https://doi.org/10.35336/VA-1300

THE EFFECTIVENESS OF CARDIAC CONTRACTILITY MODULATION: RESULTS OF TWO-YEAR FOLLOW-UP

E.M.Rimskaya, M.M.Belyaeva, N.A.Mironova, S.V.Dobrovolskaya, G.S.Tarasovskiy, H.F.Salami, V.G.Kiktev, S.P.Golitsyn

FSBI "Chazov NMRC of Cardiology" of the MH RF, Russia, Moscow, 15a Academician Chazov str.

Aim. To evaluate the survival and dynamics of clinical and instrumental data in patients with chronic heart failure (CHF), atrial fibrillation (AF) and cardiac contractility modulation (CCM).

Methods. There were included 54 patients (40 men, median age 59.7 [56.6; 63.9] years) with signs of CHF II (n=27, 50%) functional class and III (n=27, 50%) NYHA functional class, significantly decreased left ventricular ejection fraction (LVEF=30 [24,7; 35,5]%), LV dilatation and paroxysmal (n=27, 50%) or permanent (n=27, 50%) AF. In all patients, devices for CCM were implanted. The dynamics of clinical and instrumental parameters were assessed in 2, 6, 12 and 24 months after implantation. The actual survival patients with CCM was compared with the predicted survival calculated using the Seattle model of heart failure and MAGGIC risk score.

Results. In 14 (28%) of patients CCM resulted in significantly increased clinical, echocardiographic parameters (increase in LVEF by 15 [11; 20]%, decrease in end-systolic volume by 68,5[37.5;104.5] ml and end-diastolic volume by 44 [30,100] мл), increase in walking distance during 6-minute walking test and decrease of NT-proBNP. The only factor significant for maximal response was non-ischemic etiology of CHF (χ^2=4.54, p=0.034). During 2 years 21 (42%) patients died. The all-cause mortality in patients with CCM to the first year of observation was 16%, two-year all-cause mortality - 40%. These figures turned out to be significantly higher than predicted according to the Seattle model (χ^2=10.93, p=0.001). The predicted and actual risk of death at 12-month follow-up turned out to be comparable when assessing survival parameters according to the MAGGIC scale. (χ^2=2.24, p=0.134).

Conclusion. CCM therapy in some patients with CHF of non-ischemic etiology can lead to an improvement of all clinical and instrumental characteristics. At the same time, there is no effect of CCM on the prognosis of patients with CHF. This fact may suggest the need of additional studies with increased number of cases.

Key words: cardiac contractility modulation; chronic heart failure; left ventricle ejection fraction; atrial fibrillation; survival

Conflict of Interest: none.
Funding: none.
Received: 28.11.2023 **Revision received:** 10.03.2024 **Accepted:** 14.03.2024
Corresponding author: Rimskaia Elena, E-mail: eleno4ka_g@mail.ru

E.M.Rimskaya - ORCID ID 0000-0002-0063-5474, M.M.Belyaeva - ORCID ID 0009-0002-7990-4581, N.A.Mironova - ORCID ID 0000-0002-2374-3718, S.V.Dobrovolskaya - ORCID ID 0000-0003-0580-393X, G.S.Tarasovskiy - ORCID ID 0000-0002-2143-8912, H.F.Salami - ORCID ID 0000-0001-9751-7767, V.G.Kiktev - ORCID ID 0000-0002-2628-3796, S.P.Golitsyn - ORCID ID 0000-0001-9913-9974

For citation: Rimskaya EM, Belyaeva MM, Mironova NA, Dobrovolskaya SV, Tarasovskiy GS. Salami HF, Kiktev VG, Golytsin SP. The effectiveness of cardiac contractility modulation: results of two-year follow-up. *Journal of Arrhythmology.* 2024; 31(2): 13-23. https://doi.org/10.35336/VA-1300.

Despite the advancements in both pharmacological and non-pharmacological therapies for chronic heart failure (CHF), a subset of patients with reduced left ventricular ejection fraction (LVEF) continue to experience persistent symptoms [1]. According to published sources, the 1-year mortality rate among patients with CHF is 7.2% and the 1-year hospitalization rate is 31.9% [2]. Even with the full spectrum of therapeutic options, there remains a subset of patients whose clinical condition does not align with the current standards for the treatment of heart failure using implantable devices. A large cohort of patients with an electrocardiogram (ECG) QRS complex duration of less than 130 ms remains outside the indication for well-established cardiac resynchronization therapy (CRT) [3]. In addition, one third of patients with CRT performed for topical indications still have symptoms of CHF and no increase in LVEF [4]. The search for other ways of treatment of these categories of patients was the basis for the development of a new approach to invasive treatment of CHF.

In 2000, clinical trials with implantable cardiac contractility modulation (CCM) devices were first initiated. The new technique is based on experimental studies demonstrating the enhancement of cardiomyocyte contractile properties when subjected to a high-amplitude biphasic electrical pulse of high voltage applied during the absolute refractory period. When applied 30 ms after the onset of the QRS complex on the ECG, the electrical impulse does not cause electrical activation of the ventricular myocardi-

um. However, it has been shown to increase the amplitude of the subsequent myocardial contraction and shorten the action potential. All these effects completely disappeared after stimulation was stopped [5, 6]. Several clinical, including randomized clinical trials (RCTs) have revealed a positive effect of CCM on functional class (FC) of CHF, exercise tolerance of patients, as well as on peak oxygen consumption and quality of life in patients with LVEF of 25-45% and absence of dilated QRS complexes [7-9]. However, the data on the effect of CCM on survival rates of patients with CHF based on the results of these studies are contradictory.

Of the RCTs conducted, only the FIX-HF-5C trial showed a significant reduction in the combined endpoint (cardiovascular mortality or hospitalization due to CHF), and this endpoint was exploratory, and the number of events was small [9]. According to meta-analyses that included all RCTs, there was no significant effect of CCM on all-cause mortality [10-11]. In addition, there is very limited information on the potential use of CCM in patients with atrial fibrillation (AF), a frequent complication of CHF.

The aim of the study was to investigate the survival rates and the dynamics of clinical and instrumental manifestations of chronic heart failure complicated by atrial fibrillation in the context of cardiac contractility modulation.

METHODS

The prospective single-center study was conducted within the framework of the clinical trial «Modulation of Cardiac Contractility in Patients with Chronic Heart Failure and Atrial Fibrillation,» approved by the Ministry of Health of the Russian Federation, index CA 2018-9-18. The clinical approbation was approved by the independent ethical committee of the Ministry of Health of the Russian Federation on May 15, 2018, protocol No.4.

The criteria for inclusion of patients in the study were: 1) presence of CHF of II-III class according to NYHA, with QRS complex duration≤130 ms (except for patients who did not respond to CRT) with LVEF value according to echocardiography (Echo) of 20-40%; 2) age of patients 18 years and older; 3) presence of any form of AF; 4) optimal in accordance with current recommendations drug therapy of CHF for at least 3 months before inclusion in the study; 5) absence of clinical signs of decompensation of CHF within 1 month; 6) signed informed consent of the patient.

Patients were excluded from the study if they were on the waiting list for heart transplantation, had terminal stage coronary heart disease (CHD), or had experienced a recent (within 3 months before inclusion in the study) myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, heart valve surgery, or acute inflammatory diseases.

For the period 2018-2019, 54 patients, 40 males and 14 females, with a median age of 59.7 [56.6; 63.9] years were selected according to the inclusion criteria. The duration of history of CHF was 48 [16; 81] months. Among the patients with CHF included in the study, 27 (50%) had NYHA FC II and 27 (50%) had NYHA FC III. Ischemic etiology of CHF was diagnosed in 15 (28%) patients, non-ischemic - in 39 (72%). In patients with ischemic heart disease, myocardial revascularization at the time of CCM device implantation was completely completed in all cases. All patients included in the study had documented AF on ECG. The paroxysmal form of AF was noted in

Table 1.

Baseline characteristics of the patients included in the study

Indicator	Value
Age, years	59,7 [56,6; 63,9]
Men, n (%)	40 (74,1)
Duration of history of CHF, months	48 [16; 81]
Non-ischemic etiology of CHF, n (%)	39 (72)
Ischemic etiology of CHF, n (%)	15 (28)
Paroxysmal AF, n (%)	27 (50)
Persistent AF, n (%)	27 (50)
Patients with CRT-D, n (%)*	6 (11,1)
ICD implantation, n (%)**	17 (31,5)
CHF II, n (%)	27 (50)
CHF III, n (%)	27 (50)
NT-pro-BNP level, pkg/mL	2493 [1210; 4489]
6-MWT, m	315 [280; 380]
LVEF, %	30 [24,7; 35,5]
LV EDV, ml	220 [193; 263]
LV ESV, ml	155 [121; 200]
LV EDD, cm	6,8 [6,4; 7,5]
LV ESD, cm	5,8 [5,1; 6,5]
ACEIs/ARBs/sacubitril/valsartan, n (%)	54 (100)
Beta-blockers, n (%)	54 (100)
Diuretics, n (%)	54 (100)
Allopurinol, n (%)	8 (14,8)
MRA, n (%)	54 (100)
Amiodarone, n (%)	16 (29,6)
Digoxin, n (%)	8 (14,8)
Warfarin/apixaban/rivaroxaban, n (%)	54 (100)
Aspirin and/or clopidogrel, n (%)	6 (11,1)

Note hereafter: CHF, chronic heart failure; AF, atrial fibrillation; CRT-D, cardiac resynchronization therapy with defibrillation function; CCM, cardiac contractility modulation; ICD, implantable cardioverter-defibrillator; FC, functional class; NT-pro-BNP, concentration of N-terminal fragment of brain natriuretic peptide; 6-MWT, 6-minute walk test; EF, ejection fraction; LV, left ventricle; EDV, end-diastolic volume; ESV, end-systolic volume; EDD, end-diastolic dimension; ESD, end-systolic dimension; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; MRA, mineralocorticoid receptor antagonists; *, at the time of CCM device implantation; **, before or after CCM implantation.

27 (50%) patients. In all cases, persistent sinus rhythm was achieved in these patients with antiarrhythmic therapy or successful radiofrequency ablation/cryoblation of the pulmonary vein orifices. In 27 patients (50%), the AF was permanent, with normosystole achieved at the time of device implantation. The average heart rate (HR) per day, according to Holter monitoring at the time of device implantation, was 75.8±9.8 beats per minute. Initially, all patients were characterized by a significant decrease in global myocardial contractility (LVEF was 30 [24.7; 35.5]%) and LV cavity dilation (LV end-diastolic volume (EDV) was 220 [193;263] ml, LV end-systolic volume (ESV) was 155 [121;200] ml). NT-proBNP levels were 2493 [1210; 4489] pg/mL. Patients walked 315 [280; 380] m as measured by the six-minute walk test. Considering the indication of primary prevention of sudden cardiac death (SCD), 6 (11.1%) patients had a cardioverter-defibrillator (ICD) implanted at the time of inclusion in the study, another 11 (20.4%) patients had an ICD implanted during follow-up. In addition, the study included 6 patients with symptoms of CHF FC 3 persisting despite existing drug therapy and CRT at the time of implantation of the CCM device.

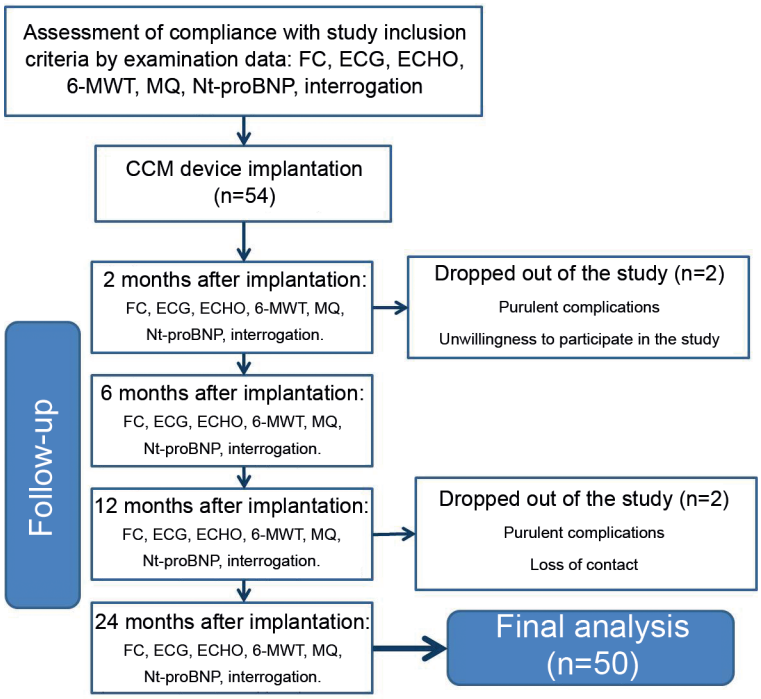


Fig. 1. Study Design. Notes: MQ, Minnesota Quality of Life Questionnaire; CCM, cardiac contractility modulation; FC, functional class of heart failure; ECG, electrocardiogram; ECHO, echocardiography; 6-MWT, six-minute walk test.

All patients signed informed consent to participate in the study. The main characteristics of the patients at the time of inclusion in the study are presented in Table 1. At the time of CCM implantation, all patients received optimal drug therapy including angiotensin-converting enzyme inhibitors or angiotensin receptor blockers or sacubitril/valsartan, mineralocorticoid receptor antagonists, beta-blockers, loop diuretics and anticoagulant drugs (warfarin or apixaban or dabigatran). 16 (29,6%) patients received antiarrhythmic therapy with amiodarone in connection with paroxysmal form of AF or ventricular heart rhythm disturbances, 8 (14,8%) patients received digoxin therapy along with beta-blockers in connection with tachysystole on the background of permanent form of AF. 8 (14,8%) patients received allopurinol therapy due to hyperuricemia, 6 (11,1%) patients continued to receive therapy with antithrombotic drugs (aspirin and/or clopidogrel).

After preliminary examination, all included patients underwent implantation of the Optimizer Smart 2-electrode system with electrode positioning in the interventricular septum on the right ventricular side for the purpose of inpatient CCM. Initial programming of the CCM device, as well as taking telemetric information about the parameters of the implanted device and the character of the heart rhythm (so-called interrogation) was performed in all patients during surgical intervention. In all cases, surgical interventions were performed without complications. After surgery, control Echo studies showed no hemodynamically significant abnormalities of tricuspid valve function by the device electrodes. Further programming of CCM devices was performed on the 1st day after implantation, further - after 2, 6, 12 and 24 months during the follow-up period. The programming followed the necessary guidelines: achieving the maximum percentage of therapeutic stimulation

Table 2.

Baseline characteristics of patients with maximal improvement on CCM (subgroup 1) and those who did not respond to MSS (subgroup 2)

	Subgroup 1 (n=14)	Subgroup 2 (n=36)	p
Men, n (%)	11 (78.6)	26 (72.2)	0.82
Age	57 [46;63]	64.5 [57;66.8]	0.067
CHF FC (NYHA)	2[2;3]	3[2;3]	0.38
Non-ischemic CHF, n (%)	13 (93)	5(24)	0.026
Paroxysmal AF, n (%)	5(35.7)	9(25)	0.31
LVEF, %	30 [26.6; 33]	29.5 [24.5; 37]	0.61
LV EDD, cm	6.8 [6.5; 7.0]	6.9 [6.3; 7.8]	0.36
LV ESD, cm	5.7 [5.4; 6.0]	6.2 [5.0; 6.8]	0.23
LV EDV, ml	220 [198; 251]	220 [180; 285]	0.72
LV ESV, ml	159.5 [121; 185]	155 [127; 208]	0.60
6-MWT, m	350 [310; 390]	300 [266; 375]	0.13
NT-pro-BNP, pkg/mL	1540 [945; 4427]	2285 [1242;4877]	0.36

time (more than 70%) and setting the maximum tolerable amplitude of ventricular myocardial stimulation. The recommended amplitude and duration of ventricular stimulation pulses during CCM are 5-7.5 V and 5.14 ms, respectively.

According to the clinical validation protocol, the follow-up period was 24 months, with 4 visits: I, 2 months after CCM implantation; II, 6 months; III, 12 months; and IV, 24 months after CCM implantation. All included patients at the selection stage and at all visits underwent 12-channel ECG, transthoracic Echo, Holter ECG monitoring, determination of N-terminal fragment of brain natriuretic peptide (NTproBNP) concentration in blood, six-minute walk test, and quality of life assessment according to the Minnesota Questionnaire. Data analysis also included an assessment of the incidence of repeat hospitalizations due to decompensation of CHF, arrhythmic events in the form of sustained episodes of ventricular tachycardia/ventricular fibrillation and SCD and all-cause mortality during the two years after hospital discharge. The study design is presented in Figure 1. During the follow-up period, 4 patients dropped out of the study - two due to infectious complications, in the form of suppuration of the CCM bed, which required removal of the device 1 month and 12 months after implantation, one patient refused further participation in the study, contact with another patient was lost, it was not possible to trace his fate.

Statistical analysis

Statistical processing of the obtained results included methods of descriptive statistics: calculation of mean values, standard deviations, as well as median, 25th and 75th percentiles depending on the normality of distribution. Normality of distribution was assessed using the Kolmogorov-Smirnov criterion (when the number of subjects n>50) or the Shapiro-Wilk criterion (when n<50). The groups were compared using Mann-Whitney U-criterion, Student's t-criterion. Nominal variables were analyzed using Pearson's χ^2 (chi-square) criterion, Fisher's exact criterion, and the conjugacy coefficient φ and Cramer's V coefficient were used to assess the measure of association between nominal variables. Relative risk was used to assess the significance of the binary values. Predicted survival parameters were calculated using the Seattle Heart Failure Model (SHFM) [12] and the MAGGIC (Meta-Analysis Global Group in Chronic Heart Failure) risk scale [13]. Baseline clinical and instrumental characteristics of each patient before device implantation were used to construct a predicted survival curve. From these, the individual risk of death was calculated, then the median predicted probability of survival at one and two years for the SHFM scale and at one year for the (MAGGIC) scale for the entire study group was calculated. To compare predicted survival with actual survival, Kaplan-Meier curves were constructed for the observed cohort. The statistical difference between the Kaplan-Meier curve and the predicted survival probabilities was tested using the log-rank test. Differences were considered statistically significant at $p<0.05$. Data entry, editing and statistical analysis were performed using Microsoft Excel 2010, statistical packages Statistics 8, SPSS 20.

RESULTS

When analyzing the dynamics of each of the studied indicators, the patients were divided into subgroups with «improvement», «worsening» and «no dynamics». The «worsening» subgroup also included patients who could not be evaluated due to the lethal outcome. A comparison of baseline characteristics of patients with maximal improvement on CCM and those who did not respond to CCM is presented in Table 2. The percentage of patients in each subgroup is shown in Figure 2a. Among the studied indicators, it was found that the most frequent - in 20 (40%) patients - positive dynamics of the six-minute walk test indicator was noted. An increase in six-minute walk distance by an average of 140 [80;175] meters was registered already 2 months after implantation of the CCM system. At follow-up visits,

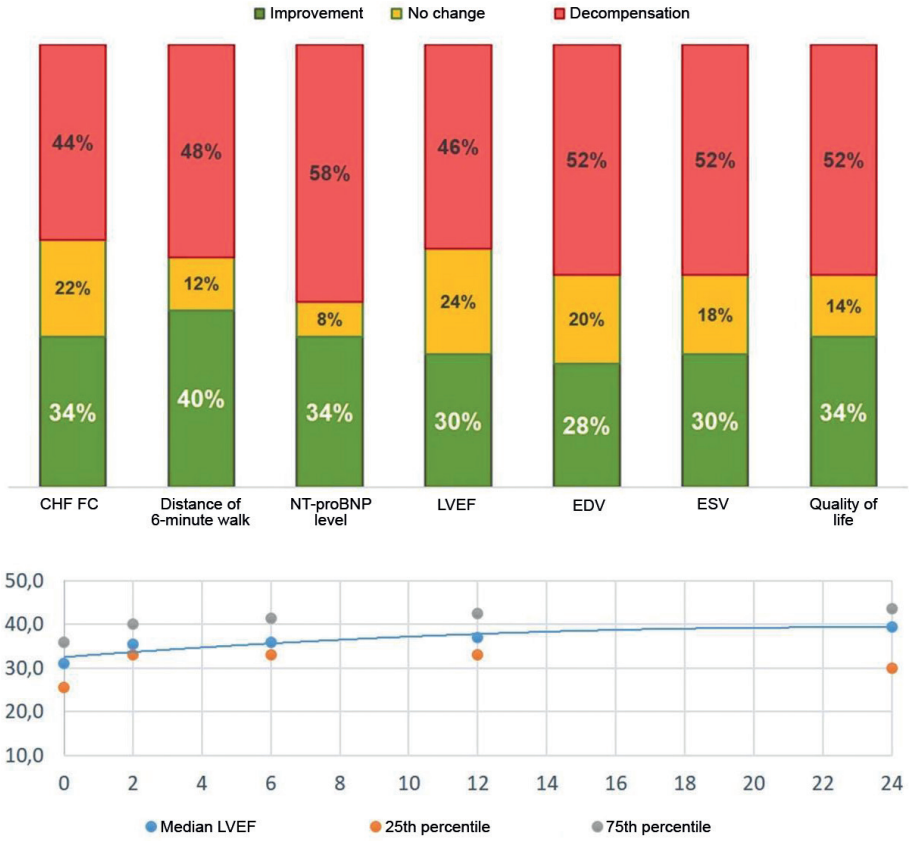


Fig. 2. Dynamics of the studied parameters in all patients (a) and LVEF in patients with positive results (b) on the background of CCM for 24 months of follow-up.

no additional significant increase in distance was found; however, at the end of the study, the median and 25-75 quartiles of six-minute walk test values were 450 [380; 550] meters, with 9 (31%) of the remaining patients having test results approaching the upper limit of the group values and reaching the normal value of 550 meters. Absence of six-minute walk test dynamics was observed in 6 (12%) patients, 24 (48%) patients had worsening of this index or lethal outcome.

Improvement of six-minute walk test index in 17 (34%) cases was accompanied by improvement of CFH FC, with 10 (20%) patients showing a decrease in 2 FC, and 7 (14%) patients - in 1 FC. In 11 patients, the CHF FC remained without dynamics. Deterioration / fatalities were recorded in a further 22 (44%) cases. In parallel with the decrease in the CHF FC, the same 17 (34%) patients showed a decrease in the laboratory marker of CHF - NT-proBNP level by an average of 1431[660; 3629] pg/mL. Improvement of clinical and laboratory parameters in this subgroup of patients was accompanied by positive subjective feelings. The same 17 (34%) patients reported improvement in the form of a mean 35 [17.5;44.5] point decrease in Minnesota Quality of Life Questionnaire scores.

According to the data of repeated Echo studies in 15 (30%) patients a significant increase in LVEF was registered in average by 15 [11, 20]%. Considering the possible error in the measurement of this index, an increase in LVEF by 5% or more was taken as positive dynamics. It should be noted that the increase in LVEF developed gradually with reaching a plateau by the second year of follow-up (Fig. 2b). The increase in LVEF in the same 15 (30%) patients was accompanied by a significant decrease in LV ESV by an average of 68.5[37.5;104.5] mL and by a decrease in LV EDV in 14 (28%) by an average of 44 [30;100] mL.

Thus, among the examined patients a subgroup of 14 (28%) patients with significant positive dynamics on the background of CCM was manifested. These patients showed significant improvement in all investigated clinical and instrumental parameters corresponding to reverse cardiac remodeling. When analyzing baseline data, it was found that among patients with maximal improvement on CCM background patients with CHF of non-ischemic etiology were more frequent (χ^2=4.54, p=0.034) than among those who did not respond to therapy (Fig. 2). Additional statistical analysis demonstrated a medium strength of association between non-ischemic etiology of CHF and maximal improvement on the CCM background (Criterion φ = Cramer's *V* Criterion = 0.31). It should be noted that patients with non-ischemic etiology of CHF predominated in the study (38 vs. 16 patients with ischemic etiology of CHF). These patients were distinguished by younger age (58 [54;64] vs. 71 [66;71,5] years, p=0,000001) and initially greater degree of pathological remodeling of LV myocardium than patients with ischemic etiology of CHF, which was manifested by greater values of EDV (7,0 [6,5; 7.6] vs. 6.5 [6.2; 6.9], p=0.02) and ESV (6.1 [5.4; 6.8] vs. 5.4 [5.0; 6.0], p=0.02) and a tendency to smaller (LVEF 28.3 [23.5; 33.5] vs. 32.0 [29.5; 36]), p=0.057), which was not an obstacle to achieving maximal improvement on the CCM background (Table. 3). Other

Table 3.

Baseline characteristics of patients with CHF of different etiologies

	Patients with non-ischemic CHF, (n=38)	Patients with ischemic CHF, (n=38)	p
Men, n (%)	29 (76.3)	13 (81.3)	0.92
Age	58 [54;64]	71 [66;71.5]	0.000001
CHF FC (NYHA)	2 [2;3]	3 [2;3]	0.19
Paroxysmal AF, n (%)	14(36.8)	7(43.8)	0.31
LVEF, %	28.3 [23.5; 33.5]	32.0 [29.5; 36]	0.057
LV EDD, cm	7.0 [6.5; 7.6]	6.5 [6.2; 6.9]	0.02
LV ESD, cm	6.1 [5.4; 6.8]	5.4 [5.0; 6.0]	0.02
LV EDV, ml	220 [198; 280]	192 [174; 228]	0.18
LV ESV, ml	165.5 [130; 208]	142.5 [114.5; 174]	0.17
6-MWT, m	310 [280; 380]	311 [275; 385]	0.75
NT-pro-BNP, pkg/mL	1666 [1200; 4460]	2264 [1349;5772]	0.52

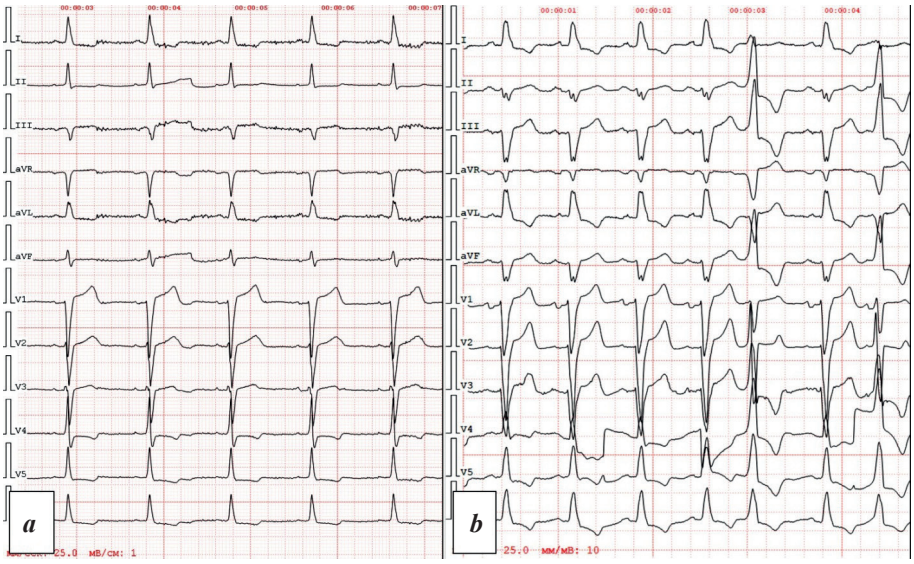


Fig. 3. ECG of patient R. before CCM device implantation with a «narrow» (130 ms) QRS complex (a) and 24 months after implantation with a «wide» (154 ms) QRS complex, signs of left bundle branch block (b).

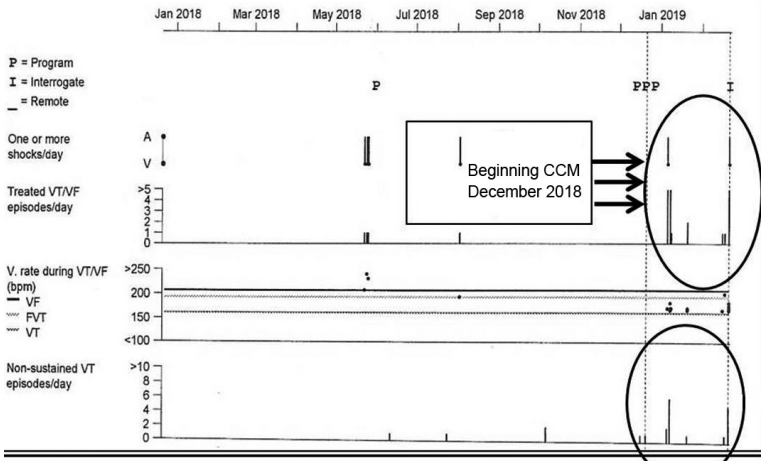
distinctive features, except for non-ischemic etiology of CHF, allowing to characterize patients with maximal improvement on the background of CCM, could not be revealed during our study (see Table 2).

The development of decompensation episodes of existing heart failure, which required hospitalization and use of intravenous diuretics, was considered as one of the criteria of no effect or worsening on the background of CCM. During follow-up, 1 or more episodes of decompensation were reported in 32 (64%) patients. The mean time to development of a decompensation episode was 11.4±7.0 months after implantation. It should be noted that progression of CHF in 4 (8%) patients was associated with QRS complex dilation on ECG above 150 ms and formation of left bundle branch blockade (Fig. 3). This prompted the implantation of a de novo CRT device in two cases and in another two cases the replacement of the existing ICD with CRT-D, which led to the subsequent stabilization of the patients' clinical condition.

In addition, in 13 (26%) patients, episodes of aggravation of the course of ventricular cardiac rhythm disorders in the form of development of repeated sustained paroxysms of ventricular tachycardia and/or ventricular fibrillation or electrical storm or SCD among patients without ICD were recorded during the follow-up period on the background of CCM. Episodes of threatening ventricular tachyarrhythmias were recorded at 13[6;19] months after CCM implantation. It should be noted that the development of episodes of life-threatening arrhythmias in all cases was observed in patients who did not have positive results from CCM and was accompanied by decompensation of heart failure or preceded by death. An example of the development of aggravation of the course of ventricular arrhythmias is shown in Figure 4.

Twenty-one (42%) patients died during the follow-up period. The mean time to the occurrence of death was 16 [7;20] months. In most cases (n=10, 48%) death was due to progression of heart failure, four cases (19%) had development of SCD, three cases (14%) the cause of death was acute cerebral circulatory failure, and one case (5%) death was due to gastrointestinal bleeding. It was impossible to determine the cause of death in three cases (14%) (Fig. 5).

Analysis of baseline parameters in surviving (group 1) and deceased patients (group 2) revealed some differences. Thus, at the time of inclusion in the study, the patients of both groups did not differ in terms of CHF FC, LVEF, LV volumes, as well as the results of six-minute walk test. The group of deceased patients was characterized by significantly higher baseline NT-pro-BNP levels (4220.5 [1455;7177] vs. 1641 [909.5; 3564] among survivors, p=0.014), as well as a higher percentage of patients with persistent AF (85.7 vs. 55.2% among survivors, χ^2 criterion=5.22, p=0.023). The presence of a persistent form of AF was directly associated with the development of mortality (φ = Cramer criterion = 0.32, average strength of association). In addition, in the deceased patients, there was a trend toward baseline greater LV EDD (7.2 [6.4; 7.9] vs. 6.8 [6.3; 7.0], p=0.07) and greater LV ESD (6.4 [5.1; 7.0] vs. 5.7 [5.1; 6.1], p=0.05) (Table 4). Additional analysis confirmed the association between the development of lethal outcome and the baseline absolute value of LVEF (r=0.4, p<0.05), LV ESV (r=0.31, p<0.05), LV EDD (r=0.41, p<0.05), LV ESD (r=0.47, p<0.05), and LVEF (r=-0.29, p<0.05). The obtained data indicate an initially



Type	ATP Seq	Shocks	Success	ID#	Date	Time hh:mm	Duration hh:mm:ss	Avg bpm A/V	Max bpm A/V	Activity at Onset
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VT	11		Yes	53	21-Feb-2019	09:37	:01:29	57/171	---/171	Active
VT	3		Yes	52	21-Feb-2019	09:36	:28	---/167	---/167	Active
VT-NS				51	21-Feb-2019	09:10	:01	---/171		Rest
VT-NS				50	21-Feb-2019	08:58	<:01	---/171		Active
VT-NS				49	21-Feb-2019	08:58	:01	60/167		Active
VT-NS				48	21-Feb-2019	08:58	:01	---/171		Active
VT	3	35J	Yes	47	21-Feb-2019	08:54	:32	---/182	---/214	Active
VT	3		Yes	46	21-Feb-2019	08:53	:30	35/176	---/176	Active
VT	5		Yes	45	21-Feb-2019	08:51	:39	36/176	---/---	Active
VT	3		Yes	44	21-Feb-2019	08:50	:22	---/176	---/176	Active
VT	3		Yes	43	21-Feb-2019	08:49	:23	38/176	---/---	Active
VT	5		Yes	42	21-Feb-2019	08:49	:40	36/171	---/171	Active
VT-NS				41	21-Feb-2019	08:48	<:01	<30/167		Active
VT	2		Yes	40	21-Feb-2019	08:36	:15	---/171	---/176	Active
FVT	1		Yes	39	18-Feb-2019	01:28	:08	---/200	---/200	Rest
VT-NS				38	18-Feb-2019	01:18	:01	---/170		Rest
VT	2		Yes	37	16-Feb-2019	14:21	:14	61/167	---/176	Active
AT/AF				36	10-Feb-2019	18:47	:41	160/82	214/VP	Rest
VT	1		Yes	35	21-Jan-2019	04:59	:17	54/176	---/176	Rest
VT-NS				34	21-Jan-2019	04:59	:03	73/169		Rest
VT	2		Yes	33	21-Jan-2019	03:55	:14	---/171	---/188	Rest
VT	6		Yes	32	09-Jan-2019	05:09	:49	71/167	---/176	Rest
VT-NS				31	08-Jan-2019	21:11	:03	33/181		Rest
VT	3		Yes	30	08-Jan-2019	20:41	:23	53/171	---/176	Rest
VT-NS				29	08-Jan-2019	16:07	:02	54/168		Rest
VT	2		Yes	28	08-Jan-2019	15:56	:13	---/188	---/200	Rest
VT-NS				27	08-Jan-2019	15:56	<:01	---/188		Rest
VT-NS				26	08-Jan-2019	11:46	:02	36/176		Rest
VT	3		Yes	25	08-Jan-2019	07:43	:23	51/167	---/182	Rest
VT	2		Yes	24	08-Jan-2019	05:46	:15	37/171	---/182	Rest
VT-NS				23	08-Jan-2019	01:54	:02	51/175		Rest
VT	3		Yes	22	08-Jan-2019	01:11	:23	54/171	---/176	Rest
VT	3		Yes	21	08-Jan-2019	00:48	:23	47/167	---/176	Rest
VT-NS				20	08-Jan-2019	00:17	:01	75/171		Rest
VT	2		Yes	19	06-Jan-2019	05:52	:15	42/171	---/176	Rest
VT	2	35J	Yes	18	06-Jan-2019	05:36	:34	37/171	---/194	Rest
VT	2		Yes	17	06-Jan-2019	05:05	:15	54/171	---/182	Rest
VT	3		Yes	16	06-Jan-2019	04:56	:23	---/171	---/176	Rest
VT-NS				15	06-Jan-2019	04:56	:04	---/173		Rest
VT	9		Yes	14	06-Jan-2019	04:35	:01:09	36/171	---/171	Rest
VT-NS				13	06-Jan-2019	04:35	:03	34/172		Rest

Fig. 4. Example of developmental aggravation of the course of ventricular cardiac rhythm disturbances according to device interrogation in a patient with CCM and CHF of nonischemic etiology. CCM device implantation in December 2018, in January-February 2019 development of electrical storm on the background of decompensation of CHF, requiring emergency hospitalization, where the upper oval - episodes of VT, controlled by ICD, the lower oval - episodes of unstable VT.

more severe condition of patients who subsequently developed lethal outcome. This was reflected in the greater dilatation of LV cavity, lower LVEF, which is probably due to the longer duration of the disease.

Along with the above-mentioned importance of the non-ischemic nature of CHF in achieving maximal response to CCM, the role of etiology in the development of mortality in patients was analyzed. The percentage of patients with ischemic etiology of CHF in the groups of surviving and deceased patients was comparable (21% vs. 24% criterion χ^2=0.315, p=0.58). Additional analysis also showed no significant difference in the probability of fatal outcome in patients with different etiologies of CHF (relative risk=1.034 95%CI 0.38-2.8, p=0.95). Thus, there was no association between the etiology of CHF and the probability of mortality. In addition, the etiology of CHF did not influence the development of decompensation episodes (criterion χ^2=0.189, p=0.66), or the development of arrhythmic events (criterion χ^2=0.34, p=0.56).

The efficacy of CCM in 6 patients previously refractory to CRT was analyzed separately. Improvement of clinical and instrumental manifestations of CHF with the help of CCM could not be achieved in any of these cases. Three patients developed lethal outcome during the follow-up period (in two cases due to the progression of CHF, in one case due to acute cerebral circulatory failure), three more patients demonstrated no dynamics of the available parameters.

Patient survival parameters were analyzed by constructing Kaplan-Meier curves. Actual survival rates were compared with predicted parameters calculated using the Seattle model, as has been done in other similar studies (Fig. 5b) [14-16]. The one-year mortality thus calculated in the study group was 6 [3;12]% two-year mortality 12.5 [7;23.8]%. At the same time, the actual incidence of death from any cause in patients with CCM by the end of the first year of follow-up was 16%, the two-year incidence was 40% and was significantly higher than that predicted by the Seattle model (χ^2=10.93, p=0.001). When survival was assessed according to the MAGGIC scale, the predicted risk of death in the study group of patients by the end of the first year of follow-up was 9.3[6.5-13.6]%, and by the end of the third year -22.7[16.4;33.1]. Because this scale does not allow calculation of the 2-year risk of death, observed and predicted survival parameters were compared using Kaplan-Meier curves at the 12-month follow-up point (Fig. 5c) and were found to be comparable (χ^2=2.24, p=0.134). However, in patients with a response to CCM that developed by the second month after device implantation, no deaths were reported during follow-up (next 22 months).

DISCUSSION OF FINDINGS

Considering the multidirectional dynamics of clinical and instrumental parameters on the background of CCM, during the analysis, the division of patients into subgroups of «improvement», «worsening» and «no dynamics» was applied for the first time. This approach allowed us to identify a subgroup of 14 (28%) patients with maximal improvement on the background of the conducted CCM. The use of CCM in these patients was accompanied by significant improvement of clinical and echocardiographic parameters, including LV EF, the 6-minute walk test distance and a significant decrease in NT-proBNP level. Such results of using CCM may contribute significantly to the treatment of this extremely severe category of patients. At the same time, patients with maximal improvement in our study were characterized by non-ischemic etiology of CHF and slightly younger age. It was not possible to identify other distinctive features that predetermine the effectiveness of using this methodology.

At the same time, it should be noted that RCTs demonstrate no obvious effect of CCM on LVEF [17]. In addition, the positive dynamics with CCM may be due not to the direct effect of this method of treatment, but to the delayed effects of optimal drug therapy [18-21], which requires further clarification. The

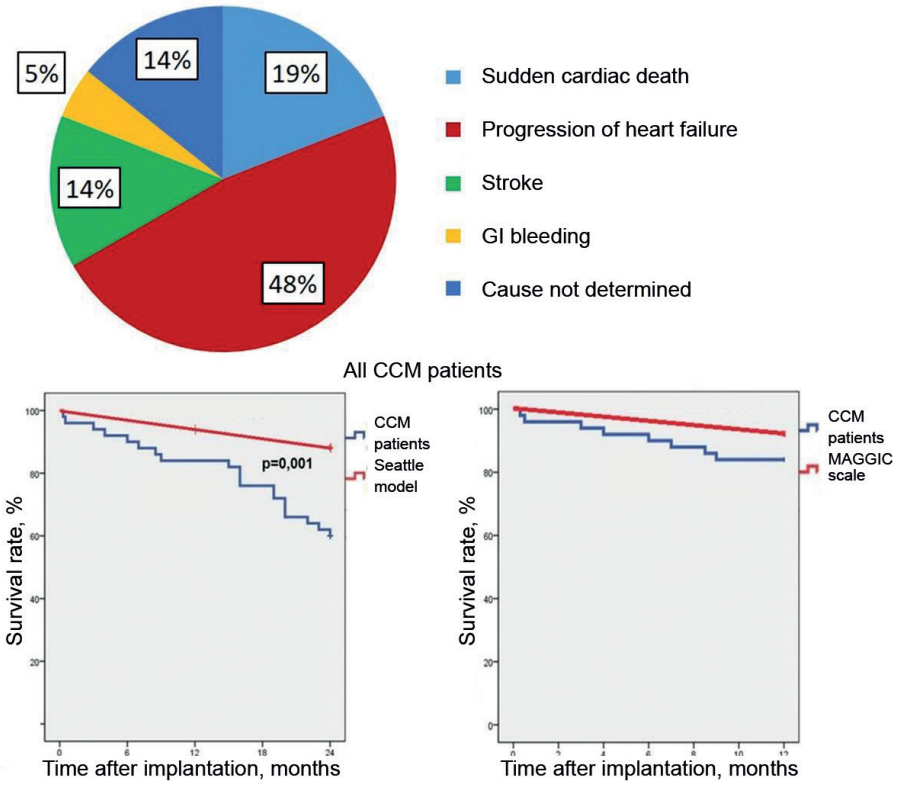

Fig. 5. Causes of death in patients (n=27) with CCM (a), where ACCF - GI bleeding - gastrointestinal bleeding; Kaplan-Meier curves illustrating the survival of patients with CCM compared with that calculated according to the Seattle Heart Failure Model (b) and the MAGGIC risk scale (c) based on the baseline of each patient before device implantation.

absence of reliable effect of CCM on LVEF according to RCT data, probably, agrees with the results of our study: 14 (28%) patients were in the subgroup of maximal response, 23 (46%) patients had worsening or lethal outcome, the remaining 13 (26%) patients had no dynamics of LVEF. Probably, similar multidirectional changes of instrumental indices in existing RCTs resulted in the absence of total reliable improvement of LVEF and are typical for similar observational studies [22, 23].

A significant limitation of this study is the lack of a control group formed based on randomization. This limitation prompted a comparison of the actual survival parameters obtained in our patients with those predicted by the Seattle Heart Failure Model (SHFM scale) and the MAGGIC risk scale. A similar comparison methodology has been used previously in works on CCM [14-16]. The SHFM scale is based on simple clinical, laboratory and therapeutic characteristics available for use in the outpatient phase of life prognosis construction. Using this model, A.Kloppe et al. (2016) demonstrated a positive effect of CCM on survival rates of patients with CHF [14].

Using the same SHFM scale in the European CCM-REG registry, differences in 1-year, 2-year, and 3-year survival were found in a subgroup of patients with CCM and LVEF of 35-45%, while in patients with LVEF of 25-34%, actual survival rates were comparable to those expected [16]. However, in our analysis, patient survival parameters were significantly worse than those predicted by the Seattle model (χ^2=10.93, p=0.001). Moreover, the incidence of death from any cause in patients with CCM at the end of the first year of follow-up was 16%, with a predicted 6%; after 2 years, the incidence of death from any cause was 40%, with a predicted 12.5%. It should be noted that in a similar domestic prospective study including 55 patients with CCM, the SHFM scale also predicted higher patient survival rates: the expected survival rate by the end of the first year by 3.2% and by the end of the second year by 13.8%, significantly exceeding the actual survival rates of patients with CCM, which amounted to 5.5% by the end of the first year and 20% by the end of the second year [15].

Such differences in the expected and actual life expectancy of patients are probably due to the known limitations to the application of the Seattle model in hospitalized patients with significant life-threatening comorbidity (liver cirrhosis, diabetes mellitus, chronic renal failure, chronic obstructive pulmonary disease, cancer). It also underestimates or overestimates risks in elderly patients and patients with implanted devices. Therefore, the predicted survival rates of our patients were re-evaluated using data from the MAGGIC risk scale. The use of this scale to assess the survival rates of patients with CCM has been used in foreign studies [15, 24, 25] and has indicated the benefits of CCM two out of three times [15, 24]. However, when our data were analyzed using the MAGGIC scale, the survival rates of patients with CCM were comparable to those predicted (χ^2=2.24, p=0.134), for all groups of patients included in the study, which is in contradiction with the results of the CCM-REG registry and a domestic study [15, 24].

It is likely that the positive results of the CCM-REG registry may have been influenced by limitations recognized by the authors: the analysis did not include patients who dropped out of follow-up or died. In addition, the authors of this registry do not provide data on the incidence of death during the follow-up, which could affect the results [24]. Obviously, the actual incidence of death in patients with CCM is significantly influenced by the initial severity of patients. Patients with CCM whose participation in the study ended in death were characterized by an initially more severe condition, manifested by a higher baseline NT-pro-BNP level, a greater degree of LV cavity dilatation, a lower LVEF value, and the presence of concomitant permanent form of AF. These data are consistent with the results of both domestic [16, 26] and foreign studies [15], which demonstrated a more unfavorable prognosis in the conditions of CCM in initially more severe patients with CHF of more than III class and with LVEF less than 25%. Probably, the same factors may explain the lack of improvement in clinical status from the use of CCM in patient's refractory to CRT, as shown in our study.

CONCLUSION

On the background of application of cardiac contractility modulation, it was possible to achieve improvement in 14 patients, which amounted to 28% of all cases. These patients registered significant improvement in all clinical and instrumental parameters. The only factor significant for maximizing the effect of CCM appeared to be the non-ischemic etiology of CHF. The conducted study demonstrated that there was no significant effect of CCM on survival rates of patients with CHF, but the significant limitations of the conducted study suggest the need for additional randomized trials with a larger number of observations.

Table 4.

Baseline characteristics of the groups of surviving and deceased patients

	Surviving patients (n=29)	Deceased patients (n=21)	p
Men, n (%)	20 (69)	19 (90.5)	0.07
Age, years	63[55;66]	64[57;66]	0.54
CHF FC (NYHA)	2[2;3]	3[2;3]	0.28
Ischemic CHF, n (%)	9 (21)	5(24)	0.58
Permanent AF, n (%)	16(55.2)	18(85.7)	0.023
LVEF, %	31 [25.5; 36]	29 [23; 31.7]	0.21
LV EDD, cm	6.8 [6.3; 7.0]	7.2 [6.4; 7.9]	0.07
LV ESD, cm	5.7 [5.1; 6.1]	6.4 [5.1; 7.0]	0.05
LV EDV, ml	220 [180; 250]	221 [200; 330]	0.23
LV ESV, ml	151 [120; 183]	167 [135; 272]	0.12
6-MWT, m	330 [300; 380]	300 [265; 385]	0.39
NT-pro-BNP, pkg/mL	1641 [909.5; 3564]	4220.5 [1455;7177]	0.014

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