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REDUCTION IN PACING RATE AND PAIN DURING CARDIAC CONTRACTILITY MODULATION: AN OVERVIEW OF THE PROBLEM AND ITS SOLUTION USING DEVICE PROGRAMMING

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Aim. Evaluation of a patient group with a reduced percentage of stimulation, pain sensation, and the impact of adjusting stimulation programming parameters on achieving a positive effect from cardiac contractility modulation (CCM) therapy.

Methods. The study included 117 patients implanted with a CCM device. Personalized parameter settings were programmed intraoperatively and postoperatively. Transthoracic echocardiography (TTE) was performed before implantation and 6 months after surgery.

Results. The median age was 59.5 years, with 93.7% being male patients. The primary etiology of heart failure was ischemic heart disease (53.8%). A part of patients required a reduction in stimulation amplitude from 7.5 V (79%) to a maximum of 5 V (9%). After 6 months, the group with 7.5 V stimulation amplitude showed a significant increase in LVEF to 37 [32; 43] % (p=0.0001). However, in the group with 5 V stimulation amplitude, the increase in LVEF did not reach statistical significance during follow-up: 35 [34; 40] (p=0.211). Patients without discomfort during CCM therapy had lower LVEF (p=0.048), increased LV volumes (p=0.024; p=0.034), and a thinner LV posterior wall (p=0.028). However, the relationship between cardiac wall thickness and pain during CCM therapy requires further research. Also, in patients without stimulation discomfort, the electrodes were more frequently implanted in the middle third of the interventricular septum (p=0.025). 83.7% of patients were programmed with standard stimulation duration - 7 hours per day (hrs/day). For 5.9%, the stimulation duration was 10 to 14 hours due to failure to achieve the required stimulation percentage. In this patient group, increasing the stimulation duration achieved a stimulation percentage exceeding 70%. In 15.3% of cases, patients with a CCM device had a therapy percentage above 90%. In 68.3% of cases, the daily therapy percentage was 80-90%, and in 12% - 70 to 80%. A positive, moderate, significant correlation was noted between the stimulation percentage and the increase in LVEF (r=0.3; p=0.05).

Conclusion. CCM is an effective method of interventional treatment for patients with CHF. When programming CCM devices, it is necessary to achieve a stimulation percentage exceeding 70% per day, as the stimulation percentage directly correlates with an increase in myocardial contractility. Additionally, the stimulation amplitude should reach the target level of 7.5 V. If pain occurs, a reduction in stimulation amplitude to the minimum tolerable level is permissible. Further study of the nuances of device operation and training of specialists in programming intracardiac devices are necessary.

Key words: cardiac contractility modulation; reduced stimulation percentage; pain sensation

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Cardiac contractility modulation (CCM) is a modern treatment for chronic heart failure (CHF) in addition to optimal medical therapy (OMT) and is intended for patients without indications for cardiac resynchronization therapy (CRT), who account for about 60-70% of all CHF patients [1, 2].

The CCM method is unique because it is based on highamplitude stimulation delivered during the absolute refractory period of cardiomyocyte contraction, which does not produce subsequent contraction. It is believed that such stimulation increases phospholamban phosphorylation, which in turn may improve calcium metabolism in cardiomyocytes [3, 4]. Thus, CCM therapy exerts a positive inotropic effect on the myocardium without increasing oxygen demand.

In the current literature, the nuances of programming CCM devices are virtually not addressed. Nevertheless,

this is a fundamental process that determines the overall effectiveness of the method. To achieve maximum results with CCM therapy, proper electrode positioning and programming that ensures an adequate stimulation percentage at an appropriate amplitude are essential.

Over the entire period of development of CCM systems, programming principles have changed. Initially, both highamplitude biphasic pulses and lowamplitude monophasic pulses were used in preclinical studies [5]. Currently, the standard programming protocol for CCM devices involves the delivery of paired biphasic pulses with an amplitude of 7.5 V and a pulse duration of 5.14 ms each. In studies on isolated healthy ferret hearts stained with aequorin (a calcium-sensitive dye), highamplitude single biphasic pulses of CCM therapy were applied [6]. These studies showed that such stimulation accelerated calcium entry into the cell, which correlated with increased contractility of individual cardiomyocytes.

Table 1.

Clinical and demographic characteristics of the study patients (n=117)

Parameter	Value
Age, years	59.5 [53.5; 66]
Male, n (%)	98 (83.7)
BMI, kg/m^2	29 [26; 33]
Ischaemic CHF, n (%)	63 (53.8)
Non ischaemic CHF, n (%)	54 (46.2)
AF, n (%)	112 (95.7)
Paroxysmal AF, n (%)	56 (50)
Permanent AF, n (%)	56 (50)
Sinus rhythm, n (%)	5 (4.3)
Diabetes mellitus, n (%)	37 (31.6)
LVEF, %	31 [28; 37]
NYHA functional class	2.58±0.49
NYHA II, n (%)	48 (41.0)
NYHA III, n (%)	69 (59.0)
Transvenous ICD, n (%)	23 (19.7)
Subcutaneous ICD, n (%)	6 (5.1)
CRT D, n (%)	4 (3.4)
Pacemaker, n (%)	3 (2.5)

Note: BMI - body mass index; CHF - chronic heart failure; AF - atrial fibrillation; LVEF - left ventricular ejection fraction; NYHA - New York Heart Association; ICD - implantable cardioverter defibrillator; CRT D - cardiac resynchronisation therapy defibrillator.

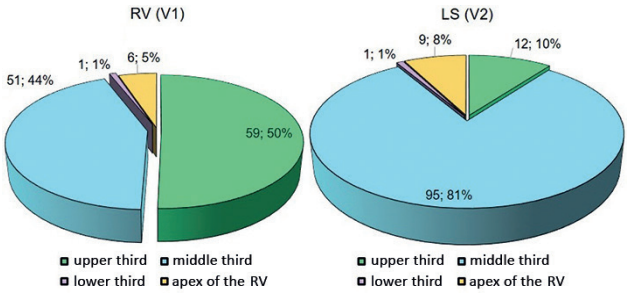

Fig. 1. Areas of electrode positioning of the CCM device.

The efficacy of highamplitude biphasic pulses was also studied in vivo. A current pulse of ±20 mA was delivered via epicardial electrodes placed on the anterior and posterior walls of the left ventricle (LV) in dogs. Based on the ratio of endsystolic pressure to volume, a global increase in LV contractility was observed. In contrast, lowamplitude monophasic pulses did not change myocardial contractility [7].

The system using the Optimizer® II (Impulse Dynamics, USA) was studied in a canine model of ischaemic CHF. Stimulation of the interventricular septum (IVS) for 2 hours with highamplitude biphasic pulses reduced LV dilation and increased LV ejection fraction (LVEF) by 5%. However, in that study, the effect was local and did not extend to more distant myocardial regions [7]. Subsequent studies demonstrated that local effects after 3 months of CCM therapy translate into remote myocardial regions, resulting in global contractility improvement [3, 8].

In 2003, a study was published that evaluated the efficacy of CCM therapy in dogs. The programming protocol included delivery of biphasic shocks with an amplitude of 5 V and a pulse duration of 14.5 ms each. CCM therapy duration varied from 1 to 6 hours per day. A positive effect of CCM therapy was observed even in the group with only 1 hour of stimulation per day [9].

Thus, through numerous experimental studies, a programming protocol for CCM devices was established and subsequently used in all major clinical trials [10]. However, in the series of clinical studies on CCM therapy, only major complications (electrode dislodgement, pocket haematoma, tricuspid valve dysfunction, infectious complications, CHF decompensation, etc.) are mentioned, while issues such as reduced CCM stimulation percentage and painful sensations from stimulation are not addressed. In realworld clinical practice, it is not always possible to achieve the recommended target stimulation percentage. Moreover, the standard programmed amplitude of 7.5 V is often quite perceptible to patients, necessitating programme adjustments.

The aim of this study is to identify patients with reduced stimulation percentage or painful sensations from CCM therapy and to evaluate the impact of these conditions on the effectiveness of the method.

MATERIAL AND METHODS

The study included 117 patients with LVEF between 25% and 40% and narrow QRS complex who underwent implantation of a CCM system. All patients provided written informed consent to participate. Preoperative evaluation included 24hour Holter ECG monitoring and echocardiography with assessment of LVEF, LV endsystolic and enddiastolic volumes. After final determination of indications for CCM device implantation, the surgical procedure was performed.

CCM device implantation was performed via the right subclavian approach. Under local anesthesia, an incision was made along the deltopectoral groove on the right. Puncture of the right subclavian vein was performed. Through introducers, ventricular leads with active fixation

were placed in the IVS segments. The upper lead (RV - right ventricular) and the lower lead (LS - local sense) were intraoperatively tested using an analyzer. Stimulation thresholds, Rwave amplitude, and impedance were determined. Then, using the Impulse Dynamics® programmer (Impulse Dynamics, USA), preliminary programming of the CCM device was performed.

The programming protocol was standard. In all patients, the OVOLSCCM mode was set. Stimulation was delivered for 7 hours per day, with 2 biphasic pulses from each of the two ventricular leads at an amplitude of 7.5 V and a total pulse duration of 20.56 ms. The timing of pulse delivery was adjusted individually according to the electrophysiological characteristics of each patient.

Some patients with indications for CCM implantation also had indications for an implantable cardioverter-defibrillator (ICD). This study included patients who already had an ICD implanted. Patients planned for or already having a device that includes a defibrillation lead constitute a separate group. In these cases, the surgical procedure for CCM device implantation has specific features. An important point is the need to fix the CCM leads at least 2 cm away from the defibrillation lead. In addition, these patients undergo a special software test - the Crosstalk test - to rule out double sensing of the CCM signal, which could be interpreted by the defibrillator as ventricular tachycardia and trigger antitachycardia pacing or defibrillation.

In patients with a previously implanted CRTD device, it is necessary to programme the CCM device with therapy delivery both on the native QRS and on the paced complex during CRTD operation to determine the most optimal settings for both states. Initial programming of the CCM device was performed in the operating room, then on the next day after surgery and before discharge from the hospital.

Followup visits with echocardiographic assessment (LVEF, enddiastolic and endsystolic volumes and dimensions) and device programming were performed 6 months after implantation. During device interrogation, special attention was paid to the stimulation percentage and stimulation amplitude level. If painful sensations occurred, the stimulation amplitude was adjusted: the minimum value at which CCM therapy was not perceived was programmed. If the stimulation percentage was insufficient, the device operating time was extended.

Statistical analysis was performed using Excel 2010 and STATISTICA 10 (StatSoft Inc., USA). Qualitative variables are presented as absolute numbers and percentages. The Mann-Whitney Utest was used. Sample parameters presented in the tables are shown as M (sd) and Me [Lq; Uq], where M is the mean, sd is the standard deviation, Me is the median, and Lq; Uq is the interquartile range. Differences were considered significant at $p < 0.05$; p values 0.05-0.10 were interpreted as a trend.

Correlation analysis was performed using Pearson's rank correlation coefficient. The strength and direction of the relationship between variables were assessed. For positive correlations, values from +1 to +0.7 were considered strong, from +0.699 to +0.3 - moderate, and from +0.299 to 0 - weak. For negative correlations: from -1 to -0.7 - strong, from -0.699 to -0.3 - moderate, and from -0.299 to 0 - weak. Correlations are presented as scatter plots.

RESULTS

The study included 117 patients, median age 59.5 years, 83.7% male. The predominant aetiology of CHF was ischaemic heart disease (53.8%). In addition, 95.7%

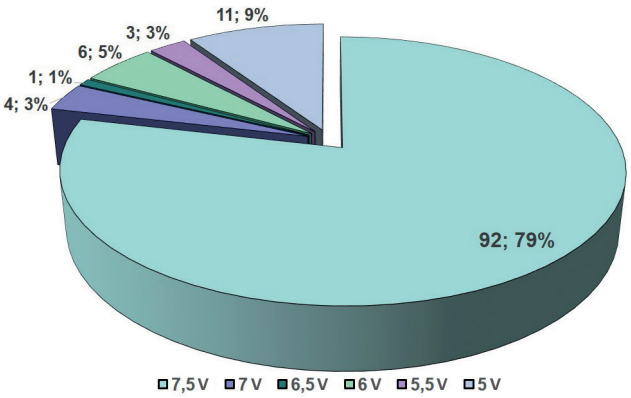

Fig. 2. Distribution of programmed stimulation amplitudes for CCM therapy.

Table 2.

Statistically significant parameters in patient groups with and without pain at the programmed CCM amplitude of 7.5 V

Parameter	Pain present (n=25)	Pain absent (n=92)	p
LV EDD, mm	63 [58; 71]	68 [62; 73]	0.05
LV ESV, mL	124 [96; 181]	148 [117; 174]	0.024
LV EDV, mL	187 [155; 251]	218 [176; 265]	0.034
LV EF, %	35 [29; 37]	30 [27; 36]	0.048
LV PWT, mm	0.9±0.15	0.8±0.15	0.028
MTIVSLP	0.8±0.4	1.08±0.3	0.025

Note: LV - left ventricle; EDD - end diastolic dimension; ESV - end systolic volume; EDV - end diastolic volume; EF - ejection fraction; PWL - posterior wall thickness; MTIVSLP - middle third interventricular septum lead placement.

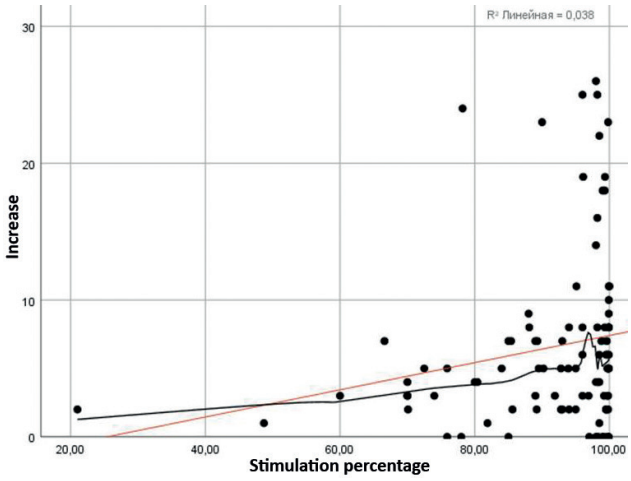

Fig. 3. Correlation between the increase in LVEF and the stimulation percentage during CCM therapy (r=0.38; p=0.05).

of patients had some form of atrial fibrillation. A subset of patients (n=36, 30.7%) had additional antiarrhythmic devices, mostly various types of ICD (29, 24.7%). Four patients had previously been implanted with a CRTD but showed no positive response to resynchronisation therapy, and therefore also received a CCM device (Table 1).

The device leads must be implanted 1.0-1.5 cm apart to correctly sense the intracardiac signal and, accordingly, to properly programme the therapy timing. In this study, leads were fixed in the upper, middle, and lower thirds of the IVS (Fig. 1). Initial programming was always performed intraoperatively with mandatory verification of stimulation tolerance by the patient. Evaluation of programming parameters and stimulation percentage was performed on the day after surgery after patient mobilisation.

In our study, some patients required a reduction in stimulation amplitude from 7.5 V (79%) down to a maximum of 5 V (9%) (Fig. 2). Both leads were active in these patients. Before surgery, LVEF in the groups with 7.5 V and 5 V stimulation amplitudes was 30 [27; 36] % and 32.5 [28; 37] %, respectively (p=0.65). After 6 months, the 7.5 V group showed a significant increase in LVEF to 37 [32; 43] % (p=0.0001). However, in the 5 V group, the LVEF increase did not reach statistical significance during followup: 35 [34; 40] % (p=0.211).

To identify possible causes of pain, we compared clinical and demographic characteristics of patients who experienced this problem with those who did not. Table 2 presents preimplant variables that showed statistical significance. According to the data, patients without discomfort during CCM therapy had lower LVEF, larger LV volumes, and a thinner LV posterior wall. In addition, in patients without stimulation discomfort, leads were more frequently implanted in the middle third of the IVS.

There are several situations in which CCM therapy may be inhibited:

- Development of a heart rate exceeding the maximum programmed threshold - usually 110 bpm.
- Frequent premature ventricular contractions - the device does not deliver a stimulus on the ectopic beat and the following complex.
- Presence of noise sensed by the leads.

During CCM device programming, use of information from the “Statistics” window helps determine the cause of stimulation inhibition.

In our study, 83.7% of patients had a standard stimulation time of 7 hours per day. In 5.9%, the stimulation time was 10 to 14 hours due to failure to achieve the required stimulation percentage. In this group, increasing the stimulation duration achieved a stimulation percentage exceeding 70%. During followup, one patient in this group experienced excessive heating of the device during battery recharging.

In patients with a CCM device, 15.3% had a therapy percentage above 90%. In 68.3%, the daily therapy percentage was 80-90%, and in 12% - 70 to 80%. A positive, moderate, significant correlation was observed between the stimulation percentage and the increase in LVEF (Fig. 3).

DISCUSSION

The use of CCM requires careful attention both to patient selection and to postimplant management.

Although device programming is fundamentally based on classical electrophysiological principles, there are a number of nuances that should be known to the implanting surgeon and the physician who will subsequently adjust the device parameters.

Protocols describing the principles of CCM device programming are virtually nonexistent and are limited to experimental studies [7-10]. Based on the results of this study, several key conclusions can be drawn. Stimulation amplitude influences the increase in LVEF, however, to improve tolerability, the amplitude can be reduced to 5 V according to patient perception.

A key factor affecting the increase in LVEF during CCM therapy is the stimulation percentage. It is known that with a standard stimulation time of 7 hours per day, pulses are delivered according to the algorithm: 1 hour of device operation followed by a 2hour25minute pause [11, 12]. The target stimulation percentage should exceed 70. To achieve the required daily stimulation percentage, the stimulation time can be increased beyond 7 hours, but values above 10 hours should be avoided, as this may cause excessive heating of the device during recharging.

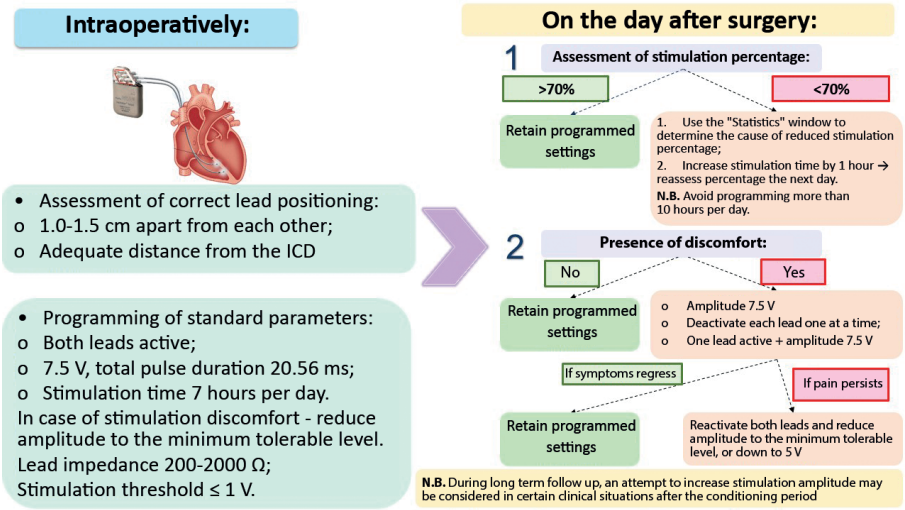

Fig. 4. Algorithm for programming CCM devices.

In our study, both leads were active for delivery of the cardiac-modulating signals in all patients. There is a study that compared the efficacy and safety of one versus two active ventricular leads. The results showed improvement in functional class ($p<0.001$) and quality of life ($p=0.002$ and $p=0.003$) at 6 months after implantation, with improvement observed equally in both the single-lead and duallead groups. Thus, this study provides another mechanism for eliminating CCM therapy discomfort if necessary. A brief algorithm for CCM device programming is presented in Fig. 4.

CONCLUSION

Cardiac contractility modulation is an effective interventional treatment for patients with chronic heart failure. With careful patient selection and meticulous postoperative followup, maximum results can be achieved. Further study of device operational nuances and training of specialists in intracardiac device programming are necessary.

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