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Radionuclide imaging for feasibility of target left ventricular lead placement in patients with heart failure scheduled for cardiac resynchronization therapy

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Aim. To assess the feasibility and effectiveness of target left ventricular (LV) lead placement using the radionuclide imaging and changes of myocardial perfusion (MP) and cardiac sympathetic neural activity (SNA) in patients with heart failure (HF) before and after cardiac resynchronization therapy (CRT).

Material and methods. This prospective, observational study included 15 patients (9 men, 61 [58; 72] years old) with HF who were referred for CRT. Patients underwent radionuclide imaging with assessment of MP and cardiac SNA with ^{123}I-MIBG. All patients underwent implantation of CRT devices with target LV lead placement. Target LV lead placement was performed in accordance with preoperative data on ^{99m}Tc-MIBI myocardial perfusion scintigraphy and intraoperative data on coronary sinus (CS) anatomy. After successful implantation, patients were assigned to the group 1 (target LV lead placement). In case of targeted placement inability, the LV lead was implanted into the available CS branches — group 2. The patients were followed up within period of 3-6 months after surgery.

Results. Target LV lead placement was performed in 9 (60%) of 15 patients (group 1). In 6 (40%) of 15 patients, targeted implantation was not possible and LV lead was implanted anatomically (group 2). The follow-up period was 4 [3.5; 4.5] months. Patients from group 1 demonstrated a significant improvement of myocardial perfusion compared with preoperative data: summed stress score improved from 16,2±12,2 to 10,8±12,8 (p=0,007), summed rest score — from 15,2±12,5 to 9,8±12,9 (p=0,008), respectively. A significant change in the ^{123}I-MIBG scintigraphy of cardiac SNA was also observed: an improvement in the delayed heart/mediastinum ratio from 1,4±0,2 to 1,63±0,1 (p=0,02) and an improvement in the washout rate from 13,2±5,6% to 7,8±4,7% (p=0,026), respectively. These parameters did not show any significant difference between the groups and within the anatomical positioning group.

Conclusion. In patients with HF scheduled for CRT, the target LV lead placement using radionuclide imaging results in an improvement of myocardial perfusion and cardiac SNA compared with baseline data and does not have differences compared to anatomical positioning. Further studies are needed to assess the role of radionuclide imaging in CRT.

Key words: cardiac resynchronization therapy, myocardial perfusion, sympathetic neural activity, scintigraphy.

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Over the past two decades, cardiac resynchronization therapy (CRT) has proven the effectiveness in the treatment of patients with heart failure (HF), left ventricular (LV) systolic dysfunction and a wide QRS complex, leading to an improvement in the clinical and functional status, a decrease in morbidity and mortality [12]. Nevertheless, despite the search for optimal candidates, the proportion of non-responders to CRT can reach 40% [3, 4].

Currently, the search for methods improving the efficiency of patient selection is relevant, which in turn will improve the response to CRT [5, 6]. Among the methods of preoperative selection, there are data on the use of radionuclide imaging, which still have no alternative in the comprehensive assessment of LV myocardial perfusion [7] and sympathetic activity [8].

We hypothesized that target lead placement during CRT to the area of preserved myocardial perfusion (MP) may lead to a decrease in the severity of perfusion disorders and an improvement in cardiac sympathetic neural activity (SNA).

Material and methods

This prospective, observational study included patients with NYHA class II-III HF, QRS >130 ms, LV ejection fraction (LVEF) <35%, corresponding to class I or IIA for the CRT device implantation [2]. The main exclusion criteria were severe non-cardiac comorbidities with a life expectancy <1 year, acute cardiovascular diseases requiring urgent intervention, persistent atrial fibrillation. This study was performed in accordance with the Helsinki declaration and Good Clinical Practice standards. The medical ethics committee of Meshalkin National Medical Research Center approved this study. All patients signed informed consent. This study was supported by a grant from the Russian Science Foundation (project № 17-75-20118).

After screening, patients meeting the inclusion/exclusion criteria underwent electrocardiography, echocardiography, stress/rest myocardial perfusion scintigraphy with ^{99m}Tc-methoxyisobutylisonitrile (^{99m}Tc-MIBI), myocardial scintigraphy with ^{123}I-meta-iodobenzylguanidine, coronary angiography as indicated. After that, all patients underwent implantation of CRT devices with an attempt of targeted placement (TP) of LV lead. Targeted LV lead placement was defined as a combination of preoperative scintigraphy data and the presence of a corresponding branch of the coronary sinus (CS) during surgery with the possibility of lead implantation with satisfactory stimulation thresholds. At the same time, according to scintigraphy data, the accumulation of the perfusion indicator was semi-quantitatively determined in each segment. LV segments with accumulation of radiopharmaceutical >50% were considered as areas of optimal lead position [9, 10] (Figure 1A). Upon successful implantation, patients were assigned to group 1 (lead TP). If TP was impossible, the LV lead was implanted into the accessible CS branches with satisfactory thresholds of stimulation and sensitivity (group 2, anatomical placement).

The main purpose of the study was to assess the feasibility and effectiveness of target LV lead placement using the radionuclide imaging and changes of MP and cardiac SNA in patients with HF before and after CRT.

There were following secondary aims: intraoperative complications, percentage of responders, and echocardiography data. Responders were defined as patients with a 15% decrease in LV end-systolic volume (ESV) compared to baseline EchoCG data [4, 11].

Radionuclide imaging. All patients underwent stress/rest cardiac single-photon emission computed tomography (SPECT) with ^{99m}Tc-MIBI, as well as planar scintigraphy with ^{123}I-MIBG to assess the cardiac SNA (Figure 1D).

Scintigraphy were performed using a dual detector system Infinia Hewkeye (GE Healthcare, Israel). During cardiac SPECT, 16 projections were recorded with each detector located at an angle of 90° to each other with 180° orbit around the patient.

Myocardial perfusion scintigraphy with ^{99m}Tc-MIBI. Myocardial perfusion scintigraphy was performed using ^{99m}Tc-MIBI at a dose of 570-950 MBq. Image recording was performed 40-60 min after injection. ^{99m}Tc photopeak of 140 keV was set as

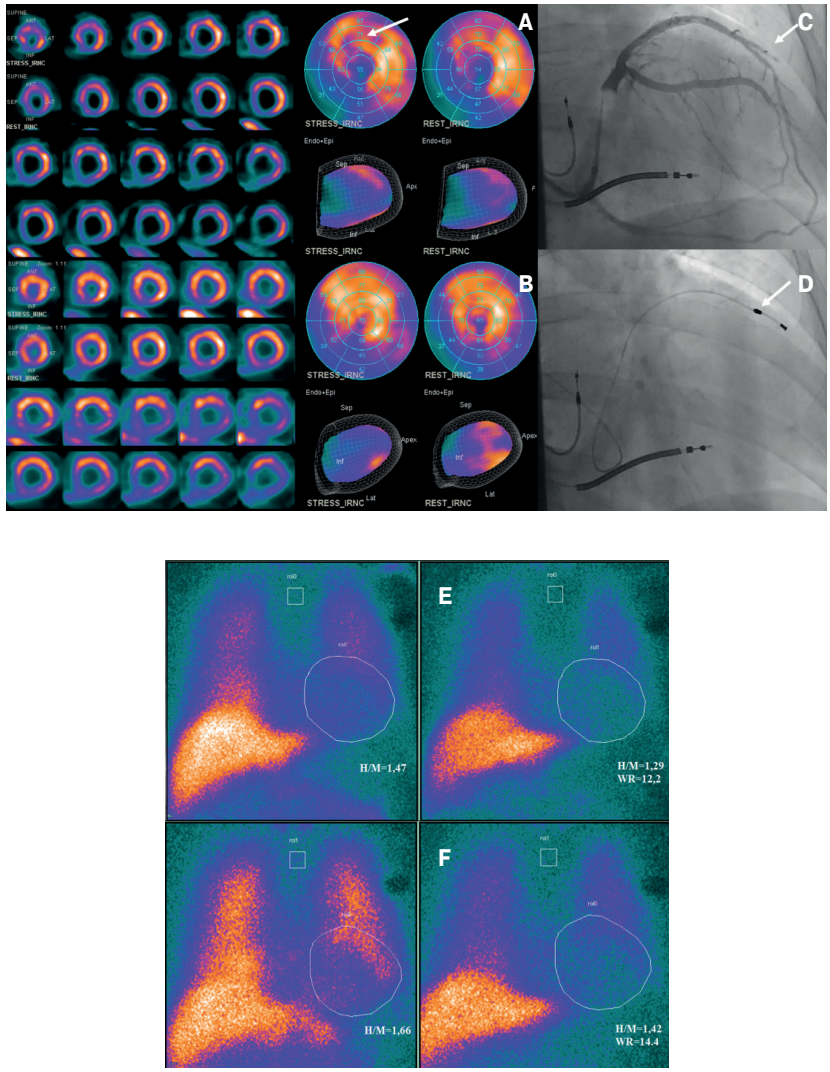

Figure 1. Assessment of myocardial perfusion and cardiac sympathetic neural activity before and after CRT.
Note: A — data of myocardial perfusion scintigraphy before CRT device implantation. There are signs of hypoperfusion in the apical, inferior and inferior septal areas of the LV (indicated by the red arrow). **B** — results of control myocardial perfusion scintigraphy 4 months after TP of LV lead during CRT implantation. There is an improvement in LV myocardial perfusion in the apex, as well as in the apical and middle parts of the inferior, inferior septal area (indicated by the green arrow). **C, D** — intraoperative data. **C** — contrasting of coronary sinus branches. **D** — TP of lead into the anterolateral coronary sinus branch. The white arrow indicates the anterolateral branch of coronary sinus and the LV lead position. **E, F** — cardiac scintigraphy with ^{123}I-MIBG. According to cardiac scintigraphy with ^{123}I-MIBG, compared with preoperative values (**E**), control images (**F**) showed a significant improvement in radiopharmaceutical accumulation.

the energy window; the energy window width was symmetrical and amounted to 20%. The recording duration was 15 minutes. The results were processed using a specialized workstation (Xeleris; GE Healthcare, Haifa, Israel).

For the study, a 2-day protocol (stress-rest) was used. We performed adenosine pharmacological stress (0,14 mg/kg/min) for 4 minutes. Images were recorded 40-60 minutes after the radiopharmaceutical introduction. The rest testing was carried out 24 h after the stress injection. The imaging was also carried out after 40-60 min.

Evaluation of LV MP was performed in accordance with the guidelines of the European Association for Nuclear Medicine (EANM) using a 17-segment model, a 5-point scale [12]. We calculated summed rest score (SRS), summed stress score (SSS) and summed difference score (SDS). The SRS and SSS are calculated during the rest and stress parts of the study, respectively, and the SDS is the difference between the two. Stress-induced perfusion defects were established when the accumulation of radiopharmaceuticals improved (by more than 10%) at rest, compared with the stress imaging.

Table 1

Preoperative characteristics of patients

Parameter	n=15
Men, n (%)	9 (60)
Age, years	61 [58; 72]
Hypertension, n (%)	10 (66,7)
Diabetes, n (%)	4 (26,7)
History of stroke/TIA, n (%)	1 (6,7)
Paroxysmal AF, n (%)	4 (26,7)
Coronary artery disease, n (%)	11 (73,3)
NYHA class II, n (%)	1 (6,7)
NYHA class III, n (%)	14 (93,3)
QRS width, ms	157,3±26,3
LVEF, %	28±7
LV EDV, %	226±91
LV ESV, %	162±78
PD corresponding to CA system	
ADA	6
CxA	1
RCA	11

Abbreviations: PD — perfusion defect, CA — coronary artery, EDV — end-diastolic volume, ESV — end-systolic volume, CxA — circumflex artery, RCA — right coronary artery, ADA — anterior descending coronary artery, TIA — transient ischemic attack, LVEF — left ventricular ejection fraction, AF — atrial fibrillation, NYHA — New York Heart Association.

Myocardial scintigraphy with ^{123}I-MIBG was performed 1-2 days after myocardial perfusion 15 and 240 minutes after intravenous administration of 110-370 MBq. The recording duration was 10 min. ^{123}I-MIBG photopeak of 159 keV was set as the energy window; the energy window width was symmetrical and amounted to 20%. To assess the total cardiac SNA in early and delayed phases, the heart-to-mediastinum ratio (H/M) and the washout rate (WR) were calculated [13].

Implantation of CRT devices. The implantation technique was standard and was described in detail earlier [14]. Briefly, after contrasting the CS branches, a pt of LV lead TP was made to the area of the preserved MP according to the scintigraphy data (Figure 1A, C, D). In case of TP impossibility in this area, the LV lead was implanted into the CS branch with satisfactory thresholds of sensitivity and stimulation, avoiding the LV apex. Right atrial (RA) leads were implanted into the RA appendage, and in the right ventricular (RV) leads — into the middle third of the interventricular septum.

Follow-up examinations. After the surgery, all patients were advised to continue taking optimal drug therapy for HF. The stimulation parameters were adjusted using programmers of certain CRT models without echocardiography guiding, focusing on the QRS width. AV delay parameters were kept nominal, and interventricular delay was optimized to achieve the minimum QRS width. Follow-up examination was carried out in the period of 3-6 months after surgery. Patients underwent functional status assessment, echocardiography, as well as stress/rest myocardial scintigraphy with ^{99m}Tc-MIBI (Figure 1B) and scintigraphy with ^{123}I-MIBG for comparison with preoperative data (Figure 1E, F).

Statistical analysis. Statistical processing was performed using the STATA software (version 12.1). Quantitative variables are presented as median and interquartile range [25 and 75] or mean ± standard deviation and compared using Wilcoxon's test or Student's t-test. Qualitative variables are presented as absolute values/percentages and compared with

Table 2

Comparison of myocardial perfusion scintigraphy (^{99m}Tc-MIBI) data and parameters of cardiac sympathetic neural activity (^{123}I-MIBG) in patients with targeted and anatomical placement of LV lead

Parameter	Targeted placement (Group 1; n=9)	Anatomical placement (Group 2; n=6)	p*	Targeted placement (Group 1; n=9)	Anatomical placement (Group 22; n=6)	p**	p***	p****
	Baseline data			Follow-up period				
SSS, points	16,2±12,2	10,3±7,6	0,3	10,8±12,8	10,3±9,6	0,9	0,007	0,42
SRS, points	15,2±12,5	8,6±8,4	0,28	9,8±12,9	8,8±9,2	0,9	0,008	0,2
SDS, points	1±1,9	1,6±2,7	0,6	1,1±1,5	1,5±2,3	0,7	0,9	0,9
H/M early	1,6±0,1	1,6±0,2	0,9	1,8±0,2	1,6±0,2	0,09	0,04	0,9
H/M delayed	1,4±0,2	1,6±0,2	0,3	1,63±0,1	1,47±0,2	0,08	0,02	0,6
WR, %	13,2±5,6	11,4±7,7	0,6	9,2±4,4	7,8±4,7	0,6	0,026	0,2

Note: * — baseline data between groups, ** — intergroup follow-up data, *** — intragroup (1) follow-up data, **** — intragroup (2) follow-up data.

Abbreviations: SSS — summed stress score, SRS — summed rest score, SDS — sunned difference score, H/M — heart-to-mediastinum ratio, WR — washout rate.

Table 3

Comparison of echocardiographic parameters during the follow-up period in patients with targeted and anatomical placement of LV lead

Parameter	Targeted placement (Group 1; n=9)	Anatomical placement (Group 2; n=6)	p*	Targeted placement (Group 1; n=9)	Anatomical placement (Group 2; n=6)	p**	p***	p****
	Baseline data			Follow-up period				
LV EDV, ml	232,2±88,9	217±104,6	0,8	202,2±86,4	195,2±104,9	0,9	<0,01	0,11
LV ESV, ml	167,9±74,8	152±89,5	0,7	136,3±72	133,5±80,2	0,9	<0,01	0,2
LVEF, %	25,4±6,7	31±7,5	0,2	33,6±6,5	33,1±8,9	0,9	<0,01	0,6

Note: * — baseline data between groups, ** — intergroup follow-up data, *** — intragroup (1) follow-up data, **** — intragroup (2) follow-up data.

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

Fisher's exact test. Differences were considered significant at $p<0,05$.

Results

Characteristics of patients. The study included 22 patients with HF scheduled for CRT. Seven (28%) patients did not meet the inclusion/exclusion criteria; the remaining 15 patients were included in the study. The study design is shown in Figure 2.

The age of the patients was 61 [58; 72] years. Fourteen patients (93,3%) had NYHA class III HF. Eleven (73,3%) patients were diagnosed with coronary artery disease (CAD). The mean QRS width and LVEF was 157,3±26,3 ms and 28±7%, respectively. Perfusion scintigraphy changes were detected in all 15 patients. In 9 patients (5 patients with CAD and 4 with dilated cardiomyopathy), perfusion defects were detected in the inferior, inferior septal and partly inferior lateral LV wall. In 3 patients (all with CAD), perfusion defects were localized in the LV apex and anterior wall. In 1 patient with CAD, a perfusion defect was detected in the lateral wall, and in 2 patients with CAD — in the LV anterior and inferior wall. The preoperative patient characteristics are presented in Table 1.

Intraoperative data. Target LV lead placement (group 1) was performed in 9 (60%) of 15 patients. In

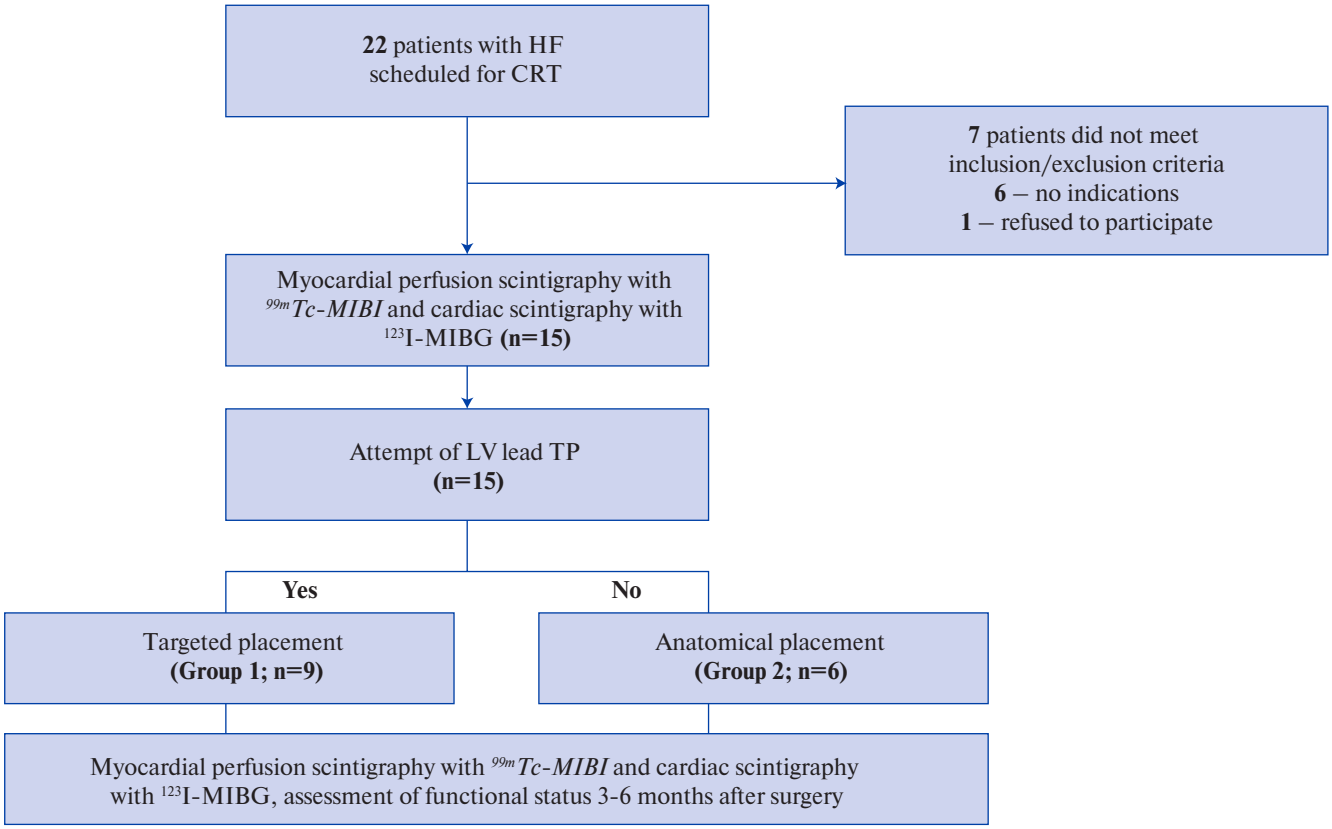

Figure 2. Study design.
Abbreviations: HF — heart failure, CRT — cardiac resynchronization therapy, LV — left ventricle.

7/9 (77,8%) patients, the LV lead was implanted in the posterolateral branch of CS, and in 2/9 (22,2%) patients — in the anterolateral and anterior branches of CS. These branches were located in the LV area with radiopharmaceutical accumulation >50% according to perfusion scintigraphy.

In 6/15 (40%) patients, TP of LV lead was impossible due to high stimulation thresholds or the absence of CS branch in the corresponding area. The LV lead was implanted anatomically (group 2). The position of the LV lead was as follows: posterolateral branch of CS (n=3), anterolateral (n=2), posterior (n=1).

All implanted LV leads were bipolar (Easytrak 2 IS-1, Boston Scientific, US — 10 leads, Attain Ability Plus 4296, Medtronic, US — 5 lead).

The total time of fluoroscopy and procedure duration in the first and second groups did not differ from each other and amounted to 21,9±19,2 vs 29,9±15,5 min, respectively (p=0,41), and 117,2±55,6 vs 131,7±38,2 min, respectively (p=0,6). Intraoperative stimulation thresholds in both groups did not exceed the recommended values. Intraoperative complications were not detected in any of the groups.

Radionuclide imaging. The follow-up period was 4 [3,5; 4,5] months. Parameters of MP (SSS, SRS, SDS) did not initially differ between groups, as well as cardiac SNA (H/M and WR; Table 2).

During the follow-up period, a significant decrease in the severity of MP defect was noted in the TP group compared to preoperative values: SSS decreased from 16,2±12,2 to 10,8±12,8 (p=0,007); SRS from 15,2±12,5 to 9,8±12,9 (p=0,008), respectively. There was also a significant change in cardiac SNA values: an increase in the ^{123}I-MIBG accumulation on a delayed imaging from 1,4±0,2 to 1,63±0,1 (p=0,02), and a decrease in WR from 13,2±5,6% to 7,8±4,7% (p=0,026), respectively.

At the same time, there were no significant differences both between the groups and within the anatomical placement group (Table 2).

Echocardiography and responders. LV ESV and end-diastolic volume (EDV) significantly decreased in the TP group compared to preoperative values (p<0,01). The increase in LVEF was also significant

in this group compared to the initial data (33,6±6,5% vs 25,4±6,7%, respectively; p<0,01). Parameters of LV systolic function did not significantly change in the anatomical placement group and did not differ between groups (Table 3). During the follow-up period, the number of echocardiographic responders in the TP group was 8/9 (88,9%) patients vs 4/6 (66,7%) patients in the anatomical placement group (p=0,5).

Discussion

This pilot study demonstrated that TP of LV lead during CRT using the radionuclide imaging data improves perfusion and cardiac SNA parameters. Despite the relatively short follow-up period, these changes were accompanied by an improvement in LV systolic function in TP group compared with the initial data. However, there was no significant differences compared with the anatomical placement group. The number of echocardiographic responders did not differ between the groups, although there was a trend towards an increase in responders in TP group.

To date, the issue of patient selection for CRT is still relevant. A fairly large number of works have been focused on assessing the LV desynchrony according to echocardiography as one of the selection methods [1-3]. However, research results are inconsistent and patient selection by desynchrony criteria requires further study.

In a number of works, it was suggested that TP of LV lead, on the one hand, and the sufficient volume of viable tissue, on the other, is important for the selection and prediction of a positive response to CRT [15].

Myocardial perfusion scintigraphy is today considered one of the most accessible and accurate methods for assessing cardiac perfusion, the degree and localization of viable myocardium among the widely used imaging techniques (for example, magnetic resonance imaging, positron emission tomography, echocardiography, multislice tomography) [15].

Some studies revealed that the degree of viable myocardium, expressed in the number of segments, is linearly related to the increase in LVEF with CRT. This is natural, since a significant number of viable cardiomyocytes are required to improve LV systolic function after CRT. In this case, an important role will be played by determining the most suitable area for lead placement. In a number of studies, it was shown that scarring in the LV lead area lead to an insufficient effect of CRT [15].

According to study by Bleeker GB, et al., contrast-enhanced magnetic resonance imaging data revealed that the transmural lesions in the lead area led to a negative response to CRT [16]. Similar results were obtained by Ypenburg C, et al. using myocardial perfusion scintigraphy [17]. The results of this study showed that in patients with transmural scar according to myocardial scintigraphy with ^{99m}Tc-tetrafosmin, LV systolic function did not increase, reverse remodeling was not observed, and clinical characteristics did not improve. These observations indicate that extensive scar tissue in the LV area leads to inadequate pacing.

At the preoperative phase, the posterolateral and lateral LV areas are undoubtedly considered anatomically targeted. However, this anatomical placement is dependent on the availability of CS branches and satisfactory stimulation thresholds, which may not always be achieved. In such a situation, during surgery, it is not clear which of the alternative branches of the CS will be optimal for a certain patient. In this case, preoperative scintigraphy data on perfusion can determine the best place for implantation of LV lead, as well as avoid implantation into the area of impaired perfusion.

According to the results, we have shown that the severity of perfusion defects and cardiac SNA between the groups of targeted and anatomical lead placement did not differ significantly. A significant difference was observed only within the TP group. The significant difference in this group may be due to the large number of patients and a more pronounced difference between the baseline and control data. Initially, all patients were planned for TP, but this was achieved only in 60% of patients, which led to a "randomization" into 2 groups. An unequal number of patients in the two groups with a small sample size in the anatomical placement group could lead to no difference between groups and within anatomical placement group. In addition, it is necessary to search for a preoperative assessment of the CS anatomy for using radionuclide tests in this category of patients and increasing the proportion of TP.

In this study, all patients received optimal medication therapy for HF according to the guidelines, which did not change during the follow-up period. At the same time, drugs of other classes were not added. The effect of drug therapy for HF on MP and changes in markers of SNA requires further study.

Study limitations. This study has a number of limitations. This was a pilot prospective observational study to determine the possibility of TP of LV lead based on radionuclide imaging and individual anatomy of CS. A small number of patients and short-term follow-up period do not allow extrapolating the data to the entire population of HF patients and CRT candidates. In addition, this was a feasibility study without clear hypothesis and endpoints, with

a small sample size. Nevertheless, the initial positive results obtained can be used to conduct further randomized studies.

Due to the limited follow-up period, we did not assess the clinical parameters of the patients, as well as the long-term functional parameters. This study included >70% of patients with CAD and, due to the small sample size, we cannot make a comparison with non-CAD patients.

Targeted LV lead placement was defined as a combination of preoperative scintigraphy data and the presence of a corresponding branch of the CS during surgery with the possibility of lead implantation with satisfactory stimulation thresholds. In this study, we did not take into account the detailed anatomical segmentation, which is a topic for future research, as well as the randomized comparison of anatomical and targeted placement of LV lead. Further work will help to confirm or disprove the initial results obtained.

Conclusion

In patients with HF scheduled for CRT, the target LV lead placement using radionuclide imaging results in an improvement of myocardial perfusion and cardiac SNA compared with baseline data and does not have differences compared to anatomical positioning. Further studies are needed to assess the role of radionuclide imaging in CRT.

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