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RESYNCHRONIZATION THERAPY: RESULTS OF THE 2 YEAR FOLLOW-UP

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Aim. Cardiac contractility modulation (CCM) is a device therapy for patients with heart failure with reduced ejection fraction (HFrEF), most of the data on its programming are concerned patients with narrow QRS and of limited follow up. Our aim was to propose programming approach for Optimizer device in setting of wide QRS complex and fragmented ventricular local activation.

Methods. We enrolled 11 patients with HFrEF (median age, 8 males, median NYHA class 3) and LBBB-related wide QRS complex, who underwent Optimizer™ device implantation. Three patients got Optimizer™ IV system and eight patients were implanted Optimizer™ Smart. Ten patients were previously implanted with CRT-D due to HFrEF and LBBB; one patient received CRT-D after Optimizer™ implantation.

Results. During the implantation procedure ventricular local sense (LS) channel signal fragmentation was detected in all patients. In five patients signal detection was optimized by lead relocation. In six patients LS signal sensitivity limitations were resolved by programming. At two-year follow-up survival 4 patients died of noncardiac causes (1 intracranial hemorrhage, 1 gastrointestinal bleeding and 2 - terminal kidney failure). At 12-month follow-up we observed a non-significant improvement in 6-minute walking distance (300 vs 305, p=0.093), NYHA class (2.75 vs 2, p=0.085), MLHF score (53 vs 42, p=0.109) and left ventricular ejection fraction (LVEF) (30 vs 33.5, p=0.212).

Conclusion. CCM system implantation is feasible and safe in patients with HFrEF and LBBB-related wide QRS complex. Device programming maneuvers can resolve the challenges of ventricular local signal detection in these patients.

Key words: heart failure; cardiac contractility modulation; wide QRS; left bundle branch block; cardiac resynchronization therapy

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Cardiac contractility modulation (CCM) is a relatively new method (the Optimizer™ system by Impulse Dynamics, Orangeburg, NY, USA) used to treat patients with heart failure with reduced ejection fraction (HFrEF).

CCM is an invasive treatment that involves implantation of a pulse generator and two ventricular electrodes into the myocardium of the interventricular septum on the right ventricular side. Therapy consists of applying biphasic stimulation to the myocardium of the interventricular septum during the period of absolute refractoriness. High-amplitude pulses (7.5 V with a stimulus duration of 5.14 ms) are applied approximately 30 ms after the onset of the QRS complex and do not initiate a new ventricular contraction. The effect of CCM on cardiomyocytes normalizes cellular calcium metabolism without increasing myocardial oxygen demand, as has been shown in in vitro studies [1].

Data from clinical trials indicate a reduction in the severity of heart failure (HF) symptoms and a decrease in the number of hospitalizations due to decompensation in patients with New York Heart Association (NYHA) functional class (FC) II-IV and left ventricular ejection fraction (LVEF) <40% [2-5]. In the performed meta-analysis of these studies, improvements in exercise tolerance and quality of life were confirmed; however, no indication of a positive effect on patient prognosis and left ventricular remodeling was demonstrated [6, 7].

The relatively large studies performed to date have included only patients with a narrow QRS complex. Data on the use of in patients with a wide QRS complex are limited. H.Nagele et al (2008) [8] and J.Kuschyk et al (2019) [9], which included sixteen and seventeen patients respectively, showed the potential for implantation of CCM in

patients who have not responded to cardiac resynchronization therapy (CRT). All patients in these studies had sustained sinus (or artificially atrial) rhythm, and follow-up periods were predominantly limited to 6 months.

The aim of this work was to evaluate the use of CCM systems in patients with wide QRS complex, the clinical effect and the interaction between implanted CCM systems and CRT.

METHODS

Eleven patients with HFrEF and persistent HF symptoms at NYHA II-IV FC and wide QRS complex on external ECG were implanted with CRT and CCM systems (Optimizer IV (n=2) and Optimizer Smart (n=9) (Impulse Dynamics, Orangeburg, NY, USA) from December 2016 to November 2019.

Inclusion criteria were age >18 years, HFrEF with NYHA ≥ II FC, presence of implanted CRT-D and no increase in LVEF (less than 5%), decrease in end-systolic volume (less than 15%), NYHA reduction of I or more, after CRT-D implantation, QRS complex width after CRT-D implantation ≥130 ms.

Exclusion criteria included waiting for heart transplantation, myocardial infarction, coronary artery bypass surgery or angioplasty with coronary artery stenting less than 3 months before inclusion, acute myocarditis, hypertrophic cardiomyopathy, reversible causes of heart failure, mechanical tricuspid valve, severe comorbid pathology.

Implantation and device programming

The devices were implanted under local anesthesia with lidocaine (10 mg/mL). The incision was performed in the subclavian region. Electrodes through the subclavian vein were guided to the heart. Optimizer IV devices were implanted - with three electrodes: one atrial (Boston Scientific 7741 Ingevity IS-1 52cm) and two ventricular (Boston Scientific 7742 Ingevity IS-1 59cm (Boston Scientific, Massachusetts, USA) or St Jude Tendril STS IS-1 59 cm (St. Jude Medical, Minnesota, USA)); and Optimizer Smart - with two ventricular electrodes (Boston Scientific 7742 Ingevity IS-1 59cm (Boston Scientific, Marlboro, Massachusetts, USA) or St Jude Tendril STS IS-1 59 cm (St. Jude Medical, Saint Paul, Minnesota, USA)). The atrial electrode was fixed in the region of the right atrial appendage, ventricular electrodes were fixed in the interventricular septum on the right ventricular side. The distance between ventricular electrode implantation sites was at least 2 cm. In the presence of implanted shock electrode CRT-D in the region of the right ventricular apex or interatrial septum, the distance between it and the nearest ventricular electrode of the modulator was also more than 2 cm. Parameters at the electrodes were tested using a Medtronic CareLink 2290 external analyzer (Medtronic, MN, USA) and after connection to an CCM pulse generator using an OMNI™ II Programmer (Impulse Dynamics, NY, USA).

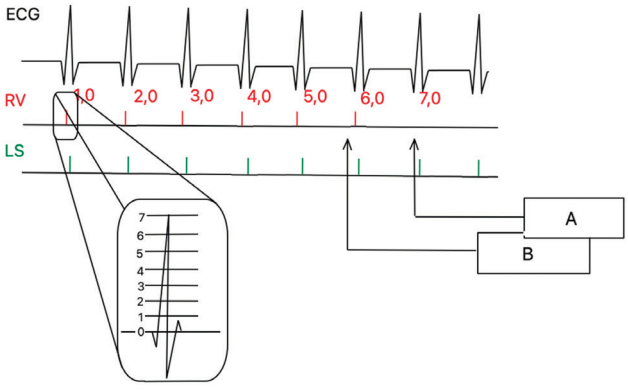

Fig. 1. Determination of sensitivity on the RV channel. Note: during control by ECG on both electrodes events are recorded, which are recognized by the system, gradually increasing the sensitivity parameter on the RV-channel, the maximum amplitude of the local activation signal recognized by the system is determined. RV, LS - diagrams marking the recorded events on the corresponding ventricular electrodes, A - maximum sensitivity parameter, B - hyposensing on the RV-channel.

When programming the devices, the main point was to adjust the sensitivity on the ventricular channels (hereinafter labeled as RV and LS channel) and the algorithm for discrimination of «normal» and abnormal contraction. Determination of the sensitivity amplitude was performed by gradually increasing the sensitivity value until the next ventricular channel event was no longer labeled by the system (Fig. 1). The sensitivity level and time intervals of the discrimination algorithm were set individually for each patient. The sensitivity on the LS channel varied from 5.4 to 24.5 mV. The peculiarity of sensitivity tuning on LS turned out to be a pronounced fragmentation of the local activation signal (Fig. 2).

When the system was turned on, the initial amplitude of the therapy delivery was 5 V, and when the therapy was satisfactorily tolerated, the amplitude was increased to 7.5 V. In case of poor tolerance to stimulation, the symptom-related electrode was repositioned. After the procedure, a «cross-talk» test was performed, for the interaction between the two devices (CRT and CCM).

The minimum follow-up period was 24 months with outpatient visits at 2, 6, 12, 18, and 24 months. Verification, and if necessary, adjustment of both devices (CCM and CRT-D), consultation with a heart failure specialist, echocardiography, and six-minute walk test were performed at all visits at 6 and 12 months. From 2020, the follow-up protocol was modified due to events resulting from the Covid-19 pandemic. 8 out of 11 patients received telephone counseling without outpatient visits at 18 and 24 months after implantation.

Statistical analysis

Statistical analysis was performed using the Stata program (v15.0 for Windows, StataCorp., USA). Median and interquantile spread were used to describe quantitative variables, while qualitative variables were described by absolute and relative frequencies (percentages). The Wilcoxon sign rank test was used to assess the significance of the indicators. Differences were considered statistically significant at two-sided p values <0.05.

RESULTS

Patient characteristics

Eleven patients with HFrEF and wide QRS who were implanted with Optimizer IV (2 patients) and Optimizer Smart (9 patients) devices were included in the study. Device implantation was performed from December 2016

through November 2019. The median age of the patients was 61.5 years, 8 males. The median NYHA FC was 3 [2;3], median LVEF was 30.0% [24.0;32.75], median QRS complex width was 167 ms [158;180], and median 6-minute walk distance was 300 meters [180;310]. Ten patients had an implanted CRT-D at the time of inclusion. Almost all patients had >95% biventricular stimulation, patient #7 had a significant burden of polymorphic premature ventricular complexes (9 thousand per day). Iron deficiency anemia, suboptimal AV delay programming were excluded. One patient had a narrow QRS complex at the time of cardiac contractility modulator implantation. At 6 months after implantation, at the scheduled visit, the ECG showed a dynamic increase in QRS duration up to 150 ms with morphology of LBB blockade, and therefore the patient was implanted with CRT-D. Most patients had atrial fibrillation (AF) (9/11), two had persistent AF at the time of CCM implantation. All patients were receiving maximally tolerated heart failure therapy at the time of CMM system implantation, and left ventricular CRT electrodes were implanted in the lateral or posterior veins of the heart according to fluoroscopy. The baseline characteristics of the patients are presented in Table 1.

Device implantation

Successful implantation of the devices was performed in all patients. At intraoperative sensitivity tuning on the LS channel, pronounced fragmentation of local myocardial activity was registered in all patients (example - Fig. 1 B: 1 cardiac contraction corresponds to 3 separate events on the LS channel). Similar findings were revealed both against the background of their own rhythm in patients with preserved atrioventricular conduction and against the background of biventricular stimulation. In five patients, monolithic adhesions of local activation were achieved after repeated repositioning of the electrode. In six patients, electrode repositioning did not result in a significant change in the local activation pattern. The procedure time was 90 minutes [80;135].

Follow-up

Seven patients completed the two-year follow-up. Four patients (36.4%) died due to noncardiac causes: intracranial hemorrhage (11 months after implantation), gastrointestinal bleeding (2 months after implantation), two patients - terminal renal failure (at the 18th and 22nd month of follow-up), in patient #4 - renal failure was considered because of HF, in patient #5 - as an outcome of long-term chronic pyelonephritis.

Device programming

The median duration of therapy application in patients was 7.5 hours/day [7.0; 10.5]. The target volume of applied therapy (>90%) at interim visits was achieved in 8 patients (72.7%) and maintained for at least 12 months after implantation. A prerequisite for the application of CCM therapy is a sustained ventricular rhythm that the device would consider «normal». «Normality» of each heartbeat is determined by the interval between the local activation times at the RV and LS electrodes. The parameter that is responsible for discrimination is the Alert interval (referent is the time of local activation at the RV electrode, «alert start» is the time from the moment of activation at the RV to the beginning of the interval, «alert width» is the duration of the interval). If activity is logged on the RV, activity is expected to be logged on the LS channel in the «Alert» interval. A reduction is considered «normal» when the local activation on the LS channel falls within the «Alert» interval. Fragmentation of the signal on the LS-channel and, therefore, registration of more than one signal in the «alert» interval leads to the error «Double LS» (Fig. 3) - double signal perception. This circumstance required a tuning correction, for which the following tactic was used.

During sensitivity scanning on the LS channel (see Fig. 2), the morphology of the commissure of myocardial contraction was assessed by recording the number of isolated events on the LS channel during 1 cardiac contraction. The signal on the LS channel was defined as either monolithic (single) or fragmented (more than one isolated signal corresponds to a single reduction). The optimal level of sensitivity was determined by the maximum time interval between the end of the penultimate event and the beginning of the last event on the LS channel. Then, taking the event on the RV channel as a reference, we set the parameters of the «Alert» time interval as «Alert start» and «Alert width» so that the Alert interval starts no earlier than the middle of the interval between the last and previous event on the LS channel, defined as: X=B-A, where X is the in-

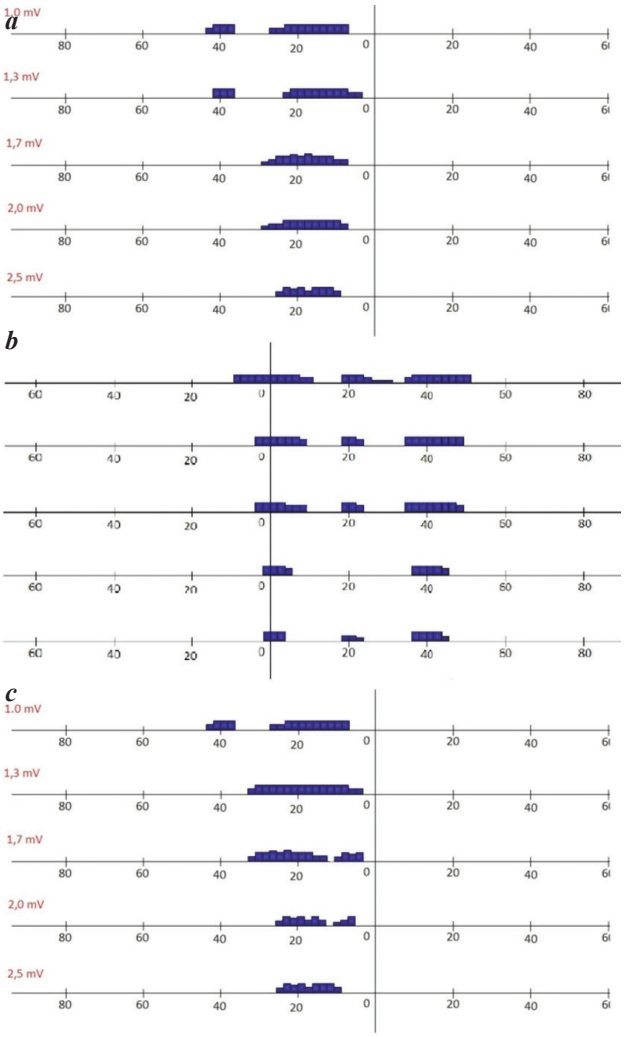

Fig. 2. Sensitivity setting screen on LS-channel. Note: a - monolithic activation spike, b - pronounced fragmented activation spike - two/three separate events corresponding to one heartbeat, c - partial fragmentation of ventricular signal spike.

terval between events on the LS channel, «A» and «B» are the end time of the penultimate event and the beginning of the last event on the LS channel, respectively (Fig. 4).

Patient #10 (Optimizer IV implanted) initially demonstrated close to 100% effective therapy delivery during device setup, against the background of which he noted an improvement in his well-being. The patient presented with a persistent AF for 6 months after device implantation. The development of AF stopped the application of therapy because a regular atrial rhythm was required for the Generation IV Optimizer to work. An attempt to restore rhythm by external cardioversion was ineffective. It was decided to refrain from performing catheter isolation of the pulmonary vein orifices due to the extremely high probability of surgical complications. The setting of the CRT-D and CCM was modified as follows. The sensitivity of the atrial electrode is maximized so that the CRT-D, ignoring the FA rhythm, applies sequential atrial-ventricular stimulation. The sensitivity of the atrial CCM channel was also increased to record only the artifact of atrial stimulation. Thus, an attempt was made to «mimic» a regular atrial rhythm to ensure stable Optimizer IV operation. Nevertheless, this adjustment resulted in a 44% CCM stimulation percentage.

Patient #6 died 2 two months after device implantation from gastrointestinal bleeding. Device verification and functional performance evaluation were not performed.

During the first outpatient checkup in patient #7 2 months after implantation, transient ventricular conduction disturbances were detected accompanied by fragmentation of the local activation signal recorded on the LS-channel. Attempts to program the device did not increase the percentage of CCM stimulation above 40%.

No episodes of CCM recording interpreted as ventricular rhythm disturbances were recorded during checks of implanted CRT-D.

In patient #9 (Boston Scientific 7742 Ingevity IS-1 59 cm and Optimizer Smart electrodes implanted), 1.5 and 2 years after implantation of the CCM system, bed stimulation was detected when delivering therapy from the RV and LS channels, respectively. The patient underwent revision of the modulator bed, and no mechanical defects of the electrodes were found on inspection. It was decided to form a separate bed for the electrodes and for the body of the device. No bed stimulation was noted after relocation of the electrode loops to a separate bed and inclusion of therapy. This patient continues to be followed up and at the time of publication 3 years after revision, no bed stimulation is noted.

Echocardiography, quality of life, exercise tolerance

During follow-up, there was no significant improvement in NYHA FC (3 [2;3] vs 2 [2;3] p=0.085), LVEF

Table 1.

Initial characteristics of patients

	Patient (#)										
	1	2	3	4	5	6	7	8	9	10	11
Date of CCM implantation, m/y	11/18	12/18	12/16	11/18	12/18	12/18	9/19	12/18	5/17	12/16	11/19
Date of implantation of CRT-D, m/y	6/19	6/16	6/16	2009	12/14	6/16	07/15	6/16	11/12	11/12	7/19
Device type	smart	smart	IV	smart	smart	smart	smart	smart	smart	IV	smart
Age, years	67	69	68	67	66	66	61	61	60	59	57
Sex	m	f	m	m	m	m	f	m	m	m	f
QRS length, ms	150	170	130	210	158	174	167	180	160	180	160
CAD	yes	yes	yes	no	no	no	no	no	yes	yes	no
Hypertension	yes	yes	yes	no	no	no	no	yes	yes	yes	no
Atrial fibrillation	yes	yes	no	yes	yes	yes	yes	yes	no	yes	yes
NYHA	4	4	3	3	2	4	3	2	2	2	3
LVEF, %	24	32	30	33	20	29	31	28	33	30	24
6-minute walk distance, meters	200	315	180	300	400	340	200	390	300	310	100
MLHF, points	60	53	23	33	40	52	74	39	39	57	55
Pharmacotherapy of heart failure											
ACEI/ARB/ARNI	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Beta-adrenoblocker	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Loop diuretics	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
MRA	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Digoxin	yes	yes	no	yes	no	no	no	no	no	no	yes
Amiodarone	no	no	no	yes	no	no	no	yes	no	yes	no

Note: m/y, month, and year; CCM - cardiac contractility modulation; CRT-D - cardiac resynchronization therapy with defibrillator function; LVEF - left ventricular ejection fraction; MLHF - Minnesota Heart Failure Quality of Life Questionnaire; ARA - angiotensin-receptor antagonists; ARNI - angiotensin receptor angiotensin and neprilysin inhibitor; ACEI - angiotensin-converting enzyme inhibitors; MRA - mineralocorticoid receptor antagonists.

(30 [24.0;32.75] % vs 30.4 [25.25;35.75], p=0.212) and 6-minute walk distance (300 [180;310] vs 300 [270;320] p=0.095) 12 months after implantation. Regurgitations on mitral (2 [2;3] vs 2 [2;3] vs 2 [2;3] and tricuspid (2 [2;3]) vs 2 [1;3]) remained the same. There was also no significant improvement in NTproBNP (1319 [185;3760] vs 916[173;1165] p=0.225) and Minnesota Heart Failure Quality of Life Questionnaire (53 [36.0;58.5] vs 42 [30.0;53.5] p=0.109).

DISCUSSION

Our study evaluated the feasibility and efficacy of CCM in patients with wide QRS complex with LBBB and persistent circulatory failure despite optimal drug therapy. Previously performed randomized controlled trials included only patients with narrow QRS [2-5]. The currently published observational studies of patients with an implanted CCM device and wide QRS included only patients with sinus rhythm or sustained atrial stimulation and were limited to a short follow-up period [8, 9]. In addition, these works did not describe the nature of the local activation signal changes or the results of CCM programming.

The proportion of patients not responding to CRT remains significant in both randomized and observational studies, and the cause may be atrial or ventricular rhythm disturbances, inadequate device settings, implantation of a left ventricular electrode in a non-target vein, and iron deficiency anemia [10]. In our study group, predictors for lack of response to resynchronization therapy were only in 3 patients (significant ventricular ectopy burden in patient #9, presence of persistent AF in patients #1 and #4). However, although the remaining patients had predictors of response to CRT (achieving biventricular stimulation >95%, ensuring sinus rhythm or adequate atrial stimulation, adequate device settings, titration of drugs to maximum tolerated dosages, and exclusion of iron deficiency), there was also no clinical benefit to CRT-D implantation. Patients had both ischemic and non-ischemic genesis of heart failure. Among the patients with CAD, only two suffered an anterior-posterior localization infarction. The lack of response may have been due to the terminal nature of heart failure and lack of contractile reserve.

In these clinical cases, we attempted to improve the condition of patients who did not respond to maximally tolerated pharmacologic and resynchronization therapy. When analyzing the literature, we were unable to find a description of the features of implantation of the CCM system in patients with CRT or their setting. The patients underwent surgery without any peculiarities. In addition, implantation of devices with two additional electrodes into the interventricular septum did not worsen regurgitation at the tricuspid valve.

The main feature we encountered during device implantation is fragmentation of the ventricular signal recorded by the device. Such signal fragmentation in patients with LBBB has been previously described in electrophysiologic mapping of interventricular septal myocardium in patients with LBBB [11]. The most likely cause of ventricular signal fragmentation may be myocardial fibrosis or LBBB-associated intraventricular conduction abnormalities. The same reason may be the presence of multipolar stimulation of the ventricular myocardium in patients with CRT-D. When analyzing the available literature, we did not find a description of the algorithm of CCM programming in this situation.

Ventricular signal fragmentation was noted in all patients, in five patients the situation resolved after repositioning of the electrode. In a proportion of patients, the change in sensitivity level was sufficient to achieve the target amount of applied therapy. However, in patients with pronounced signal fragmentation, changes in parameters of both the stimulation level and the parameters defining the Alert readiness window and refractoriness window for the LS channel were required.

The development of persistent AF in patient #10 with the Generation IV Optimizer prevented an assessment of the potential efficacy of therapy. Lack of stable rhythm in the atria led to inhibition of therapy, which was accompanied by worsening exercise tolerance. Similarly to the described method of S.Roger et al (2014) [12] we increased the sensitivity and amplitude of stimulation on the atrial channel of CRT-D. Although the described work indicates 60-95% successfully applied therapy, in our observation the percentage of effective stimulation was 44%. The latest generation of devices, the Optimizer Smart, does not require implantation of an atrial electrode, thus eliminating such complications in the future.

Electrode repositioning and/or correction of device parameters resulted in achieving the target stimulation

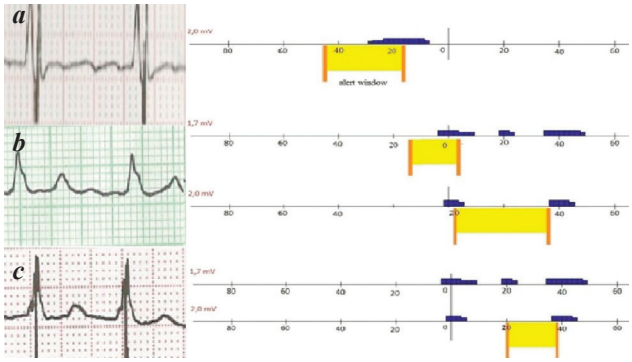

Fig. 3. ECG and alert window positioning. Note: a - patient with monolithic signal of local activation on LS channel, b - patient with fragmented signal, «double LS» marker and inhibition of therapy, c - patient with fragmented signal and successful application of therapy.

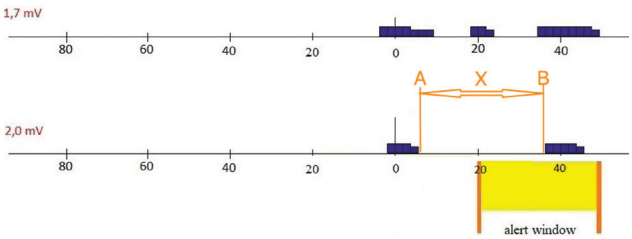

Fig. 4. The scheme of setting the «Alert» window when there are two or more events on LS channel, where X is the time interval between events on LS channel, A is the time of the end of the penultimate event, B is the time of the beginning of the last event on LS channel, X=B-A, «Alert start» > X/2.

percentage (>90%) in 73% of cases. Despite successful implantation and device customization, patients in our study did not demonstrate meaningful clinical or functional improvement. In view of the lack of proven effects on myocardial contractility of CCM therapy in randomized trials [2-5], and the absence of RCTs evaluating the combined use of CRT and CCM, routine implantation of these systems in patients who have not responded to optimal drug therapy and CRT may be considered as a desperation therapy.

Our findings and programming approach may be useful in exceptional cases - when CRT needs to be implanted in patients with implanted CCM to preserve the clinical effect of cardiac contractility modulation, or when CCM systems are implanted in patients with a wide QRS complex who do not meet the criteria for CRT implantation.

Limitations of the study

This paper is a retrospective analysis of data from a small number of patients; moreover, only patients with LBBB were included in this analysis. It should be noted that outpatient visits at month 18 and 24 in a portion of patients were replaced by a telephone call due to restrictions related to the Covid-19 pandemic.

CONCLUSION

Implantation of CCM devices in patients with HFrEF, QRS complex dilation on the background of complete LBBB is possible and safe. The peculiarities of intraventricular conduction and the presence of CRT may require additional tuning of the CCM. The use of CCM in patients who did not respond to CRT did not lead to significant positive dynamics of echocardiographic parameters and quality of life.

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