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Evaluation of the long-term effectiveness of cardiac resynchronization therapy

Chumarnaya T. V.[1,2], Lyubimtseva T. A.[3], Solodushkin S. I.[4], Lebedeva V. K.[3], Lebedev D. S.[3], Solovieva O. E.[1,4]

Aim. To determine quantitative criteria for assessing the therapeutic benefits and the most informative time frames after cardiac resynchronization therapy (CRT) to assess its long-term effectiveness (1, 2, 3 years of follow-up) based on retrospective analysis. To assess the CRT effectiveness, parameters of left ventricular (LV) reverse remodeling and signs characterizing the clinical CRT response were considered.

Material and methods. This single-center, retrospective, non-randomized study included data from 278 patients with implanted CRT devices. Quantitative criteria for assessing CRT effectiveness were determined using a two-step cluster analysis of patients 1, 2, and 3 years after CRT by LV reverse remodeling parameters.

Results. In the dataset with satisfactory division accuracy, after the first year, two clusters were identified, which are conventionally named as "non-responders" and "responders". Two and three years after therapy, patients were classified into three clusters: "non-responders", "responders" and "super-responders". For the obtained clusters, we found cutoff values for LV reverse remodeling parameters, which can be used as criteria for response to therapy.

The study identified the most informative time frames for assessing the postoperative CRT effectiveness 1, 2, 3 years after the surgery. At the same time, the clinical response to therapy is manifested earlier in comparison with the reverse LV remodeling.

Despite the high divisibility of patients into responders and non-responders, predictive models of CRT effectiveness created using the available data from standard diagnostic protocols for heart failure patients have insufficient accuracy to be used for making decisions on therapy appropriateness. This circumstance indicates the need to receive additional data to improve the forecasting quality.

Conclusion. The study revealed a period for assessing the clinical response and changes in LV reverse remodeling after CRT surgery, which is important for the optimal choice of postoperative therapy. It has been shown that in most cases, one year after surgery is sufficient to assess the clinical response, and the process of LV reverse remodeling can last up to two years on average.

When assessing the CRT effectiveness by reverse remodeling, along with a change in LV end-systolic volume (ESV), it is necessary to take into account LV end-diastolic volume (EDV) changes. The change in LV ejection fraction showed a significantly lower value among the analyzed parameters in assessing the CRT effectiveness. Based on the cluster classification of patients, a dividing rule was established for responders and non-responders in the first and second years after surgery with an accuracy of 97%: a decrease in LV ESV and EDV by 9% or more compared to preoperative values.

Keywords: cardiac resynchronization therapy, cardiac resynchronization therapy effectiveness, forecasting models, long-term postoperative period.

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[1]Institute of Immunology and Physiology, Yekaterinburg; [2]Ural State Medical University, Yekaterinburg; [3]Almazov National Medical Research Center, St. Petersburg; [4]Ural Federal University, Yekaterinburg, Russia.

Chumarnaya T. V.* ORCID: 0000-0002-7965-2364, Lyubimtseva T. A. ORCID: 0000-0002-8651-7777, Solodushkin S. I. ORCID: 0000-0002-1959-5222, Lebedeva V. K. ORCID: none, Lebedev D. S. ORCID: 0000-0002-2334-1663, Solovieva O. E. ORCID: 0000-0003-1702-2065.

*Corresponding author:
chumarnaya@gmail.com

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Heart failure (HF) is the most severe cardiovascular disease with a high risk of adverse events, including sudden cardiac death. The prevalence of HF in Russia reaches 7% and continues to grow every year, twice exceeding this value in other developed countries [1]. Based on numerous clinical studies, cardiac resynchronization therapy (CRT) is recognized as a non-medication method that improves functional status, improves the quality of life, and the survival rate of patients with HF [2]. CRT is aimed at reducing atrioventricular, inter- and intraventricular myocardial dyssynchrony, at increasing the left ventricular (LV) contractility. This treatment leads to reverse LV remodeling, as evidenced by an increase in LV filling time and ejection fraction (EF), as well as a decrease in LV end-diastolic (EDV) and end-systolic volumes (ESV) and a decrease in mitral regurgitation and interventricular septal dyskinesia [3].

The possibility of achieving the CRT effect is individual in each case, since it is associated with the functional and structural cardiac features, as well as with their changes over time. On the other hand, unsafe for patients and expensive implantation of such devices is often redundant due to inappropriate patient selection [4].

The development of patient selection algorithms, the choice of optimal conditions for surgical intervention and postoperative treatment based on modern research technologies remain urgent tasks of cardiology.

Numerous studies have made it possible to expand indications for CRT for patients with lower HF class, but more significant systolic dysfunction or a wide QRS complex with a failure of optimal medication therapy and disease progression [5, 6]. To date, there remains a number of potential opportunities for clarifying the stratification of patient selection for CRT and increasing the efficiency of these devices.

The question remains, in what time frame after CRT and by what indicators to evaluate the its effectiveness. Thus, the parameters used to assess the success of CRT in randomized clinical trials are not consistent with clinical practice [7, 8]. In most studies, efficacy is assessed by the characteristics of LV reverse remodeling, such as ESV and EF, while in clinical practice, an important criterion of efficacy is a relief of HF symptoms and improvement of the quality of life [9].

This study was aimed at finding the most informative period for assessing the effectiveness of CRT and quantitative criteria for it, as well as identifying predictors of response to CRT.

Material and methods

Study design. This single-center retrospective non-randomized study included 278 patients with implanted CRT devices according to national clinical guidelines [6]. The data collection period was 36 months. Patients were examined before CRT and after CRT in multiples of 12 months. The study was approved by the ethics committee of the Almazov National Medical Research Center.

Population. The mean age of patients was 63±12 years. At the time of CRT, 76% had sinus rhythm, 21% — permanent AF, 3% — complete atrioventricular block and atrial fibrillation. We analyzed LV remodeling parameters and heart valve status by transthoracic echocardiography. In addition, six-minute walk test and EQ- 5D-5L (Kansas) questionnaire results were analyzed to assess HF functional class.

There were following inclusion criteria:

- age >18;
- NYHA class II-IV HF at the outpatient stage of treatment;
- LVEF ⩽35% (Simpson method);
- QRS complex >20 ms;
- sinus rhythm, complete left bundle branch block;
- optimal medication therapy for HF;
- signed informed consent.

There were following exclusion criteria:

- prior myocardial infarction, transient ischemic attack, stroke <3 months before the start of the study;
- patients who were scheduled for myocardial revascularization or heart transplantation during the follow-up period;
- congenital and acquired defects, as well as heart tumors, LV aneurysm, when their surgical treatment was planned during the follow-up period;
- active inflammatory and autoimmune myocardial diseases;
- thyrotoxicosis at the time of enrollment;
- anemia with a hemoglobin ⩽90 g/l;
- diseases limiting life expectancy (<1 year).

Parameters for assessing the CRT effectiveness. Parameters of LV reverse remodeling: relative decrease in LV EDV (ΔEDV), relative decrease in LV ESV (ΔESV). A negative ΔEDV and ΔESV means a decrease in LV volumes in comparison with preoperative indicators. The relative increase in LVEF (ΔEF). A positive ΔEF means an increase in LVEF in comparison with the preoperative indicator. The clinical response was assessed by a decrease in HF functional class compared with the preoperative one.

Methods for determining the criterion for assessing the CRT effectiveness. The classification of these patients to determine quantitative criteria for assessing the effectiveness of CRT at various postoperative periods was carried out using a two-step cluster analysis. To assess the quality of connectivity and separability of clusters, a silhouette value was used, which is measured from -1 to 1. The value from -1 to 0,2 is considered unsatisfactory for separation into clusters, from 0,2 to 0,49 — moderate separability, from 0,5 to 1 — good separability. ROC analysis was used to assess the diagnostic value and find cut-off thresholds for clustering parameters. The area under the ROC curve (AUC) was used as a measure of diagnostic value. Cut-off thresholds were determined with a balance of sensitivity and specificity.

Models for predicting changes in reverse remodeling parameters at different postoperative periods. The following blocks of standard preoperative diagnostic protocols were used to construct models for predicting the values of ΔEDV, ΔESV, ΔEF at different postoperative periods:

- Demographic: sex, height, weight;
- Cardiovascular disease and prior surgery: myocardial infarction, stenting, CABG, radiofrequency ablation, valve replacement;
- Heart failure (HF): etiology of dilated cardiomyopathy (ischemic and non-ischemic), HF class (six-minute walk test, EQ-5D-5L questionnaire (Kansas));
- Electrocardiography: QRS, P, PQ, QT, the presence of blocks and delayed conduction;
- Echocardiography: LV EDV and ESV, LVEF, end-diastolic and end-systolic dimensions of the LV and right ventricle, left and right atrial dimensions. Presence/absence of interventricular and intraventricular dyssynchrony, according to tissue Doppler echocardiography;
- Medication therapy.

To improve the predictive models, the following characteristics obtained during the implantation of an implantable electronic device (IED) were used: location of pacing poles in right and left ventricular leads; electrocardiographic characteristics during pacing. For the forecast in 2nd and 3rd years after the operation, to improve the quality of models, we also used the characteristics ΔEDV, ΔESV, ΔEF in the first year after CRT.

Predictive models were created using stepwise logistic regression (criterion for stepwise selection of parameters: inclusion of a parameter in model with a significance $\leqslant$0,05; excluding a parameter from the model with a significance <0,10). The determination coefficient R^2 was used to assess the linear relationship between predicted parameters and predictors: the closer the value is to 1, the stronger the relationship. The R^2 coefficient provides an estimate of model quality: what percentage of cases this model is able to describe.

Statistical analysis and creation of information models were carried out using the IBM SPSS 23 program. For quantitative variables, the arithmetic mean and standard deviations (m±sd) were calculated in case of normal distribution. For nonnormally distributed variables, median and [25%; 75%] percentile were used. The critical level of significance was 0,05. The normal distribution of variables was assessed using the Shapiro-Wilk test. For pairwise comparisons, the nonparametric Wilcoxon signed-rank test was used. Comparison of two independent groups was carried out using the Mann-Whitney Test. Comparison with hypothetical median was performed using the one-sample Wilcoxon signed rank test.

Results

Analysis of CRT effectiveness in long-term postoperative period

The analysis of CRT performance within three years after surgery was carried out in order to determine the optimal postoperative period for assessing the CRT effectiveness.

LVEF

The analysis of changes in LVEF was carried out according to echocardiography before CRT and 1, 2 and 3 years after surgery (Figure 1).

It was shown that the mean LVEF increased significantly after implantation of CRT devices for all considered stages in comparison with the preoperative data (Figure 1).

For pairwise comparisons, in the first year after CRT initiation, there was a subgroup of 173 patients, of which in 77% of cases, LVEF increased, in 17% — decreased, and in 6% — remained unchanged. The percentage of LVEF increase in the first year after CRT was 28% [4; 57]. There was a significant difference in percentage of increase from zero (p=0,000).

The mean LVEF value 2 years after CRT did not significantly differ from the value of 1 year after CRT (35±9 and 33±8, p=0,070). However, the additional increase at the stage from 1 to 2 years was significantly different from zero (p=0,033) and amounted to 3% [-10; 24] (Figure 1). For pairwise comparisons, in the interval from one to two years, there was a subgroup of 119 patients, in 54% of which LVEF became higher, in 43% — lower, and in 3% — remained unchanged.

When comparing LVEF at the stage from 2 to 3 years after surgery, the difference was insignificant (35±9 and 36±9, p=0,459) and the additional increase in LVEF did not significantly differ from zero (p=0,326) (Table 1). For pairwise comparisons in the interval from 2 to 3 years after CRT, the subgroup included 88 patients: in 48% of cases, LVEF became higher, in 42% — lower, in 10% — remained unchanged.

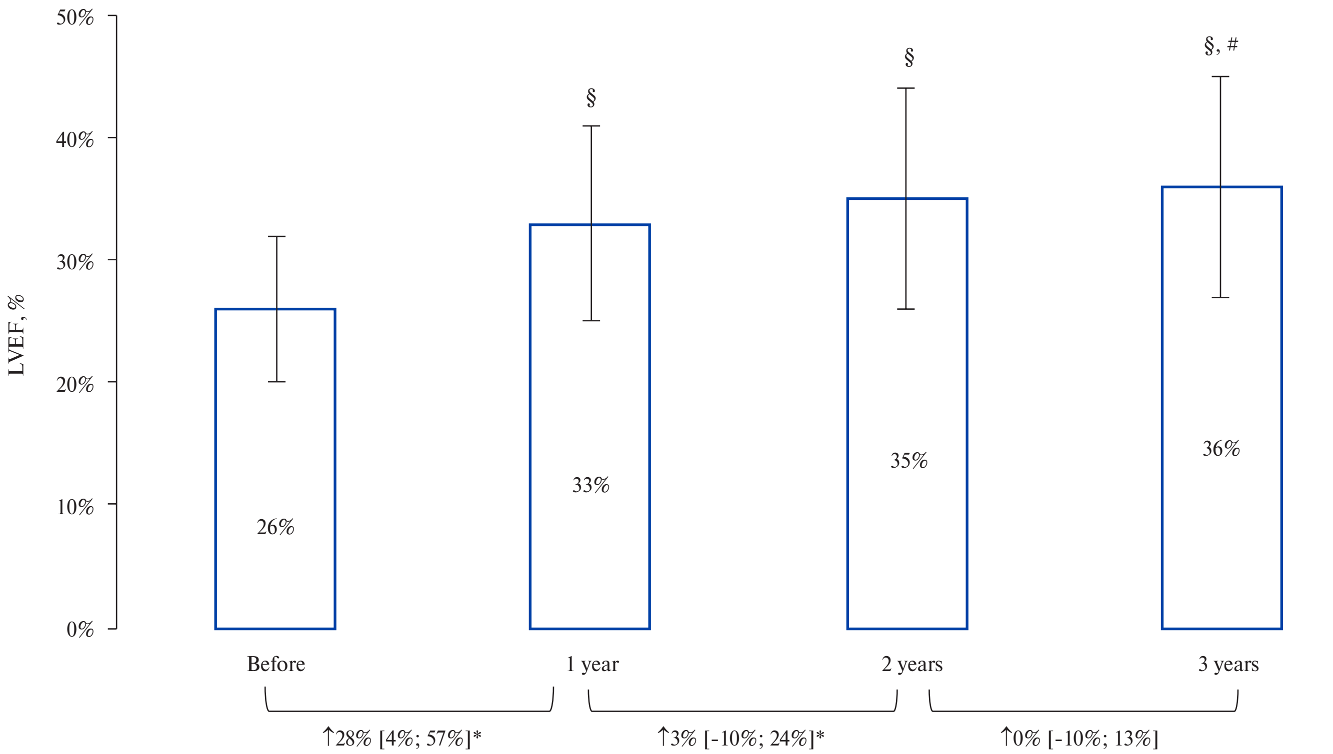

Figure 1. LVEF 1, 2, 3 years after CRT.
Note: ↑ — ΔEF (%) Me [25%;75%], * — p<0,05 ΔEF is significantly different from zero, § — p<0,05 comparison with LVEF before CRT, # — p<0,05 comparison with LVEF 1 year after CRT.
Abbreviations: LVEF — left ventricular ejection fraction, CRT — cardiac resynchronization therapy.

LV EDV

The analysis of changes in LV EDV was carried out according to echocardiography before CRT and 1, 2 and 3 years after surgery (Figure 2).

It was shown that the mean value of LV EDV significantly decreased after CRT device implantation at all considered stages in comparison with the preoperative data (Table 2).

For pairwise comparisons, in the first year after device implantation, there was a subgroup of 173 patients, of whom in 71% of cases, LV EDV decreased, in 29% — increased. The percentage of LV EDV reduction in the first year after CRT was 17% [-6%; 35%] with a significant difference from zero (p<0,001).

LV EDV value at 2 years after CRT did not significantly differ from the value at 1 year after CRT (240±101 and 231±91, p=0,286). The decrease at the stage from 1 to 2 years also did not differ significantly from zero (p=0,968) (Figure 2). For pairwise comparisons, in the interval from 1 to 2 years, there was a subgroup of 119 patients, of whom in 70% of cases, LV EDV decreased, in 29% — increased, in 1% — remained unchanged.

When comparing LV EDV at the stage from 2 to 3 years after surgery, the difference was insignificant (231±91 and 220±90, p=0,171) and the decrease did not significantly differ from zero (p=0,342) (Figure 2). For pairwise comparisons, in the interval from 2 to 3 years after CRT, the subgroup included 88 patients, of whom in 72% of cases, LV EDV decreased, in 28% — increased.

LV ESV

The analysis of changes in LV ESV was carried out according to echocardiography before CRT and 1, 2 and 3 years after surgery (Figure 3).

It was shown that the mean value of LV ESV significantly decreased after CRT device implantation at all considered stages in comparison with the preoperative data (Figure 3).

For pairwise comparisons, in the first year after device implantation, there was a subgroup of 173 patients, of whom in 73% of cases, LV ESV decreased, in 27% — increased. The percentage of LV ESV reduction in the first year after CRT was 21% [-4%; 39%] with a significant difference from zero (p<0,001).

LV ESV value at 2 years after CRT did not significantly differ from the value at 1 year after CRT (165±83 and 155±78, p=0,180). The decrease at the stage from 1 to 2 years also did not differ significantly from zero (p=0,577) (Figure 2). For

Table 1

Correlation analysis between HF class and LV reverse remodeling parameters

HF class		LV EDV				LV ESV				LVEF			
		До	1	2	3	До	1	2	3	До	1	2	3
Before	r	-0,01	-0,01	0,05	0,02	0,01	0,04	0,06	0,04	-0,06	-0,19	-0,11	-0,13
	p	0,97	0,97	0,62	0,83	0,86	0,56	0,49	0,71	0,35	0,01	0,24	0,23
1 year	r	0,08	0,20	0,17	0,32	0,08	0,23	0,22	0,34	-0,11	-0,24	-0,29	-0,31
	p	0,33	0,01	0,14	0,01	0,32	0,01	0,05	0,01	0,18	0,00	0,01	0,01
2 year	r	-0,188	0,27	0,21	0,24	-0,13	0,25	0,25	0,26	0,02	-0,16	-0,35	-0,26
	p	0,07	0,01	0,03	0,08	0,16	0,02	0,01	0,04	0,85	0,14	0,00	0,05
3 year	r	-0,14	0,32	0,33	0,27	-0,12	0,35	0,41	0,32	0,07	-0,33	-0,48	-0,41
	p	0,24	0,01	0,02	0,02	0,31	0,01	0,03	0,01	0,54	0,01	0,00	0,00

Abbreviations: EDV — end-diastolic volume, ESV — end-systolic volume, LVEF — left ventricular ejection fraction, HF — heart failure, r — Spearman's rank correlation coefficient, p — significance of difference r from zero.

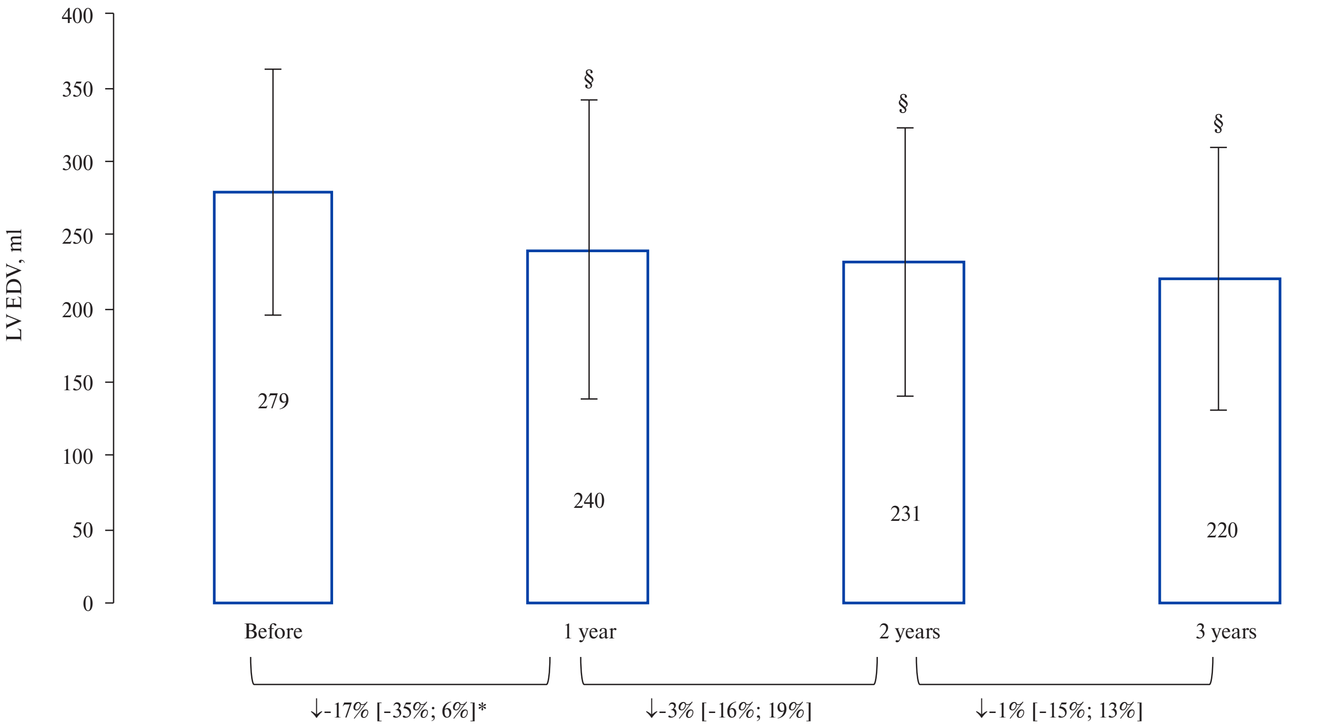

Figure 2. LV EDV 1, 2, 3 years after CRT.
Note: ↓ — ΔEDV (%) Me [25%;75%], * — p<0,05 ΔEDV is significantly different from zero, § — p<0,05 comparison with LV EDV before CRT.
Abbreviations: LV — left ventricle, CRT — cardiac resynchronization therapy, EDV — end-diastolic volume.

pairwise comparisons, in the interval from 1 to 2 years, there was a subgroup of 119 patients, of whom in 72% of cases, LV ESV decreased, in 27% — increased, in 1% — remained unchanged.

When comparing LV ESV at the stage from 2 to 3 years after surgery, the difference was insignificant (155±78 and 145±75, p=0,377) and the decrease did not significantly differ from zero (p=0,435) (Figure 2). For pairwise comparisons, in the interval from 2 to 3 years after CRT, the subgroup included 88 patients, of whom in 73% of cases, LV ESV decreased, in 27% — increased.

HF class

We analyzed changes in HF functional class in patients within 3 years after CRT (Figure 4).

In the subgroup of patients (n=80), for whom there was information on HF class at all stages, the following changes were observed — Table 3.

In 70,1% of patients, HF class improved over the entire period. After 1 year, a positive trend was observed in 48,8%. Taking into account the patients who did not show a favorable change (26%), it is possible to recommend evaluating the effectiveness of CRT 1 year after surgery.

Relationship of HF class and LV reverse remodeling parameters

The relationship between LV reverse remodeling parameters and HF was investigated. Correlation analysis showed a weak but significant relationship

Table 2

Descriptive statistics data for subgroups with/without decrease in HF class in the first year after CRT

Parameter		Decrease in HF class after 1 year		Significance of differences
		Yes	No	
LVEF (%)	Before	26±0,6	25±0,8	0,071
	1 year	34±0,8	32±1,1	0,052
	2 year	38±1,3	31±1,4	0,002
	3 year	39±1,5	32±2,2	0,007
LV ESV (ml)	Before	200±8	221±10	0,09
	1 year	142±7	190±12	0,003
	2 year	137±11	189±13	0,004
	3 year	129±11	191±16	0,006
LV EDV (ml)	Before	277±9	300±11	0,189
	1 year	213±9	275±15	0,002
	2 year	216±14	265±15	0,018
	3 year	204±14	272±19	0,011

Abbreviations: EDV — end-diastolic volume, ESV — end-systolic volume, LVEF — left ventricular ejection fraction, HF — heart failure.

Table 3

Combinations of changes in HF class

Improvement (decrease in HF class), n=56	
Decreased by 1 year and remained unchanged	32,5%
Decreased by 2 year and remained unchanged	10%
Decreased by 3 year	11,3%
Decreased by 1 and 2 years, and remained unchanged	11,3%
Decreased by 1 year, unchanged by 2 year, decreased by 3 year	5%
Unfavorable changes (increase in HF class or no changes), n=24	
Remained unchanged, increased by 2 year	1,3%
Decreased by 1 and 2 years and increase by 3 year	1,3%
Decreased by 1 year, increased by 2 year, unchanged by 3 year	1,3%
Did not change	26%

Abbreviation: HF — heart failure.

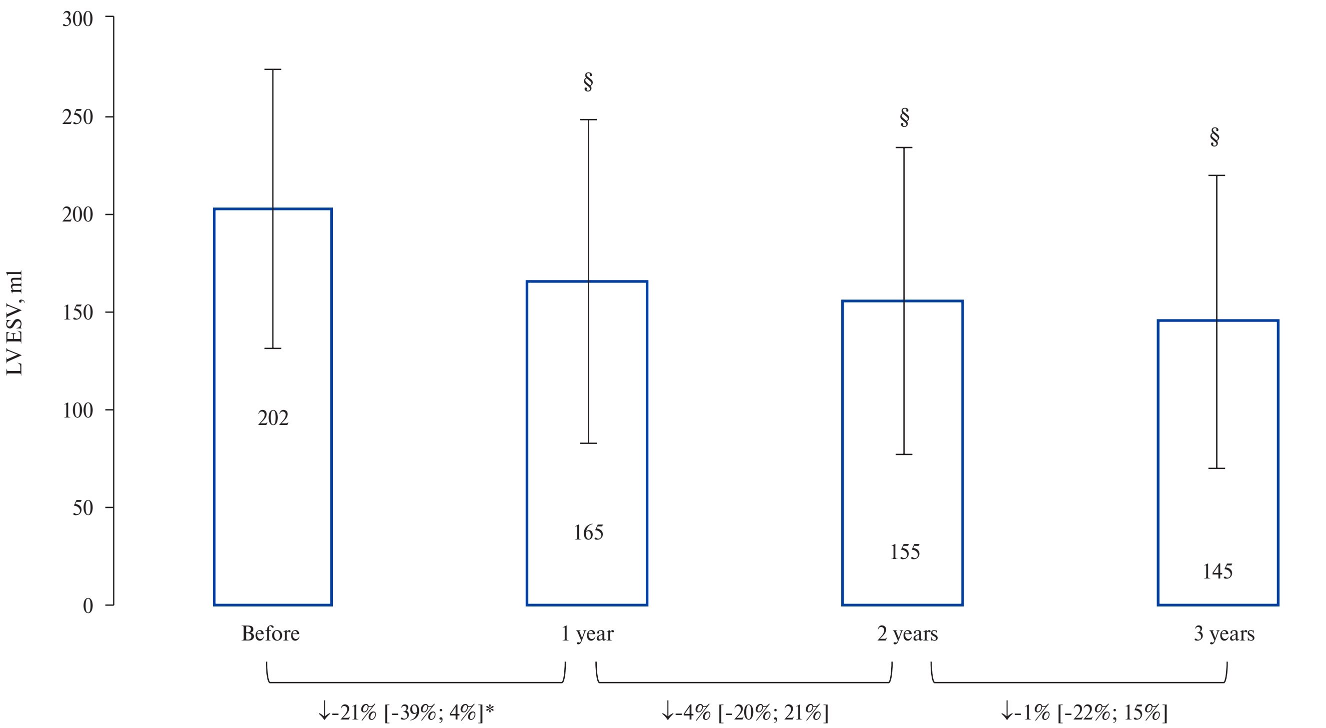

Figure 3. LV ESV 1, 2, 3 years after CRT.
Note: ↓ — ΔESV (%) Me [25%;75%], * — p<0,05 ΔESV is significantly different from zero, § — p<0,05 comparison with LV ESV before CRT.
Abbreviations: LV — left ventricle, CRT — cardiac resynchronization therapy, ESV — end-systolic volume.

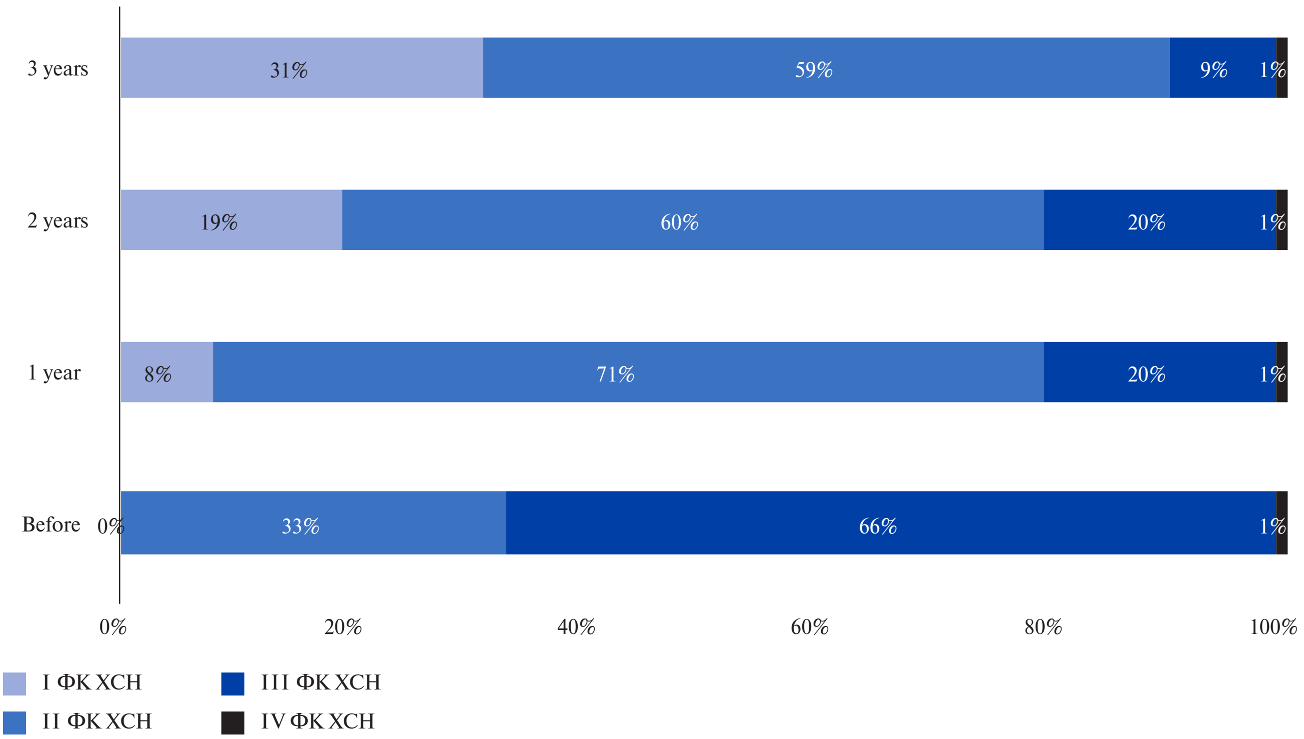

Figure 4. HF class 1, 2, 3 years after CRT.
Abbreviations: HF — heart failure.

between LV reverse remodeling parameters and HF at all postoperative stages considered (Table 1).

To compare the timing of a decrease in HF class and LV reverse remodeling after CRT, the group of patients was divided into two subgroups: group 1 — HF class decreased during the first year after CRT, group 2 — HF class did not decrease (remained the same or increased). The subgroups did not significantly differ in LVEF, ESV, and EDV before CRT initiation (Table 1). In the first year after CRT implantation, in patients whose HF class decreased, there was a tendency for a greater increase in LVEF compared with patients whose HF class did not decrease (from 26% to 34% and from 25% to 32%, respectively (Table 1)), but this trend was insignificant. Only after two years was there a significant difference between LVEF for the considered subgroups. In the group of patients whose HF class decreased in the first year after CRT, LV ESV and EDV became significantly lower compared to group of patients whose HF class did not decrease in the first postoperative year. The same findings were observed at 2 and 3 years after CRT.

Criterion for assessing the CRT effectiveness in terms of LV reverse remodeling. A two-step cluster analysis was used to classify patients at 1, 2, and 3 years after CRT. The classification was carried out depending on LV ΔEF, ΔESV and ΔEDV at the indicated time. The change in HF class was assessed during clustering, but did not participate in the classification, because for all periods, the change in HF class had practically zero importance during separation and sharply reduced the silhouette value of clustering.

In the first year, with the best silhouette value of cluster connectivity of 0,54, 2 clusters were identified (Figure 5). The most important parameter for cluster separation was LV ΔESV, then, in decreasing order of importance, LV ΔEDV and ΔEF (Figure 6). We conditionally named the first cluster "non-responders", the second cluster "responders", and found the separation criteria for them (Table 4, Figure 5). In "non-responders" cluster in a larger number of patients, the HF class did not change (increase — 2%; no changes — 51%; decrease — 47%), while in the cluster of "responders", there were more patients who had a decrease HF class (increase — 1%; no changes — 38%; decrease — 61%).

At the stage of two years after CRT, with the best cluster connectivity of 0,57, 3 clusters were identified. The most important parameter in dividing the clusters, as in the first year, was LV ΔESV with a highest value of 1,00. ΔEDV was also of high importance in separation, while ΔEF had the least effect on clustering (Figure 6). Thus, the first cluster included patients with unfavorable changes in ESV, EDV and LVEF, and 90% of it consisted of patients from the "non-responder" cluster obtained from

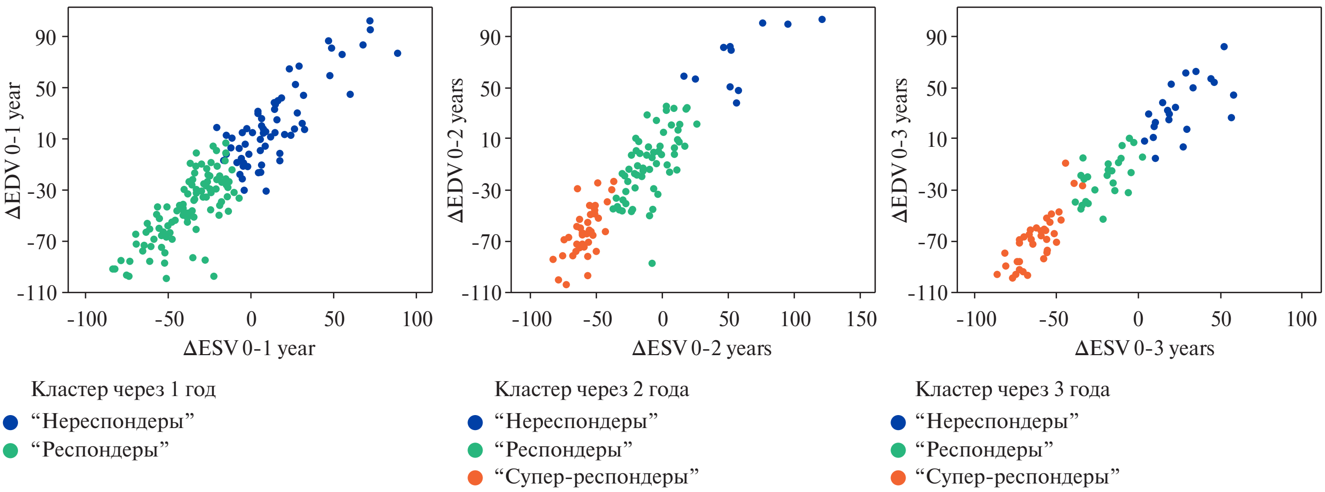

Figure 5. Clustering at different postoperative periods.
Abbreviations: ESV — end-systolic volume, EDV — end-diastolic volume.

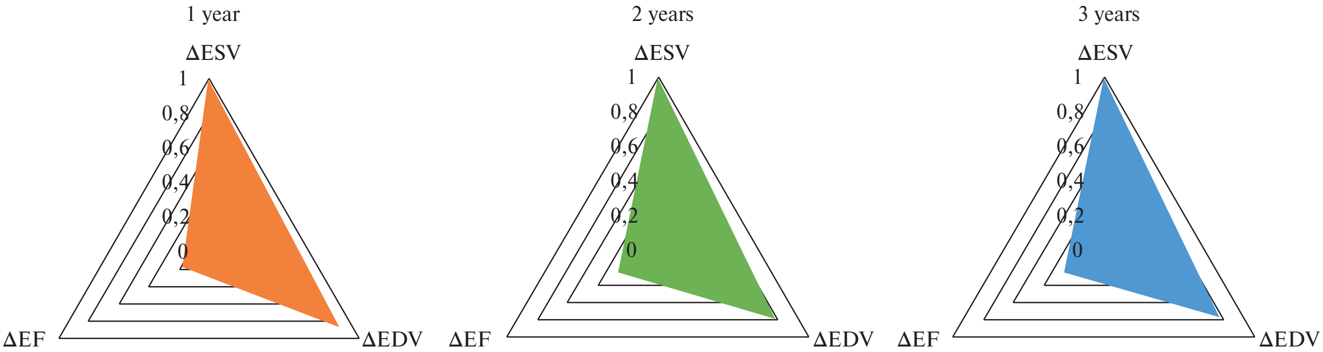

Figure 6. Importance of parameters for clustering in the considered postoperative periods.
Abbreviations: ESV — end-systolic volume, EDV — end-diastolic volume, EF — ejection fraction.

data for 1 year. The second and third clusters were patients with favorable dynamics. In the second cluster, 54% of patients in the first year were "non-responder" cluster and 46% — "responders" cluster. The third cluster consisted entirely of patients who were included in the "responders" cluster in the first year. According to data for the second year, we conditionally named the resulting clusters: the first cluster — "non-responders", the second cluster — "responders" and the third — "super-responders". In the group of "non-responders", there was an increase in HF class in 8%, no change — in 75%, and a decrease — in 17%; among "responders" and "super-responders", an increase in HF class was observed in 2%, no change — in 31%, and a decrease — in 67%.

Three years after CRT, 3 clusters were also identified with the best cluster connectivity of 0,56. The most important parameter for cluster separation was LV ΔEDV, slightly less important — ΔESV, and ΔEF had the least effect on clustering (Figure 6). As in the previous stage, the first cluster included patients with negative changes in ESV, EDV and LVEF and 100% of it consisted of patients from the "non-responder" cluster obtained from the second year. The second and third clusters are patients with favorable dynamics, consisting of patients of the "responder" and "super-responder" clusters obtained from the second year. Among "non-responders", an increase in HF class was observed in 8%, no change — in 81% and a decrease — in 11%; among the "responders" and "super-responders", HF class remained unchanged in 12% of patients, and in 88% there was a decrease in HF class.

For the obtained clusters, we found the separation criteria (Table 4, Figure 5). Based on the assessment of importance of clustering parameters, diagnostic value and obtained cut-off thresholds for these parameters, in the first year after CRT, "responders" should be considered as with a relative decrease in LV ESV ⩾10%, in LV EDV ⩾9% compared to preoperative data. Two years after CRT, there were criteria for separability of clusters as follows: "non-responders" are the same as according to first year —

Table 4

Cluster analysis of LV reverse remodeling parameters

Year	Parameter	Cluster	Median (%) [25%; 75%]	Cut-off threshold (%), (Se, Sp)	AUC [95% CI]	P
1	ΔESV	“non-responders” (n=67, 39%)	8 [-4; 25]	>-9 (0,96,0,91)	0,995 [0,989; 1,00]	0,000
		“responders” (n=106, 61%)	-36 [-52; -25]	⩽-9 (0,96,0,91)		
	ΔEDV	“non-responders”	11 [-3; 24]	>-9 (0,9, 0,89)	0,962 [0,939; 0,985]	0,000
		“responders”	-30 [-43; -18]	⩽-9 (0,9, 0,89)		
	ΔLVEF	“non-responders”	5 [-12; 26]	<15 (0,75, 0,72)	0,754 [0,678; 0,830]	0,000
		“responders”	40 [15; 71]	⩾15 (0,75, 0,72)		
2	ΔESV	“non-responders” (n=24, 20%)	52 [50; 62]	>-9 (1, 0,92)	0,998 [0,990; 1]	0,000
		“responders” (n=59, 50%)	-10 [-20; 3]	⩽-9 и >-37 (1, 0,98)		
		“super-responders” (n=36, 30%)	-56 [-64; -51]	⩽-37 (1, 1)		
	ΔEDV	“non-responders”	78 [5; 86]	>-9 (1, 0,80)	0,959 [0,929; 0,992]	0,000
		“responders”	-13 [-26; -4]	⩽-9 и >-40 (0,95, 0,85)		
		“super-responders”	-65 [-77; -52]	⩽-40 (0,9, 0,9)		
	ΔLVEF	“non-responders”	6 [-27; 25]	<0 (0,59, 0,80)	0,677 [0,491; 0,860]	0,045
		“responders”	18 [0; 40]	⩾0 и <43 (0,71, 0,80)		
		“super-responders”	72 [47; 115]	⩾43 (0,8, 0,8)		
3	ΔESV	“non-responders” (n=23, 26%)	18 [11; 33]	>0 (1, 0,99)	0,998 [0,991; 1]	0,000
		“responders” (n=26, 30%)	-19 [-33; -12]	⩽0 и >-37 (0,98, 0,98)		
		“super-responders” (n=39, 44%)	-63 [-73; -56]	⩽-37 (0,97, 0,97)		
	ΔEDV	“non-responders”	28 [20; 49]	>0 (0,95, 0,95)	0,978 [0,952; 1]	0,000
		“responders”	-20 [-37; -9]	⩽0 и >-40 (0,93, 0,93)		
		“super-responders”	-70 [-87; -61]	⩽-40 (0,92, 0,92)		
	ΔLVEF	“non-responders”	13 [0; 30]	<15 (0,69, 0,67)	0,769 [0,661; 0,877]	0,000
		“responders”	27 [13; 39]	⩾15 и <42 (0,75, 0,73)		
		“super-responders”	77 [56; 119]	⩾42 (0,82, 0,82)		

Abbreviations: CI — confidence interval, EDV — end-diastolic volume, ESV — end-systolic volume, LVEF — left ventricular ejection fraction, HF — heart failure, Se — sensitivity, Sp — specificity, P — significance of AUC.

those patients with LV ESV and EDV not exceeding 9% in 2 years. With a decrease in LV ESV and EDV by more than 37% and 40%, respectively, the patient falls into the cluster of “super-responders”. In 3 years after CRT, the border between the clusters of “non-responders” and “responders” changes. So, with any decrease in LV ESV and EDV that is different from zero, within 3 years after CRT, the patient falls into the cluster of “responders”. The borderline between “responders” and “super-responders” remains the same as for a period of 2 years (Table 4).

Information models for predicting CRT effectiveness

Using logistic regression, we created prognostic models for entering a cluster with unfavorable changes (“non-responders”) in reverse remodeling parameters and to clusters with favorable changes (“responders” and “super-responders”) (Table 5). To create the models, we used the blocks of preoperative diagnostic protocols described in the section “Material and Methods”.

The created models based on preoperative diagnostic protocols turned out to be significant, but the predictive power of these models was low and the classification accuracy did not exceed 62% (Table 5). When using the parameters obtained during IED implantation, the prediction quality in the first year improved and the classification accuracy increased to 70%. Using information on changes in LVEF, ESV, and EDV in the first year after CRT initiation, it was possible to improve the accuracy of prognostic models for the second and third postoperative years, but their accuracy also did not exceed 72%.

Discussion

Three-year analysis was carried out in order to determine the most informative postoperative period for assessing the CRT effectiveness, the search for a reliable quantitative rule for assessing the CRT

Table 5

Information models for CRT prognosis depending on postoperative period

Parameter	Unstandardized coefficients		R^2	P	Accuracy of classification
	Value	P			
1 year					
Parameters before CRT					
Sex (0-M; 1-F)	0,72	0,033	0,22	0,031	62%
Constant	0,28	0,191			
Improvement of the model (+ parameters during IED implantation)					
Sex (0-M; 1-F)	0,92	0,032	0,48	0,000	70%
Left atrial area	-0,59	0,046			
QRS on pacing	-0,02	0,019			
Constant	6,34	0,002			
2 year					
Parameters before CRT					
LV ESV before	-0,01	0,024	0,31	0,042	58%
Constant	1,58	0,026			
Improvement of the model (+ change in EF, ESV, EDV in the first year)					
ΔESV by 1 year	-0,04	0,000	0,64	0,000	69%
LV ESV before	-0,01	0,179			
Constant	1,67	0,033			
3 year					
Parameters before CRT					
LVEF before	0,07	0,059	0,19	0,010	53%
Constant	-1,68	0,80			
Improvement of the model (+ change in EF, ESV, EDV in the first year)					
LVEF	0,03	0,590	0,47	0,001	72%
ΔESV by 1 year	-0,08	0,000			
Constant	1,18	0,452			

Abbreviations: IED — implantable electronic device, EDV — end-diastolic volume, ESV — end-systolic volume, LVEF — left ventricular ejection fraction, CRT — cardiac resynchronization therapy.

effectiveness in indicated periods and the search for predictors of changes in reverse remodeling parameters at 1, 2, 3 years after surgery.

First, we assessed the response to CRT using parameters characterizing LV reverse remodeling. In the majority of patients, LV ESV and EDV decreases compared to preoperative ones during all three years after CRT. The rate of decline in these indicators slows down 2 and 3 years after CRT initiation and does not significantly differ from zero. Based on this, it is reasonable to evaluate the change in these parameters 1 year after CRT implantation. At the same time, in most patients, LVEF continues to increase in comparison with the preoperative value for a longer period at three years after CRT placement, although the growth rate of LVEF 2 and 3 years after surgery also slows down compared to the first year after implantation. Considering that in the interval from a year to two years, an increase in LVEF is observed that is significantly different from zero, and at the stage from two to three years, the increase does not significantly differ from zero, to assess the change in LVEF 2 years after CRT should be considered. Similar results were obtained in studies reviewed by Cleland JG, et al. [10].

The assessment of clinical response to CRT was carried out by assessing the change in HF class within three years after CRT initiation. A decrease in HF class is observed throughout the study as compared to the preoperative data, while improvement in HF class over the entire follow-up period is demonstrated by 70,1% of patients. After 1 year, improvement is observed in 48,8%, and in 26% of patients there is no improvement either in the first year or in further periods under consideration. So, 74,5% of patients after the first year have a clinical response to therapy. In this regard, evaluating the effectiveness of CRT in changing the HF class 1 year after implantation should be considered.

Based on results obtained, a hypothesis has been developed that the decrease in HF class occurs earlier than the reverse LV remodeling. We showed that in patients with decrease in HF class a year after CRT, both EDV and ESV is significantly less compared to LV volume in patients without a decrease in HF class, but the difference between the LVEF in the considered groups remains insignificant up to 2 years of CRT. Reverse remodeling lasts up to 2 years after the CRT initiation, while we observe a decrease in HF class already a year after implantation, and then it does not decrease in most cases. These findings support the hypothesis of an earlier decrease in HF class compared with reverse remodeling. The time interval for assessing the success of CRT remains an open question [7, 10]; in most studies, the success of CRT is considered 6 months after therapy. As our studies show, this period is insufficient to assess the effectiveness of therapy. Similar conclusions were made in the study by V. Kuznetsov, et al. [11], which showed that the most "responders" and all "super-responders" appear in the late postoperative period. Moreover, patients with a rapid response to CRT in 3-month postoperative period had lower 5-year survival rates after starting CRT [11].

Quantitative criteria for assessing CRT success are also under discussion. A review [4, 10] provides about ten criteria for CRT effectiveness used in different studies using the parameters of LV reverse remodeling. To objectify quantitative parameters to assess the effectiveness of CRT, we applied a two-step cluster analysis and performed an automated classification of patients at 1, 2, and 3 years after CRT according to reverse remodeling parameters. For all postoperative periods, the relative decrease in LV ESV and EDV are of high importance when dividing into clusters, while the change in LVEF had lower significance during clustering. In a period of 1 year after CRT, there are 2 clusters with good separability. We conditionally named one cluster with unfavorable changes of reverse remodeling parameters "non-responders", and a cluster with improvement in reverse remodeling parameters — "responders". There were following criterion for evaluating the effectiveness in the first year after CRT based on cluster analysis: a decrease in LV ESV and EDV by 9% or more compared to preoperative data [4]. In further periods after the start of CRT, 3 clusters with good separability are distinguished. One cluster, as in the first year, is "non-responders". But patients with improvement are divided into 2 clusters, which we called "responders" and "super-responders". Stratification of patients into a cluster of "super-responders" is consistent with studies that indicate super-responders precisely in the long-term postoperative periods [11-13], and according to our data, this occurs 2 years after CRT. There were following cluster separability criteria: "non-responders", as in the first year, are patients with change in LV ESV and EDV did not exceed 9% for 2 years. With a decrease in LV ESV and EDV by more than 37% and 40%, respectively, the patient falls into the cluster of "super-responders". Three years after CRT, the border between the clusters of "non-responders" and "responders" slightly changes, so with any decrease in LV ESV and EDV within 3 years after CRT, the patient falls into the cluster of "responders". This result may be associated with the smallest, compared to the past, cohort of 88 patients whose data were used for clustering. The criteria for falling into the "super-responders" cluster are the same as in the previous period.

Using the criteria for evaluating the success of CRT, obtained based on our cluster analysis, using logistic regression, prognostic models of CRT effectiveness were constructed according to preoperative parameters obtained in the clinic with standard diagnostic protocols for patients with HF. Although the created models show significance, the predictive power of these models is low. Thus, the model created based on preoperative data for predicting the response to therapy after 1 year includes only patient sex, has a R^2 <0,22. So, the model correctly describes only 22% of cases, while the classification accuracy in the considered sample of 62% is also low. With an increase in postoperative period, the predictive power of models decreases even more. When using the additional characteristics obtained during IED implantation, as well as LV ΔEDV, ΔESV, ΔEF one year after CRT implantation, to predict the response in 2- and 3-year period, the predictive power of the models increases, but R^2 does not exceed 0,64, and the classification accuracy is 72%. The results obtained indicate that the considered blocks of preoperative diagnostic parameters and patient stratification for CRT do not allow significantly predicting the effectiveness of CRT in the long-term postoperative period, which is consistent with studies [14, 15].

Study limitations. The study considered intervals that are multiples of 1 year after therapy; retrospective data did not allow for an additional study at 3, 6, 18, 30 months after therapy, which would make it possible to more accurately assess the timing of response to CRT.

A decrease in the number of patients in a cohort after 2 and especially 3 years after CRT compared to the number of patients after 1 year could affect the accuracy of assessing changes in EDV, ESV, EF, HF class and the accuracy of clustering.

Conclusion

The study revealed a period for assessing the clinical response and changes in LV reverse remodeling after CRT surgery, which is important for the optimal choice of postoperative therapy. It has been shown that in most cases, one year after surgery is sufficient to assess the clinical response, and the process of LV reverse remodeling can last up to two years on average.

When assessing the CRT effectiveness by reverse remodeling, along with a change in LV ESV, it is necessary to take into account LV EDV changes. The change in LVEF showed a significantly lower value among the analyzed parameters in assessing the CRT effectiveness. Based on the cluster classification of patients, a dividing rule was established for responders and non-responders in the first and second years after surgery with an accuracy of 97%: a decrease in LV ESV and EDV by 9% or more compared to preoperative values.

Predictive models of CRT effectiveness, based on standard preoperative diagnostic protocols for HF patients, are not sufficiently accurate to be used for making decisions about the appropriateness of therapy. This indicates the need to receive additional data to improve the quality of prediction.

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