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IMPLANTATION OF A CARDIAC CONTRACTILITY MODULATOR IN CHRONIC HEART FAILURE AND ATRIAL FIBRILLATION: RESULTS OF A 6-MONTH FOLLOW-UP OF ONE HUNDRED PATIENTS

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Objective: to study the effect of cardiac contractility modulation (CCM) in patients with chronic heart failure (CHF) and atrial fibrillation (AF). **Materials and methods.** In a group of 100 patients with CHF and AF, the following studies were performed before implantation of the CCM and after 6 months of follow-up: 12-channel ECG, transthoracic Echocardiography, 6-minute walk test, determination of the level of pro-natriuretic N-terminal peptide (NT-proBNP), and a questionnaire based on the Minnesota quality of life questionnaire for patients with CHF (MHFLQ). All patients received long-term optimal medication therapy for CHF before surgery. **Results.** The results show a positive effect of the use of MCC in patients with CHF and AF on reverse LV remodeling, functional class of CHF, and levels of NT-pro-BNP regardless of the form of AF. **Conclusion.** The use of MCC may be a promising treatment method in addition to optimal medication therapy in patients with CHF and AF.

Keywords: heart failure, atrial fibrillation, modulation of heart contractility, left ventricular ejection fraction, quality of life.

INTRODUCTION

Chronic heart failure (CHF) and atrial fibrillation (AF) are common cardiovascular diseases that often complicate each other's course and have a significant impact on prognosis in both cases. AF is the most common arrhythmia that occurs in CHF, with an average prevalence of 30 to 50% [1–5]. Having common risk factors, AF and CHF often coexist or can accelerate / exacerbate each other's course, which leads to a significant increase in mortality, which is higher with a combination of diseases than with any condition alone [6, 7]. According to the large ACALM registry, where 929,552 patients were analyzed, 31,695 (3.4%) had AF without CHF, 20,768 (2.2%) had CHF in sinus rhythm, and 10,992 (1.2%) had CHF with AF [7]. Patients with CHF in AF had the highest all-cause mortality (70.8%), followed by patients with CHF in sinus rhythm (64.1%), and in patients with AF alone, mortality was lower at 45.1% ($p < 0.0001$). Patients who developed new-onset AF, CHF, or both had significantly higher mortality rates (58.5%, 70.7%, and 74.8%, respectively) compared with those who already had these conditions long-term (48.5%, 63.7% and 67.2%, respectively, $p < 0.0001$).

Despite a significant number of studies aimed at studying CHF and AF, it is still unclear which treatment approaches can affect the prognosis and delay the development of the end stage of CHF in this group of patients [8]. Patients with CHF and AF with disease progression are potential recipients for heart transplantation. Currently, there are several therapeutic approaches in the treatment of patients with AF and CHF. These are pharmacological tactics of frequency and rhythm control for AF, the increasing importance of catheter ablation, as well as optimization of cardiac resynchronization therapy (CRT), and, of course, optimization of CHF therapy in this group of patients. Pharmacological control of rhythm in patients with AF and CHF did not lead to an improvement in severe outcomes such as death from cardiovascular disease [9]. Studies of the use of AF catheter ablation have shown improvements in symptoms, exercise tolerance, quality of life and increased left ventricular ejection fraction (LVEF) in AF patients with CHF [10], as well as reduced all-cause mortality and hospitalizations for worsening CHF after catheter ablation of AF in patients with low LV ejection fraction [11]. According to the 2020 European guidelines for atrial fibrillation, AF catheter ablation may be considered on a case-by-case

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basis in patients with CHF with low LVEF (CHF/lLVEF) to improve survival and reduce hospitalization, and for patients with a high likelihood of tachy-induced cardiomyopathy, regardless of symptom severity recommended with class IB [12]. Atrioventricular node ablation with biventricular pacemaker placement is considered for patients with persistent AF and systolic dysfunction who have a rapid ventricular rate refractory to pharmacological therapy [13, 14]. Thus, the limited efficacy of drug therapy, catheter ablation, and CRT in patients with CHF and AF currently requires a search for new treatments in this category of patients. Today, patients with AF and CHF, who, on the background of optimal drug therapy, who retain the clinical picture of CHF and do not have indications for CRT and catheter ablation, can be offered such a type of treatment as implantation of a new generation cardiac contractility modulator (CCM) (Optimizer® Smart). This is an electrophysiological method of treatment, which is based on the application of a biphasic electrical impulse in the absolutely refractory period of the cardiomyocyte depolarization (CMC) phase, 30 ms after the QRS complex is detected [15]. The effect of CCM differs from other implantable devices (CRT, cardioverter-defibrillator) in that it does not affect the heart rate. As a result of CCM work, the contraction of the heart muscle improves, exercise tolerance increases, and the quality of life of patients increases [15]. The expert consensus on CHF considers this method of treatment as possible in patients with LVEF 25–45%, QRS complex <130 ms, without specifying the presence or absence of AF [16]. A new method of treatment, CCM implantation in such a severe category of patients with CHF and AF, may make it possible to postpone and/or even avoid heart transplantation.

The paper presents the results of a follow-up of CHF and AF patients with implanted Optimizer® Smart devices for 6 months. The aim of the study is to evaluate the efficacy of CCM in patients with CHF and various forms of AF.

MATERIALS AND METHODS

The study included 100 patients who signed informed consent and met the following inclusion criteria: documented clinically manifested CHF/lLVEF (20–40%), II–III FC according to the classification of the New York Heart Association (NYHA) during at least 3 months before screening in combination with AF, optimal CHF therapy according to current recommendations, stable condition for the last 30 days or more. The exclusion criteria were: the patient's refusal to participate in the study; being on the active list of heart transplantation or after heart transplantation, terminal CHF; acute diseases that, in the opinion of the investigator, could adversely affect the safety and/or effectiveness of treatment; reversible causes of CHF; recent major surgery or trauma; recent cardiac events, including myocardial infarction, percutaneous coronary intervention, or heart surgery within the previous 3 months; decompensation CHF; acute myocarditis; hypertrophic obstructive cardiomyopathy; angina pectoris IV FC or CHF IV FC (NYHA); mechanical tricuspid valve prosthesis; obstruction of vascular access; medical conditions that limit life expectancy to 1 year. The implantation of CCM Optimizer® Smart devices was performed in 2018–2019.

The CCM electrodes were inserted through the subclavian vein, and the CCM was implanted on the right side of the chest. Two ventricular electrodes with active fixation – Ingevity (Boston Scientific) – were positioned in the projection of the interventricular septum, mainly in its lower and middle third. Upper – RV (right ventricular) and lower – LS (local sense) electrodes were also tested intraoperatively using an analyzer (Medtronic). The sensitivity (R-waves), stimulation thresholds, and resistance were measured standard for the implantation of a pacemaker (pacemaker). After obtaining satisfactory parameters, a test was carried out using the Optimizer programmer. All patients were given special chargers to charge the CCM system from the mains weekly for 40–50 minutes. According to the study protocol, all patients before device implantation and after 2 and 6 months of follow-up underwent the following studies: 12-channel ECG (electrocardiogram), transthoracic echocardiography (EchoCG), 6-minute walk test, NT-proBNP level determination, questionnaire according to the Minnesota quality questionnaire life of patients with CHF (MH-FLQ). A 6-minute walk test was used to objectively assess the CHF FC.

Transthoracic echocardiography was performed on an expert-level ultrasound machine (Vivid E9, GE, Norway) with M5Sc-D matrix ultrasound transducer. with the patient in LLP, with ECG synchronization and standard echocardiographic positions in B, M, PW, CW, tissue myocardial Doppler sonography. The study data were saved in digital format for offline analysis. The image was then processed with EchoPac workstation (version 6.1, General Electric Medical Health). According to transthoracic echocardiography, the following standard parameters were assessed: anteroposterior LA size, maximum LA volume, maximum LA volume index, end-diastolic and systolic LV dimensions, antero-posterior and basal RV dimensions, PP area, myocardial mass and LV myocardial mass index, end LV diastolic and systolic volumes with LVEF (biplane Simpson) determination.

NT-proBNP concentration was determined with Cobas 411 (Roche Diagnostics, Switzerland) automatic analyzer.

The data were statistically analyzed with Excel 2010 and STATISTICA 10 (StatSoft Inc., USA). Qualitative values are presented as absolute values and percentages. The following methods of statistical analysis were used: two-sided F-Fisher's test and U-Mann–Whitney test. Correlation analysis was performed with Spearman's

rank test. The sample parameters given in the table are presented as M (sd) and Me [Lq; Uq], where M, the mean; sd, standard deviation, Median, Lq; Uq, interquartile range. $P < 0.05$ was taken as the minimum level of significance. After installation of the device, all patients were observed on an outpatient basis and all studies were carried out at baseline and after 6 months of observation.

RESULTS

The clinical and demographic characteristics of the patients are given in Table 1. Of the 100 patients included in the study, 83% were male. Age was 60 [56.0; 66.0] years, the duration of CHF at the time of inclusion was more than 1 year and the duration of the disease was 24 [18; 44] months. Of the entire cohort of patients with CHF, 41 had FC II (41%), 59 – FC III (59%). The analysis included patients with both paroxysmal – 51 (51%) and permanent forms of AF – 49 (49%), AF duration was 24 [12; 48] months.

All patients included in the study, prior to CCM implantation, received optimal CHF drug therapy (angiotensin converting enzyme inhibitors / angiotensin II receptor blockers / angiotensin receptor blockers and neprilisin inhibitors, beta-blockers, mineralocorticoid antagonists as mineralocorticoid receptor antagonists, loop diuretics) and have been compensating for CHF events for at least 30 days (Table 2).

There were no registered intraoperative complications during the implantation of the CCM system. It should be noted that 5 out of 100 patients felt discomfort in the form of pulsation with minimal parameters (complaints arose a day after the operation, when patients were activated, the dislocation of the electrodes was excluded by a control check of the parameters with a programmer and x-ray of the chest organs), so these required disconnec-

Table 1

Clinical and demographic characteristics of the patients

Parameter	Value
Age, years	60 [56.0; 66.0]
Male / Female, n (%)	83 (83) / 17 (17)
Ischemic / non-ischemic CHF genesis, n (%)	54 (54%) / 46 (46%)
CHF FC (NYHA), n (%)	II FC-41 (41%) / III FC-59 (59%)
LVEF, %	33 [28; 37]
CHF duration, months	24 [18; 44]
AF duration, months	24 [12; 48]
AF paroxysmal form, n (%)	50 (50%)
AF permanent form, n (%)	50 (50%)
Type 2 diabetes mellitus, n (%)	30 (30%)
BMI, kg/m^2	29 [27; 33]
ICD / CRT-D / ECP, n (%)	24 (24%) / 1 (1%) / 3 (3%)

Note. ICD, implantable cardioverter-defibrillators; ECP, electric cardiac pacemaker.

Table 2

Patients drug therapy during follow-up

Drug	% prescr.	Average dosage, mg
Angiotensin-converting enzyme inhibitors	43	
Perindopril / Enalapril	35 / 8	5 ± 2.5 / 27.5 ± 5
Angiotensin II receptor blockers	25	
Candesaran / Losartan / Valsartan	5 / 18 / 2	8 ± 4 / 50 ± 25 / 160 ± 160
Angiotensin Receptor and Neprilisin Inhibitors Sakubitril / Valsartan	32	200 ± 100
Beta-blockers	100	
Bisoprolol / Carvedilol / Metoprolol	85 / 5 / 10	7.5 ± 2.5 / 50 ± 25 / 200 ± 50
Amiodarone	13	200
Digoxin	15	0.25
Mineralocorticoid receptor antagonists	100	
Eplerenone / Spironolactone	17.5 / 82.5	50 ± 12.5 / 25 ± 12.5
Diuretics	100	
Torasemide / Furosemide	65 / 35	10 ± 5 / 40 ± 20
Anticoagulants	100	
Apixaban / Rivaroxaban / Dabigatran / Warfarin	30 / 45 / 15 / 10	10 / 20 / 300 / 25 ± 12.5

tion of one of the ventricular electrodes. In one case, an electrode dislocation was detected during a patient visit 2 months after CCM implantation, which required re-hospitalization and correction of the electrode position. One patient developed a complication in the form of suppuration of the CCM bed, which required removal of the system after 1 month after implantation. Three out of five patients whose electrodes had previously been disconnected were able to turn on the second ventricular electrode after 2 months. All other patients responded to the device satisfactorily.

Six months after CCM implantation, in 99 patients, the percentage of therapeutic stimulation was 93.7 [82.7; 98.2] (according to the recommendation of the device manufacturer, the optimal percentage of applied therapy is more than 70), with the time of applied therapy per day – 7 h [7; 8].

The most frequent reason for the increase in the time of the applied therapy was an insufficient percentage of stimulation due to a high heart rate (the threshold for the device's operation is limited to a heart rate of 110 beats/min). In this regard, careful monitoring of heart rate is required with a permanent form of AF.

CHF FC analysis showed a statistically significant decrease in CHF FC in the entire cohort of patients 6 months after CCM implantation: from 3.0 [2.0; 3.0] to 2.0 [2.0; 2.0] ($p < 0.0001$) and as a percentage, there was a decrease in FC to II in 84% of patients, in 10% of patients the FC level decreased to III, in the remaining 6% it remained unchanged.

After 6-month follow-up after implantation of the CCM system, all patients showed a statistically significant increase in exercise tolerance, which was objectively demonstrated by an increase in the distance traveled (m) according to the results of the 6-minute walk test and amounted to 6 months later. 340 [300; 400] compared with the initial data (330 [283; 384]) ($p < 0.0008$).

By MLHFQ, there was a significant decrease in the number of points from 40 [33; 45] to 28 [24; 29] ($p < 0.005$) after 6 months with CCM therapy.

To objectively assess the course of CHF against the background of 6 months of CCM therapy, the concentration of the NT-proBNP marker was analyzed and a tendency towards a decrease in this indicator from 1180 [482.8; 3123] to 1108 [403.2; 2000] pg/ml ($p = 0.07$).

To assess the reverse myocardial remodeling, transthoracic echocardiography was performed. The main EchoCG parameters of patients in dynamics are given in Table 3.

After 6 months, against the background of CCM implantation in patients, LVEF increased statistically significantly from 33 [28; 37]% to 38 [32; 37]% ($p = 0.000001$). In addition, by 6 months of treatment, ESD and EDD LV indicators also achieved statically significant results (Table 3). For volumetric parameters, LV significantly decreased ESV, while for EDV, there was a tendency to decrease. The same dynamics was observed in relation to LA volume.

Further, a comparative analysis of echocardiographic parameters and the level of NT-pro BNP in the group of patients with permanent ($n = 50$) and paroxysmal AF ($n = 50$) and implanted CCM was carried out; it should be noted that initially patients with permanent AF had a higher level of NT-pro BNP (1599 [820.1; 3334] and 927 [302; 2428], $p = 0.002$) and significantly larger LA sizes (linear size 49 [44; 52] and 44 [40; 46] $p = 0,000001$, volume LA 132 [110; 160] and 88 [74; 99], $p = 0.000001$). For the rest of the parameters, no statistically significant differences were found. The data are given in Table 4.

In addition, a comparative analysis was conducted of echocardiographic parameters depending on the form of AF during 6 months of CCM therapy. It should be noted that, regardless of the AF form, there was a statistically significant increase in LVEF, a decrease in the linear dimensions of LV and LV ESV, as well as a trend towards a decrease in LV EDV in the group of paroxysmal AFs, which did not reach static significance. The results are shown in Table 5.

DISCUSSION

The possibilities of using CCM therapy have become wider due to the advent of a new generation of devices that allow implanting two ventricular electrodes without atrial detection, and, accordingly, conducting CCM therapy if patients have AF. Thus, for patients with a persisting clinic of heart failure and a narrow QRS and

Table 3

Echocardiography dynamics at CCM therapy after 6 months

Parameter	Initial	6 months	*p*
LVEF,%	33 [28; 37]	38 [32; 37]	0.000001
LV at end diastole dimension (EDD) , mm	66 [62; 71]	63 [59; 69]	0.00001
LV at end systole dimension (ESD), mm	55 [49; 61]	51 [45; 58]	0.00008
LV at end-diastolic volume (EDV), ml	202 [173; 250]	196 [160; 237]	0.06
LV at end systole volume (ESV), ml	137 [110; 182]	115 [94; 160]	0.0001
LA, mm	47 [43; 5.1]	46 [42; 50]	0.55
LA volume, ml	108 [87; 140]	95 [70; 128]	0.08

Note. LA – left atrium.

AF complex against the background of optimal drug therapy, it became realistic to use this method of treatment – CCM implantation. Currently, there are very few works in the world literature devoted to the study of the effect of CCM in patients with CHF and AF, and there are insufficient data and large studies that would show the effect of CCM on reverse myocardial remodeling in this category of patients [17–19]. The results of our work demonstrate a positive effect of CCM in patients with CHF and AF on clinical status, NT-proBNP level, echocardiographic parameters of left ventricular remodeling. It should be noted that already after 6 months of treatment, a statistically significant increase in LVEF was observed during CCM therapy, regardless of the form of AF. Thus, the improvement in the contractile function of the LV myocardium makes it possible to judge the processes of reverse remodeling in patients with CHF both with paroxysmal and permanent AF with implanted CCM devices. According to a meta-analysis of randomized clinical trials that assessed the short-term effect and safety after device implantation, it was shown that the use of CCM in patients with sinus rhythm and CHF led to an improvement in the quality of life but did not show a statistically significant difference in the LVEF, the 6-minute test. walking, hospitalization for CHF and all other causes, and mortality from all causes [20]. In 2019, for the first time, the results of a long-term prospective 3-year follow-up of patients with CHF, sinus rhythm and CCM (CCM-REG) were obtained [21]. This registry included a total of 140 patients with 25% ≤ LVEF ≤ 45% receiving CCM therapy, but LVEF was assessed in only 51 patients. A significant increase in LVEF was in the subgroup with LVEF 35–45% (initially 38.2 ± 2.4% and up to 41.0 ± 7.2% after 6 months (n = 19, p = 0.081). Taking into account the above, detailed and the targeted assessment of echocardiographic parameters and assessment of the clinical status of patients with CHF and AF in patients with implanted CCM, there has been no study published to date.

Thus, the data obtained in the present study for the first time showed a positive effect of CCM therapy on the clinical course of the disease and myocardial remodeling processes in combination with CHF and AF.

CONCLUSION

Despite substantial advances in the treatment of patients with CHF and AF, the problem of increasing the duration and quality of life in such a complex group of patients remains very urgent, due to the extremely poor prognosis and imminent heart transplantation. The introduction of CCM therapy into complex treatment in patients with CHF and AF, according to our results, allows us to assert a significant improvement in the quality of life, a significant positive effect on LV remodeling, and provides an opportunity to postpone heart transplantation. Obviously, this promising treatment method requires further research on its clinical and prognostic significance in patients with CHF and AF, as well as to

Table 4

Comparative characteristics of echocardiographic parameters and NT-pro BNP values in the group of permanent and paroxysmal AF

Parameter	Permanent AF (n = 50)	Paroxysmal AF (n = 50)	*p*
LVEF,%	32 [28; 36]	35 [28; 38]	0.3
LV EDD, mm	69 [62; 72]	66 [62; 70]	0.2
LV ESD, mm	56 [49; 61]	53 [49; 61]	0.4
LV EDV, ml	201 [173; 241]	214 [170; 271]	0.5
LV ESV, ml	135 [109; 172]	138 [110; 195]	0.6
LA, mm	49 [44; 52]	44 [40; 46]	0.000001
LA V, ml	132 [110; 160]	88 [74; 99]	0.000001
NT-proBNP, pg/ml	1599 [820.1; 3334]	927 [302; 2428]	0.002

Table 5

Dynamics of echocardiographic parameters in patients with permanent and paroxysmal AF during treatment

AF	Permanent AF Group (n = 50)			Paroxysmal AF Group (n = 50)		
Parameter	initial	6 months	*p*	initial	6 months	*p*
LVEF	32 [28; 36]	37 [32; 41]	0.000004	35 [28; 38]	38 [30; 43]	0.000001
LV EDD, mm	69 [62; 72]	65 [58; 72]	0.001	66 [62; 70]	63 [60; 69]	0.001
LV ESD, mm	56 [49; 61]	52 [44; 60]	0.002	53 [49; 61]	51 [46; 57]	0.01
LV EDV, mm	201 [173; 241]	196 [153; 237]	0.44	214 [170; 271]	191 [161; 237]	0.09
LV ESV, mm	135 [109; 172]	130 [90; 160]	0.04	138 [110; 195]	111 [94; 140]	0.0009
LA, mm	49 [44; 52]	49 [46; 53]	0.8	44 [40; 46]	42 [40; 46]	0.4
LA V, ml	132 [110; 160]	127 [100; 150]	0.2	88 [74; 99]	77 [65; 97]	0.2

assess the safety, complication rate, number of hospitalizations, and survival of this group of patients on the background of CCM therapy.

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