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LONG-TERM RESULTS OF CARDIAC CONTRACTILITY MODULATION IN PATIENTS WITH CHRONIC HEART FAILURE

A.Yu.Amiraslanov, V.A.Vaskovskiy, E.A.Artyukhina, A.Sh.Revishvili

A.V. Vishnevsky National Medical Research Center of Surgery of the Ministry of Health of the Russian Federation, Moscow, 27 Bolshaya Serpukhovskaya str.

Aim. Evaluate the overall effectiveness of cardiac contractility modulation (CCM) therapy in patients with chronic heart failure of various etiology.

Methods. The study included 61 patients with chronic heart failure (NYHA class II-III), ejection fraction 20-40% and narrow QRS <130 ms, who were implanted the CCM devices. Depending on the etiology of heart failure, ischemic cardiomyopathy prevailed (41 patients). All patients were performed echocardiography, 6-min walk test and Minnesota Living with Heart Failure questionnaire (MHFLQ).

Results. The observation period was 25 months. All 54 patients significantly improved left ventricular ejection fraction from 32.2% to 37.6% ($p=0.026$) and volume parameters (left ventricle end systolic volume from 150 to 137 ml ($p=0.034$), left ventricle end diastolic volume from 220 to 201 ml ($p=0.044$), reduced the heart failure NYHA class ≥ 1 in 29 (53.7%) patients ($p=0.015$), increased 6-min walk test from 265 to 343 m ($p=0.029$), and the MHFLQ improved from 46.1 to 35.8 ($p=0.042$). Non-ischemic cardiomyopathy was associated with significant improvement in MHFLQ (from 42.7 to 30.3, $p=0.029$) and lowering the heart failure NYHA class ≥ 1 (83.3%, vs 47.2%, $p=0.012$) compared to ischemic group.

Conclusion. CCM is safe and effective in patients with chronic heart failure NYHA class II-III, ejection fraction 20-40% and narrow QRS <130 ms. Non-ischemic etiology of cardiomyopathy was associated with significant improvement in MHFLQ and lowering the heart failure class.

Key words: chronic heart failure; ischemic cardiomyopathy; nonischemic cardiomyopathy; cardiac contractility modulation; quality of life

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Corresponding author: Anar Amiraslanov, E-mail: anar_amiraslanov@list.ru

A.Yu.Amiraslanov - ORCID ID 0000-0002-3405-1063, V.A.Vaskovskiy - ORCID ID 0000-0003-3126-7106, E.A.Artyukhina - ORCID ID 0000-0001-7065-0250, A.Sh.Revishvili - ORCID ID 0000-0003-1791-9163

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Chronic heart failure (CHF) remains a major cause of cardiovascular mortality. According to the Framingham Study [1], the average five-year mortality in the overall population of patients with CHF remains high at 62-65% in men and 45-47% in women. Failure to diagnose in a timely manner, ineffective drug therapy, repeated hospitalizations, and the financial cost of health care determine not only the clinical but also the socioeconomic importance of this disease worldwide.

The prevalence of heart failure is 2-3% of the adult population in developed countries and 6-10% of those over 65 years of age. In Europe and North America, it is the most common cause of hospitalization in this age group [2]. The problem is exacerbated by a general increase in life expectancy and an aging world population. Experts predict that the incidence of heart failure will increase by 40% over the next 15 years [3].

Data from randomized clinical trials have shown that drug therapy with beta-blockers, angiotensin-convert-

ing enzyme inhibitors, mineralocorticoid antagonists, renin-angiotensin receptor blockers, and diuretics increases the life expectancy of patients with heart failure [4].

Surgical treatments for heart failure are becoming more common every year. These include implantation of cardiac resynchronization devices, artificial ventricles and, at the beginning of this century, a new treatment, cardiac modulation therapy.

The effect of cardiac modulation therapy has been demonstrated in experimental studies. It is associated with the positive inotropic effect of high amplitude electrical stimuli acting on the myocardium during cardiomyocyte refractoriness. It is achieved by increasing the intracellular supply of calcium ions, which leads to an increase in the contractility of the cell [5, 6]. The practical implementation of the method occurred in 2001, when the same effect was observed in the local application of a large group of cardiomyocytes (endocardial electrical stimulation of the right ventricular myocardium), which prepared the industrial development and appearance of the first prototype of a cardiac contractility modulator

(CCM). At the end of 2001, the first experimental device appeared, implanted for the first time and described by C. Pappone et al. in 2001 [7]. In 2004, the first clinical trial was completed, demonstrating the therapeutic efficacy of the proposed method, with significant improvements in quality of life, 6-minute walk test scores, and left ventricular ejection fraction (LVEF) [8].

Since 2016, CCMs Optimizer IVs and the next generation, Optimizer Smart, without an atrial electrode, have been implanted for the first time in patients with atrial fibrillation (AF) in various centers in the Russian Federation (Impulse Dynamics, Germany). The atrial electrode provides detection of the atrial signal and triggers the atrioventricular delay interval system. The ventricular electrodes are used to apply CCM stimuli and are placed in the interventricular septum between the base and the apical segment. According to the manufacturer's recommendations, the distance between them should be at least 2 cm. The right ventricular electrode picks up the signal first and sets itself higher than the Local Sense (LS) electrode. By default, the device delivers two stimuli from each ventricular electrode with an amplitude of 7.5 V and a pulse duration of 5.14 ms, and the duration of therapy is 7 hours per day (Fig. 1a). The desired percentage of effective stimulation should be at least 90% (Fig. 1b). The device is rechargeable. The manufacturer's stated average battery life for the CCM devices is six years before it needs to be replaced, with a maximum life of 15 years. The latest models (Optimizer Smart) have two configurable operating modes for CCM therapy: ODO-LS-CCM and OVO-LS-CCM. The former is used with an atrial electrode (as with Optimizer IVs) and has some limitations on atrioventricular delay. The patient's baseline interval PQ must be between 25 ms and 398 ms. In addition, this mode blocks CCM therapy when atrial tachysystole occurs (adjustable from 62 to 179 beats per minute, 154 is the default). The second mode (OVO-LS-CCM) is available only on Optimizer Smart models and does not require an implanted atrial electrode. It is independent of atrioventricular latency parameters and can be used in AF (including the persistent form). CCM is blocked in this mode when the ventricular contraction rate exceeds 98 beats per minute, regardless of the baseline heart rate (adjustable between 62 and 110 beats per minute). Optimizer Smart is compatible with standard bipolar electrodes with active fixation and a IS -1 connection. The aim of our study was to

evaluate the overall efficacy of cardiac modulation therapy and to compare long-term outcomes in patients with heart failure of different etiologies.



Fig. 1. Modulation of cardiac contractility: ECG shows stimulus artifacts in the refractory part of the QRS complex (a); 93.37% effective therapy (b).

Table 1.

Patient clinical characteristics

Characteristics	All patients (n=61)	ICM (n=41)	NICM (n=20)
Age, years	60.39±12.81	68.32±14.61	55.23±10.21
Men, n (%)	47 (77)	30 (73.2)	17 (85)
Patients with an ICD, n (%)	23 (37.7)	16 (39)	7 (35)
Paroxysmal AF, n (%)	25 (41)	21 (51.2)	4 (20)
Permanent AF, n (%)	8 (13.1)	3 (7.3)	5 (25)
Diabetes mellitus type 2, n (%)	17 (27.9)	12 (29.3)	5 (25)
LV EF, %, M±SD	31.3±7.8	30.8±7.1	33.1±6.9
LV ESV, ml, M±S	152.4±62.8	148.4±53.1	165.4±61.4
LV EDV, ml, M±SD	219.6±81.1	212.5±69.4	244.2±90.2
HF FC (NYHA), Me [Q1; Q3]	2 [2; 3]	2 [2; 3]	2 [2; 3]
QRS, ms, M±SD	117±27.2	121.5±31.6	106±23.7
6MWT, m, M±SD	259±109.6	253.7±99.6	280.4±112.7
MHFLQ score, M±SD	47.3±9.5	48.9±11.4	43.6±8.2
Drug therapy			
ACE inhibitors, n (%)	61 (100)	41 (100)	20 (100)
Beta-blockers, n (%)	60 (98)	40 (97.6)	20 (100)
MCR antagonists, n (%)	55 (90.2)	37 (90.2)	18 (90)
Diuretics, n (%)	57 (93.4)	38 (92.7)	19 (95)
Amiodarone, n (%)	8 (13.1)	6 (14.6)	2 (10)

Note: hereinafter n is the absolute number; Me [Q1; Q3] - median and quartiles; M±SD - mean ± standard deviation; ICM - ischemic cardiomyopathy; NICM - non-ischemic cardiomyopathy; ICD - implantable cardioverter defibrillator; AF - atrial fibrillation; LVEF - left ventricular ejection fraction; LV ESV - end-systolic volume of the left ventricle; LV EDV - end diastolic volume of the left ventricle; HF FC - heart failure functional class; 6MWT - six-minute walk test; MHFLQ - Minnesota quality of life questionnaire in patients with HF; ACE - angiotensin-converting enzyme; MCR - mineralocorticoid receptors.

MATERIALS AND METHODS

Retrospective evaluation of outcomes of 61 CCM devices implanted in patients with heart failure was performed: Optimizer IVs - 27 and Optimizer Smart - 34. The indications for implantation of the cardiac modulation devices were compensated heart failure class II-III according to NYHA, LVEF 20-40%, QRS complex width < 130 ms. In earlier models (Optimizer IVs), the PQ interval (not exceeding 400 ms) was also considered with sinus rhythm being a prerequisite. Patients with documented AF were implanted with Optimizer Smart models.

The mean age of the patients was 60.39 ± 12.81 years, 47 men and 14 women. Thirty-three patients had various forms of AF (25 with paroxysmal and 8 with persistent). All patients received beta-blockers, angiotensin-converting enzyme inhibitors, diuretics, and anticoagulants (patients with AF). No other change in drug therapy was made. Ischemic cardiomyopathy (ICMP) was the predominant etiology of CHF in 41 patients (67.2%). Postinfarction cardiosclerosis was detected in 37 patients (60.6%). Myocardial revascularization had been previously performed in 29 patients (47.5%) (in 11 patients, mammary-, aortocoronary bypass surgery; in 18 patients, coronary stenting). Twenty patients (32.8%) were diagnosed with nonischemic cardiomyopathy (NCMP). Most patients with NCMP had dilated cardiomyopathy - 15 (75%), 3 had postmyocardial cardiosclerosis, and 2 had other idiopathic cardiomyopathies. Twenty-three patients (37.7%) had previously received implantable cardioverter-defibrillators (ICD). Seventeen patients had type 2 diabetes mellitus (28%). The clinical findings of the patients at enrollment are shown in Table 1.

According to the study protocol, the following tests were performed in all patients at enrollment: 12-lead electrocardiography, transthoracic echocardiography (Echo), 6-minute walk test, and the Minnesota Chronic Heart Failure Quality of Life Questionnaire (MHFLQ). The study was approved by the local ethics committee. All patients signed an informed consent form before being enrolled in the study.

Surgical technique

Depending on the number of leads to be implanted, the left subclavian vein was first punctured two or three times and then a pocket was formed for the device under local anesthesia. Next, the endocardial leads were inserted into the right atrial cavity via 7-Fr introducers. The atrial electrode was placed at the atrium of the right atrium by

default, and the ventricular electrode was placed in the projection of the midventricular septum. In patients with the dual-electrode system, no atrial electrode was implanted. All electrodes were tested intraoperatively with an ERA 3000 analyzer (Biotronik, Germany). During surgery, standard parameters were measured: sensitivity (P- and R-waves), stimulation thresholds, and electrode resistance. After satisfactory parameters were determined, the device was tested with an Omni programmer (Impulse Dynamics, Germany) via an adapter connected to each electrode. The intervals and accuracy of stimulus application and the sensitivity of individual patients to CCM therapy were selected and evaluated.

In patients with an existing ICD, the optimizer was implanted on the right side. A mandatory test of the interaction of the ICD with the CCM system was performed to exclude cross-perception of the electrical stimuli. The intraoperative electrode parameters and the CCM therapy parameters are listed in Table 2.

All patients were telemetrically monitored with the Optimizer system on day 2 or 3 after surgery. Each patient received a dedicated charger before discharge. Outpatient follow-up of the devices was performed at 3, 6, and 12 months after implantation (further every 6 months), during which the dynamics of the Echo and 6-minute walk test were assessed, as well as the patient's quality of life and the degree of individual sensitivity to CCM therapy.

Statistical analysis

Statistical processing of the data was performed using Statistica 10 software (StatSoft). Qualitative variables were described by absolute and relative frequencies (percentages). Quantitative measures were tested for normality using the Kolmogorov-Smirnov criterion. Data are presented as mean \pm standard deviation ($M \pm SD$). Some of the data are presented as medians and quartiles. The U-Mann-Whitney test was used for nonparametric data. Qualitative indicators were compared with Pearson's χ^2 test and Fisher's test. Differences were considered statistically significant at $p < 0.05$.

RESULTS

Between 2016 and November 2019, 61 CCM devices (27-Optimizer IVs and 34-Optimizer Smart) were implanted in patients with heart failure. The final follow-up period for the entire group was 25 months. During this time, the cardiovascular mortality rate in the group was 11.5% (7 patients). All patients who died had an ICD. The cause of

Table 2.

Intraprocedural lead parameters, CCM therapy settings

P-wave, mV, $M \pm SD$	2.4 ± 0.9
RV signal amplitude, mV, $M \pm SD$	18.6 ± 5.4
LS signal amplitude, mV, $M \pm SD$	15.7 ± 5.9
RV capture threshold, V, $M \pm SD$	1.1 ± 0.3
LS capture threshold, V, $M \pm SD$	1.2 ± 0.4
Comfortable for patients CCM stimuli amplitude, V, $M \pm SD$	6.5 ± 1.0
Discomfort during CCM stimulation - change of parameters, n (%)	32 (52.4)
Discomfort during CCM stimulation - lead repositioning, n (%)	16 (26.2)

Note: CCM - cardiac contractility modulation.

death was decompensation of heart failure. Significant improvement in LVEF by Simpson's method from 32.2% to 37.6% ($p=0.026$), decrease in LV end-systolic volume (ESV) from 150 to 137 ml ($p=0.034$), LV end-diastolic volume (EDV) from 220 to 201 ml ($p=0.044$), decrease in chronic heart failure class by NYHA by > 1 in 29 (53.7%) patients ($p=0.015$). 015), increase in 6-minute walk test from 265 to 343 m ($p=0.029$) and improvement in quality of life

according to the MHFLQ questionnaire from 46.1 to 35.8 points ($p=0.042$) were observed. The mean percentage of therapeutic stimulation was $92.6\pm 9.2\%$ over the entire follow-up period.

Data were then analyzed in subgroups of patients, according to the etiology of heart failure. The 25-month follow-up was 12.2% (5 patients) in the ICMP subgroup (41 patients) and 10% (2 patients) in the NCMP subgroup (20 patients). Causes of death did not differ (decompensation of CHF). Patients in the ICMP subgroup showed a significant improvement in Simpson's LVEF from 31.9% to 36.7% ($p=0.038$), a decrease in LV CSF from 148 to 139 ml ($p=0.042$), a decrease in NYHA chronic heart failure class > 1 in 17 (47.2%) patients ($p=0.024$), and an increase in 6-minute walk test from 259 to 323m ($p=0.039$). The subgroup of patients with NCMP showed improvement in Simpson's LVEF from 33.2% to 42.5% ($p=0.015$), decrease in LV ESV from 165 to 135 ml ($p=0.027$), LV EDV from 242 to 205 ml ($p=0.034$), decrease in CHF class according to NYHA by > 1 in 15 (83.3%) patients ($p=0.002$), increase in 6-minute walk test from 282 to 382 m ($p=0.012$) and improvement in quality of life according to the MHFLQ from 42.7 to 30.3 points ($p=0.029$). In 53.7% of patients in the total group, in 47.2% in the ICMP subgroup and in 83.3% in the NCMP subgroup, CHF decreased by > 1 grade (Fig. 2). In two subgroups, NCMP was associated with a significant improvement in quality of life, and there was a significant increase in the prevalence of a decrease in CHF > 1 class compared to ischemic patients (83.3% and 47.2%, $p=0.012$). After 25 months CCM of therapy, there was a trend toward an increase in LVEF and volume measures in patients with NCMP, although the results were not statistically significant. The long-term results are shown in Table 3.

The percentage of therapeutic pacing exceeded 90% in all subgroups. Two patients with Optimizer IVs developed AF over time, reducing the percentage of effective therapy. In addition to atrial tachycardia, frequent ventricular extrasystoles, atrioventricular conduction disturbances, variations in LS signal, and electrode impedance also influenced this parameter. It should be noted that the new-gen-

eration Optimizer Smart devices required less reprogramming than the Optimizer IVs.

When assessing a patient's individual sensitivity to CCM therapy, 52.4% of patients experienced significant discomfort during therapy at the maximum settings, requiring them to be lowered. Two (3.2%) patients experienced discomfort after implantation at minimal CCM therapy (even after repositioning of the ventricular electrodes), so that one of the two stimuli had to be deactivated. It was found that patients become accustomed to the perception of CCM therapy in the postoperative period. Thus, 16 patients were able to increase the amplitude of the stimuli without experiencing discomfort as early as 3 months after implantation.

DISCUSSION

In 2014, F. Giallauria et al. performed a meta-analysis of 3 randomized trials that showed a significant increase in peak oxygen consumption (PvO_2), 6-minute walk test scores, and quality of life in patients with CHF class II-

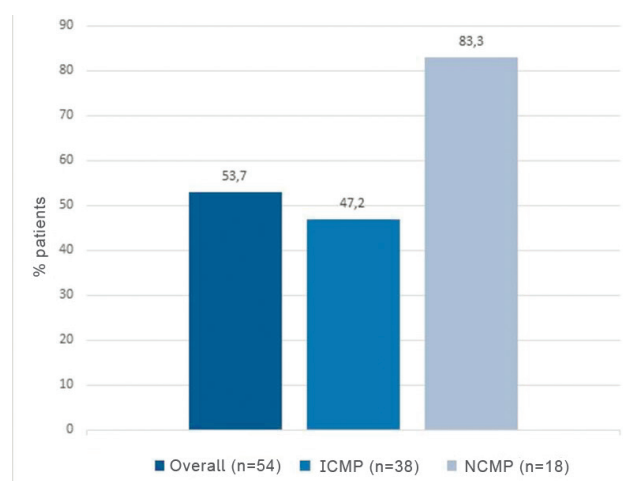


Fig. 2. Decrease in functional class of chronic heart failure according to NYHA by ≥ 1 in subgroups of patients over 25 months of follow-up, where ICMP - ischemic cardiomyopathy, NCMP - nonischemic cardiomyopathy.

Table 3.

Long-term (25 months) CCM results

Parameters	All patients (n=54)			ICM (n=36)			NICM (n=18)		
	baseline	25 months	P*	baseline	25 months	P*	baseline	25 months	P*
LV EF, %, M \pm SD	32.2 \pm 6.1	37.6 \pm 5.4	0.026	31.9 \pm 6.2	36.7 \pm 5.6	0.038	33.2 \pm 6.8	42.5 \pm 4.3	0.015
LV ESV, ml, M \pm SD	150.3 \pm 61.9	137 \pm 40.2	0.034	148 \pm 55.2	139 \pm 49.3	0.042	165 \pm 61.3	135 \pm 27.6	0.027
LV EDV, ml, M \pm SD	220 \pm 75.3	201 \pm 51.5	0.044	213 \pm 68.1	202 \pm 68.4	0.053	242 \pm 89.6	205 \pm 62.7	0.034
Decrease in HF FC > 1 , n (%)	-	29 (53.7)	0.015	-	17 (47.2)	0.024	-	15 (83.3)	0.002
6MWT, m, M \pm SD	265 \pm 103	343 \pm 102	0.029	259 \pm 99.8	323 \pm 103	0.039	282 \pm 115	382 \pm 75.4	0.012
MHFLQ score, M \pm SD	46.1 \pm 9.4	35.8 \pm 7.2	0.042	48.8 \pm 12.6	39.5 \pm 11.3	0.06	42.7 \pm 8.6	30.3 \pm 6.4	0.029

Note: P* - Significance of within-group differences at 25 months compared to baseline

III according to NYHA, against the background of applied CCM therapy [9]. In a 2016 prospective study, Ming Liu et al. achieved significant reductions in all-cause mortality and mortality due to cardiovascular events in a group of patients with heart failure and LVEF of 25-40% with implanted CCM devices compared with patients on optimal medical therapy by 22% and 32%, respectively, and a 30% reduction in hospitalizations related to heart failure decompensation after 75 months of follow-up [10]. It is also worth mentioning the large randomized multicenter trial FIX-HF -5, which was a milestone for long-term outcomes of CCM and formed the basis for further studies (FIX-HF -5C/C2 et al). FIX-HF -5 included 428 patients with heart failure. The study showed a significant decrease in hospitalizations and mortality (from all causes) over a 6-month follow-up period in patients with implanted CCM [11]. When analyzing efficacy in individual patient subgroups, it was found that particularly pronounced effects were seen in patients with NYHA class III with a LVEF >25%. This subgroup of patients was analyzed in more detail in the FIX-HF-5C study (160 patients with heart failure and an LVEF of 25-45%). The follow-up period was 6 months. There was a significant increase in PvO₂ of 0.82 ml/kg/min, 6-minute walk test of 33.7 m, improvement in quality of life by 12 points, decrease in NYHA class by > 1 CHF class in 81% of patients. It has also been shown to significantly reduce cardiovascular mortality and the incidence of hospitalization for CHF [12].

There is currently no clear opinion on whether there is a difference in the efficacy of CCM therapy in patients with different etiologies of CHF. For example, A. Kadish et al [11] showed that the etiology of CHF has no significant effect on CHF class and 6-minute walk test. Single observations describe so-called super-responders among patients with dilated cardiomyopathy [13]. At the same time, according to the original national study [14], the dynamics of Echo parameters of LV EDV and LV ESV differed in the groups of patients with ischemic and non-coronary cardiomyopathy over 1 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), which was due to the initial parameter values. When the initial value was excluded, the dynamics in the two groups were insignificant. Analysis of absolute values of LVEF showed significant differences between the two groups at 12 and 24 months. CCM therapy, ($p=0.03$ and $p=0.01$). However, there was no significant difference between the two groups ($p=0.09$).

It is important to note the individual physical and psycho-emotional sensitivity of patients to CCM therapy. According to our data, more than half (52.5%) required intraoperative reduction of stimulation parameters within the effective range during surgery. Most often, the stimulation amplitude (standard 7.5 V) was reduced, less frequently the pulse duration (standard 5.14 ms). Intraoperative ventricular repositioning was required in 16 (26.2%) patients because therapy was very uncomfortable at the lowest possible setting.

Study limitations

The lack of a control group is a major limitation of this study. A complete analysis of the effects of drug therapy was lacking. Inadequate sample of patients with non-ischemic cardiomyopathy.

CONCLUSION

Cardiac contractility modulators are effective in patients with CHF II-III class by NYHA, 20-40% LVEF, QRS complex width < 130 ms. There was significant improvement in LVEF, decrease in LV volume and CHF class, improvement in 6-minute walk test, and improvement in quality of life at 25 months follow-up. The presence of nonischemic cardiomyopathy was associated with a better decline in heart failure and improvement in patients' quality of life. Despite a trend toward higher LVEF and volume values in patients with NCMP, the results were not statistically significant. New long-term studies in a larger population may be able to determine the optimal indication for CCM therapy and predict efficacy in patients with different etiologies of heart failure. Implantation of cardiac modulation devices, their setting, and ambulatory monitoring require an individualized approach for each patient.

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