. (In Russ.) doi:10.18087/cardio.2483.
12. Witte K, Hasenfus G, Kloppe A, et al. Cost-effectiveness of a cardiac contractility modulation device in heart failure with normal QRS duration. *ESC Heart Failure*. 2019;6:1178-87. doi:10.1002/ehf2.12526.