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Central directions for reducing cardiovascular mortality: what can be changed today?

Shlyakhto E. V.[1,2], Baranova E. I.[1,2]

The article provides modern data on the prevalence of cardiovascular diseases and mortality in Europe and Russia. Groups of high-risk patients requiring special attention when conducting measures to reduce cardiovascular mortality are discussed: patients with hypertension, including resistant, patients with severe dyslipidemia, heart failure, and atrial fibrillation. Particular attention is paid to the problem of effective and safe treatment and reducing cardiovascular mortality in patients with atrial fibrillation and a high risk of stroke. The treatment of these patients may be most successful due to the availability of effective medications that reduce cardiovascular mortality. The article outlines the major paradigms of modern healthcare: focus on results and patient, integration of inpatient and outpatient health care units and accelerating the innovation in the diagnosis and treatment of patients with cardiovascular diseases.

Key words: cardiovascular mortality, resistant hypertension, dyslipidemia, atrial fibrillation, anticoagulants.

Relationships and Activities: none.

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Cardiovascular disease (CVD) is the leading cause of death worldwide. Every year 17,5 million people die due to CVD, and most of these deaths are potentially preventable [1]. In 2020, data on CVD statistics were published in 52 European Society of Cardiology (ESC) member countries [2]. In these countries, in 2018, 2,2 million women and 1,9 million men died from cardiovascular diseases, while cardiovascular mortality (CVM) was 47% of all causes in women and 39% — in men [2]. In CVM structure, the first place in women and men is coronary artery disease (CAD) (18% and 17%, respectively), and the second place is stroke (12% and 8%, respectively) [2]. In middle per capita income countries, including the Russian Federation, the proportion of CVM is higher than in countries with high-income economies [2].

Using the methods of statistical analysis, it was proved that in the countries united by the ESC, the potential years of life lost (PYLLs) due CVD in 2017 was 28 million for women and 38 million for men, which accounts for 37% of PYLLs for women and 34% of PYLLs for men [2]. CVD are more responsible for PYLLs in European countries with a middle per capita income than in high-income countries, both among women (43% and 28%, respectively) and among men (39% and 28%, respectively) [2].

In Russia, CVM is associated with every second death and exceeds CVM in Europe and the United States [3-5]. According to the Russian Federal State Statistics Service, 841915 people died due to CVD in 2018 [3]. At the same time, in recent years there has been favorable dynamics — in the period from 2005 to 2018 the CVM decreased by 36,6% [3, 4], and in the period from 2000 to 2018 the proportion of CVD in the structure of all-cause mortality decreased from 55,3 to 46,3% [4]. In addition, death is one of the most reliably ascertained outcomes in most European countries [2]. In Russia, one of the priority tasks is to increase life expectancy to 78 years by 2024 [6] and to reduce CVM to <450 cases per 100 thousand population by 2024, that is, by 21,5% over the next 5 years [7].

In 2013, the World Health Organization (WHO) announced a strategy to reduce mortality due to CVD, diabetes, cancer and chronic lung diseases by 25% by 2025 compared to 2010 [1]. By 2019, mortality in high-income European countries has decreased by 9% for women and 11% for men, while in countries with middle-income economies it has decreased by 8% for women and only 2% for men [2].

In Russia, the decrease in CVM in recent decades is largely associated with the reorganization of cardiology care, the creation of regional vascular centers, the introduction of highly effective interventional treatment of acute coronary syndrome, surgery of heart defects, interventional treatment of arrhythmias and prevention of sudden cardiac death. At the same time, only high-tech methods of treatment cannot completely solve the problem of reducing CVM. The modulation of cardiovascular risk factors (CVR), primary and secondary prevention of CVD, increasing medication adherence of patients, including after the use of high-tech methods, are also of great importance for reducing mortality. It is also important to develop pharmacology and create new drug classes. Some of these drugs affect not only hypertension (HTN), hyperlipidemia, hyperglycemia, the course of CAD, heart failure (HF), but also affect hard endpoints, including all-cause and CVM. So, it is necessary to determine the main directions for reducing CVM.

High-risk patient groups requiring special attention

Target groups of high-risk patients should be identified that require special attention and active measures to reduce mortality. These high-risk groups include patients with severe dyslipidemia, resistant HTN, HF, and atrial fibrillation (AF).

Dyslipidemia

Severe dyslipidemia is one of the modifiable risk factors for CVD and mortality. Prospective randomized clinical trials (RCT) have demonstrated that elevated levels of atherogenic lipids, including low-density lipoprotein cholesterol (LDL-C), increase the risk of atherosclerosis-related CVD [8]. One of the serious problems of modern medicine is insufficient detection of dyslipidemia for primary and secondary prevention of CVD, including in high-risk patients with type 2 diabetes, stroke, and peripheral artery disease.

There is no doubt that treatment of dyslipidemia reduces CVR. Meta-analysis of the Cholesterol Treatment Trialists' Collaboration, which included data on more than 170000 patients from 26 RCT, proved that a decrease in LDL-C by 1 mmol/L over 5 years was associated with a decrease in major vascular events by 22%, major coronary events by 23%, stroke by 17% and all-cause mortality by 10% [9]. Secondary prevention with statins reduces the risk of recurrent stroke by 12% with a decrease in LDL-C by 1 mmol/L and decreases CVM [10]. The low statin prescription rate leads to non-achievement of the lipid target level and to an increased risk of myocardial infarction (MI), stroke and premature death [11]. According to the ARGO study, in 2013-2014, hypercholesterolemia was detected in 81,3% of women and 78,9% of men [12]. Among patients with CAD, HTN, revascularization, a history of ischemic stroke or peripheral artery disease, only 43% received statin therapy, and 27,2% and 9,1% of patients received high-dose atorvastatin and

rosuvastatin therapy, respectively. At the same time, only 2,04% of patients with CAD and 7,38% of patients with a history of MI and surgical or percutaneous coronary intervention reached the target LDL-C level [12].

In patients with high CVR, ESC/EAS Guidelines for the management of dyslipidemias (2019) recommend a decrease in LDL-C by 50% or more and achieving a target level of <1,8 mmol/L, and in very high-risk patients — <1,4 mmol/L [8]. This level of atherogenic lipids is extremely difficult to achieve with statin monotherapy.

Combined lipid-lowering therapy more effectively reduces the lipid levels. According to the REDUCE-IT study, therapy with combination of statins and ezetimibe reduces the incidence of composite endpoint, including cardiovascular death, non-fatal MI, non-fatal stroke, coronary revascularization and unstable angina by 25% over 4,9 years of therapy [13].

According to FOURIER study, therapy with a combination of statins and proprotein convertase subtilisin/kexin type 9 (PCSK9) evolocumab in patients with atherosclerotic CVD not only effectively reduces the LDL-C levels during long-term treatment, but also reduces the risk of primary endpoint, including cardiovascular death, MI, stroke, hospitalization due to unstable angina or coronary revascularization by 15% [14]. At the same time, combination therapy for dyslipidemia is not used often enough due to the rigidity of physicians, low medication adherence of patients, the high cost of some drugs and, to a lesser extent, due to adverse events.

Resistant hypertension

The problem of treating HTN patients remains relevant. According to the ESSE-RF study, only 16,4% of men and 32,6% of women with essential HTN had a target blood pressure level [15]. Resistant HTN is observed in 17,7% of hypertensive patients [16]. According to a scientific statement from the American Heart Association (2018), resistant HTN increases the risk of stroke by 14%, MI by 24% and the risk of death by 6% [17]. Treatment of patients with resistant HTN is a complex problem that requires excluding the secondary HTN, treating comorbidities, stopping alcohol consumption, limiting the intake of non-steroidal anti-inflammatory drugs, increasing low physical activity and treating obstructive sleep apnea. In the treatment of hypertensive patients, it is necessary to increase the non-medication and medication adherence of patients. Drug treatment of patients with resistant HTN includes 4 or more antihypertensive drugs, including renin-angiotensin-aldosterone system inhibitors, calcium channels blockers and thiazide diuretics (chlorthalidone is preferred), and in case of insufficient effectiveness — mineralocorticoid receptor antagonists [18]. The PATHWAY-2 study proved that spironolactone is more effective in patients with resistant HTN than bisoprolol or doxazosin [19]. In case of insufficient effectiveness of therapy in patients with CAD or HF, beta-blockers should be added, and in patients without mentioned diseases — central alpha-adrenergic agonists (clonidine, methyldopa) or peripheral vasodilators (hydralazine) [18, 20]. Analysis of the SPRINT and ACCORD studies showed that the optimal systolic blood pressure to reduce incidence of adverse outcomes such as MI, stroke, HF, CVM and all-cause mortality in patients with/without resistant HTN is <120 mm Hg [21]. A serious problem in the treatment of resistant HTN is the low medication adherence of patients, which reaches only 31,2% [22]. ESC (2018) and ACC/AHA (2017) guidelines do not recommend the routine use of devices for the treatment of resistant HTN [23, 24]. Consequently, the problem of resistant HTN treatment cannot be considered solved at present. The number of hypertensive patients, including those with resistant HTN, can be significantly reduced through prevention and a healthy lifestyle.

Heart failure

HF is one of the most relevant problems of modern cardiology [25]. The prevalence of HF in developed countries among the adult population is 1-2%, progressively increasing with age [26]. There are currently 15 million HF patients in Europe [27]. The absolute number of patients with end-stage HF is increasing due to life expectancy increase and due to the improvement of methods of treating cardiovascular patients. The presence of HF increases the mortality rate by 7-17% per year [25].

Over the past 30 years, there were progressive changes in the treatment of HF patients that have increased the survival of those with HF with reduced ejection fraction (HFrEF) [25]. Neurohumoral antagonists (angiotensin-converting enzyme (ACE) inhibitors, angiotensin II type 1 receptor blockers (ARBs), mineralocorticoid receptor antagonists and beta-blockers) are recommended for all patients with HFrEF due to reducing mortality [25]. In recent years, new drugs have introduced: sacubitril/valsartan, ivabradine, sodium-glucose co-transporter-2 inhibitors. Sacubitril/valsartan is recommended for patients with HFrEF if HF symptoms maintain during therapy with ACE inhibitors/ARBs, since it is more effective than enalapril in reducing mortality and CVM [28]. Ivabradine reduces the composite endpoint — mortality or hospitalization due to HF in symptomatic patients with HFrEF and sinus rhythm ⩾70 [29].

According to EMPA-REG OUTCOME study, sodium-glucose co-transporter-2 inhibitor empagliflozin in patients with type 2 diabetes decreased the composite primary endpoint 3P-MACE (cardiovascular death, non-fatal MI, non-fatal stroke) by 14%, reduced the risk of hospitalization due to HF by 35%, reduced all-cause mortality by 32% and CVM by 38% [30].

Despite significant progress in the treatment of patients with HF, in actual clinical practice, patients with HF are often treated inadequately, which leads to unfavorable outcomes. Often, titration of ACE inhibitors/ARBs, beta-blockers and diuretics is not carried out, and drugs with verified effect on reducing mortality (sacubitril/valsartan, empagliflozin) are not prescribed [28, 30]. The main reasons for inadequate treatment of outpatients are changes in therapy regimens and ineffective hemodynamic monitoring. According to the EPOHA-D-CHF study, changes in treatment regimen after decompensated HF were carried out in 78,5% of patients within a year [31].

Atrial fibrillation

Prevalence of AF in Europe is 1-2% [32]. Mortality in patients with AF is higher 1,5-2 times [27]. The increase in mortality is due to the high incidence of stroke in AF patients, since this arrhythmia is one of the most important risk factors for stroke [32]. The number of stroke patients in ESC member countries in 2017 amounted to 20,4 million, and stroke was more common among residents of Eastern Europe and in countries with a low per capita income [2]. The age-standardized stroke prevalence in the Russian Federation in women is 1700 and more, and in men 1600-1900 per 100 thousand population [2]. Stroke prevention is one of the priorities in reducing CVM.

In 2017, in 54 ESC member countries, 10000000 AF patients were recorded; the average age-standardized AF prevalence in these countries was 571,8, and in Russia — 474 in women and 732 in men per 100 thousand population [2]. It is assumed that the number of patients with AF by 2060 will doubled (compared to 2010) and reach 17900000 patients, and AF will be observed in 1 in 4 people over 40 years of age [33, 34].

Attention should be paid to the fact that AF is often not diagnosed due to asymptomatic course or rare and short paroxysms, which does not allow registering arrhythmias. The incidence of asymptomatic AF in clinical trials varies from 1,4% to 34,8%, depending on the diagnosis method — most often AF was detected by implanted devices [35]. Asymptomatic AF significantly increases the risk of stroke and systemic embolism [36]. The ASSERT study, which included hypertensive patients over 65 years of age with an implanted dual-chamber pacemaker or cardioverter-defibrillator, showed that asymptomatic AF developed in 18,8% of patients during a mean follow-up period of 2,5 years. The risk of stroke and embolism was 3 times higher in patients with asymptomatic AF lasting more than 24 hours compared with those without AF [36]. The US study found that AF was not diagnosed in 18% of people with AF. At the same time, of particular importance is the fact that 77% of them have a $CHADS_2$ score of ⩾1, and 56% — ⩾2, that is, most have a high risk of stroke and, therefore, indications for anticoagulant therapy [37]. According to the CRISTAL-AF study, the detection rate of AF after cryptogenic stroke in patients with an implanted cardiac monitor is 14 times higher [38]. Therefore, in patients with stroke of undetermined source, electrocardiogram monitoring (at least 72 hours) should be performed in order to diagnose AF for prescribing anticoagulants for the secondary prevention of stroke. New devices are increasingly being used to diagnose AF: an Apple Watch, a BP monitor with AF detection (WatchBP Home A, Microlife), smartphones, and patch-monitors [35]. The fact that new devices and methods for AF diagnosis are being created indicates that the AF diagnosis is extremely important, since it completely changes the management strategy.

One of the main areas of therapy for patients with AF is the prevention of stroke and systemic embolism using anticoagulant therapy [32]. Anticoagulation is specified by the risk of stroke and significantly reduces the risk of thromboembolic events and death in patients with AF [32]. At the same time, according to the Risk-Stroke register, out of 94000 people with ischemic stroke, 22% were previously diagnosed with AF, but only 16% of them received anticoagulant therapy within 6 months before stroke [39]. Vitamin K antagonists effectively reduce the risk of thromboembolic events in patients with AF [40]. Well-managed warfarin therapy is associated with a 64% reduction in stroke risk and a 26% reduction in mortality compared with placebo [41], but is also associated with an increased risk of major bleeding [40]. In addition, the use of warfarin is associated with a need for laboratory monitoring, interaction with other drugs and food products, difficulties in dose selection and long-tern maintaining an optimal anticoagulant effect [42]. For effective warfarin treatment, the time in therapeutic range of international normalized ratio (INR) of 2,0 to 3,0 must be >70%. Practically, achieving such an effect is extremely difficult. In RCT, the time of therapeutic range for warfarin ranged from 55% to 66% [43-45]. In actual clinical

practice, the results of monitoring the effectiveness of warfarin therapy are usually lower. According to cohort study by E. I. Baranova et al., only 40% of patients with AF and indications for anticoagulation received these drugs, and INR within the target range was recorded only in 26,8 patients [46]. According to the analysis of anticoagulant therapy in AF patients in several Russian cities, the achievement of the target INR does not exceed 40% [47]. The efficacy and safety of direct oral anticoagulants (DOAC) has been compared with warfarin in large RCTs, including >150000 patients [48]. DOAC in RCTs and in actual clinical practice have shown no less efficacy and, undoubtedly, higher safety compared with vitamin K antagonists [49-52]. At the same time, the frequency of hemorrhagic strokes and intracranial bleeding with the use of DOAC is significantly lower in comparison with warfarin, and dabigatran etexilate is associated with a reduction in the risk of ischemic stroke by 24% [49, 53].

It should be also noted that RCTs demonstrated that long-term use of dabigatran etexilate and apixaban reduce the risk of all-cause mortality [51, 54, 55]. Of all DOACs, only dabigatran at a dose of 150 mg 2 times/day showed a significant decrease in CVM compared with well-managed warfarin with a relative risk of 0,85 (95% confidence interval 0,72-0,99), p=0,0430 [49, 53].

Despite these positive effects of DOAC, many patients with AF still do not receive effective antithrombotic therapy, although, the dynamics of anticoagulant prescription rate is undoubtedly positive. In particular, the GLORIA-AF registry demonstrated that the majority of patients with AF and a high risk of stroke on all continents receive anticoagulants, but the proportion of patients who do not receive antithrombotic therapy or receive only antiplatelet drugs varies widely depending on age and continents [52]. According to the GLORIA-AF registry, the most unfavorable situation with anticoagulant prescription in Asian countries. In particular, 41,8% of patients aged 65-74 years and 45,9% of patients 85 years and older did not receive adequate antithrombotic therapy [52]. According to the Russian cohort study with AF outpatients, anticoagulant therapy (if indicated) was not prescribed in 25,7% of patients. At the same time, 13,4% of patients after stroke or transient ischemic attack also did not receive anticoagulants [56].

Anticoagulant therapy in patients with AF, a high risk of stroke, and withoyt contraindications, should be carried out for life, since this affects the prognosis of patients with AF. At present, it is of particular importance to anticoagulant withdrawal in outpatients by a physician or by themselves. Discontinuation of anticoagulant therapy increases the risk of stroke in patients with AF by 4,21 times, and the risk of death by 3,43 times [57]. Anticoagulant withdrawal is often due to the risk of major bleeding. However, the incidence of hemorrhagic strokes and intracranial bleeding with the use of DOAC is significantly lower than with warfarin [49-51]. When DOACs is prescribed in accordance with the European guidelines, the incidence of major bleeding in RCTs with the dabigatran and apixaban is lower than with warfarin, and the number of major gastrointestinal bleeding is comparable [51, 54]. During treatment with rivaroxaban versus warfarin, the incidence of major bleeding was comparable, and the risk of major gastrointestinal bleeding was higher [50]. In actual clinical practice, a similar data is observed — in a national cohort study with 52476 patients with AF who were first prescribed DOAC, major bleeding was observed less frequently with dabigatran than rivaroxaban, and there were no differences in the frequency of bleeding between dabigatran and apixaban [58].

The safety of DOAC therapy has increased in recent years, since there are drugs for the reversal of anticoagulant effects in clinical practice, which are used for life-threatening bleeding. According to statistics, 3,5% of patients per year need urgent reversal of the anticoagulant effect [59]. It should be emphasized that the need to stop the anticoagulant action arises not only with massive bleeding or internal bleeding into a vital organ (1,5% per year), but also when emergency surgery or procedure with a high risk of bleeding is necessary (2% per year) [59]. Only dabigatran etexilate has a drug designed for the reversal of its anticoagulant effects — idarucizumab, and it is registered in the Russian Federation [60]. The ability to quickly reverse the anticoagulant effect increases the confidence of physicians and patients and, therefore, leads to an increase in the number of patients taking anticoagulants, and as a result, to a decrease in the incidence of strokes and CVM [61].

Thus, this data on the diagnosis and treatment of AF aimed at preventing stroke and systemic embolism is an example of how the high-precision available methods of early diagnosis, highly effective treatment and prevention of thromboembolic events can actually reduce CVM.

The major paradigms of modern healthcare:

1. Focus on effects and results;
2. Patient-centered care: the interests of a patient are more significant than of an institution, a system, and medical workers;
3. Process integration: continuity between in- and outpatient specialists;

4. Accelerating the innovation introduction: overcoming bureaucratic obstacles for the practical implementation of new effective technologies.

There are many challenges of modern medicine, first of all, it is patient-centered care aimed at increasing the patient's life expectancy and quality of life.

There are following key areas of modern cardiology:

1. Early diagnosis of diseases, the treatment of which can affect the prognosis and quality of life of a patient.

2. Primary and secondary prevention and treatment using modern technologies aimed at increasing the physicians' education, patient awareness, and medication adherence.

3. Setting up a task to create treatment methods that ensure high efficiency and safety of therapy, which can lead to a decrease in CVM.

The strategy for monitoring and managing risks in cardiology consists of primary prevention, early treatment, treatment of an acute event, secondary prevention, and treatment of complications. This strategy is aimed at reducing CVM, which is one of the priority tasks of Russian healthcare system [7].

Relationships and Activities: none.

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Catheter ablation of atrial arrhythmias in patients after thoracoscopic ablation of persistent atrial fibrillation

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Aim. To determine the mechanisms of development and approaches to interventional treatment of postoperative atrial tachycardia in patients after thoracoscopic ablation (TA) of atrial fibrillation (AF).

Material and methods. The results of thoracoscopic ablation of AF in 46 patients were analyzed, of which 19,5% (n=9) had atrial tachycardia after the procedure. Radiofrequency ablation (RFA) was conducted in these patients after a 3-month blanking period. Regardless of tachycardia type, the three-dimensional reconstruction including high-density right and left atrial (LA) voltage mapping was performed in order to visualize the lesions, pulmonary veins and LA posterior wall isolations. After RFA and sinus rhythm restoration, re-mapping was performed to assess conduction block and absence of electrical activity in the lesion zones.

Results. Complete pulmonary vein (PV) isolation was verified in 55,5% of patients (n=5). In 44,4% (n=4), there were residual PV fractionated potentials without conduction with LA. In 22,2% of subjects (n=2), we identified typical atrial flutter (AFL), which was terminated by RFA in cavotricuspid isthmus (CTI). There were 77,7% (n=7) of patients who were diagnosed with atypical LA flutter; 66,6% (n=6) of them had conduction reconnection at the thoracoscopic box-lesion line. Perimitral AFL with slow conduction zone which was located on the anterior wall of LA was verified in 11,1% of patients (n=1). The effective RFA was performed in these areas. Two main factors affecting failed ablation were LA volume and body mass index (BMI). In patients with arrhythmias after TA, LA volume was 180,2±35,6 ml vs 158,34±38,5 ml in patients with sinus rhythm. BMI was 30,8±3,1 kg/m^2 and 28,9±3,9 kg/m^2, respectively. The mean follow-up was 9,8±2,7 months. All patients after catheter ablation maintained a stable sinus rhythm.

Conclusion. Atrial tachycardia after TA is caused by the gaps in box-lesion lines. The main predictors of gaps are high values of LA volume and BMI. The high-density mapping increases the effectiveness of RFA. Combination of epicardial and endocardial accesses is the most effective approach to treatment of patients with persistent AF.

Key words: atrial fibrillation, thoracoscopic ablation, atrial tachycardia, high-density mapping, radiofrequency ablation.

Relationships and Activities: none.

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Atrial fibrillation (AF) is the most common type of arrhythmia. Due to the progressive increase in the incidence and high risk of related complications, the improvement of AF treatment techniques is an urgent problem [1]. Catheter ablation is the treatment of choice for medication-resistant AF. In paroxysmal AF, the efficiency of catheter ablation reaches 70-80%, while in persistent AF, patients require repeat procedures for long-term maintenance of sinus rhythm [2, 3]. As a result, in recent years, alternative surgical minimal invasive and thoracoscopic approaches have been widely used [4, 5]. Despite the higher efficiency of these methods in comparison with the catheter ablation, in some patients with persistent AF, it is necessary due to postoperative atrial tachycardia [2, 6].

The aim was to determine the mechanisms of development and approaches to interventional treatment of postoperative atrial tachycardia in patients after thoracoscopic ablation (TA) of AF.

Material and methods

Thoracoscopic AF ablation was performed in 46 patients (38 men, 8 women) with mean age of 56,5±9,4 years, performing the box-lesion procedure, which included bilateral pulmonary vein (PV) and left atrial (LA) posterior wall ablation (Figure 1A). In 78,2% (n=36) of patients, the LA appendage was amputated. In 4,3% (n=2) of patients, the linear right atrial (RA) ablation was performed: the line between the vena cava ("cava-caval") and the line to the RA appendage (Table 1).

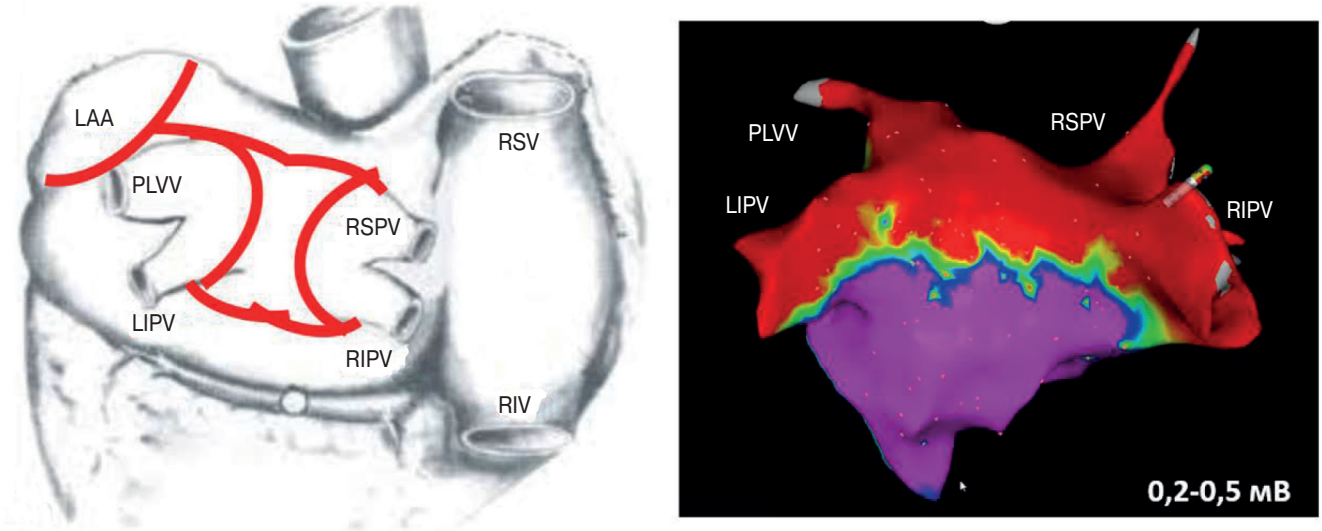
A total of 19,5% (n=9) of patients had postoperative atrial tachycardia (after 16,2±14,5 days), which required additional intervention after a three-month blind period. The characteristics of patients with atrial tachycardia are presented in Table 2.

Before thoracoscopic and catheter ablation, all patients underwent multislice computed tomography of LA and PV, 24-hour Holter monitoring, transthoracic and transesophageal echocardiography. During the perioperative period, all patients receive antiarrhythmic and anticoagulant therapy

The Seldinger technique was used for gaining central venous access. Regardless of the arrhythmia type, transseptal puncture was performed under fluoroscopic guidance to access the LA. Heparin was injected according to the generally accepted approach at a dose of 100 U/kg, followed by re-administration under the control of aspartate aminotransferase.

An ablation lead and multipolar diagnostic leads for high-density mapping with PentaRay (Biosense Webster) or Orion (Boston Scientific) were inserted into the LA. Anatomical reconstruction of LA and RA was performed with voltage mapping to visualize lesions and to assess adequateness of PV and LA posterior wall isolation. Analysis of high-density voltage maps and propagation maps of tachycardia made it possible to visualize the areas of delayed conduction, local block, and to verify the tachycardia circle.

After radiofrequency ablation (RFA) and restoration of sinus rhythm, high-density mapping from the coronary sinus were repeated to verify the



A B

Figure 1. LA after thoracoscopic AF ablation. **A.** Scheme of thoracoscopic ablation. **B.** Voltage map after three-dimensional reconstruction of LA in a patient after thoracoscopic ablation. Isolation of PV and LA posterior wall. LA voltage map (signal amplitude 0,2 mV-0,5 mV). **Abbreviations:** RSPV — right superior pulmonary vein, PLVV, LSPV — left superior pulmonary vein, RIPV — right inferior pulmonary vein, LIPV — left inferior pulmonary vein, LAA — left atrial appendage.

Table 1

Interventions within thoracoscopic ablation

Intervention	Number of patients
LA ablation ("Box-Lesion")	15,2% (7)
LA ablation ("Box-Lesion"), LAA amputation	78,2% (36)
LA ablation ("Box-Lesion"), LA appendage amputation and RA ablation ("cava-caval" line and the line to RAA)	4,3% (2)
LA ablation ("Box-Lesion"), anterior line to mitral valve, LAA amputation	2,17% (1)

Abbreviations: LA — left atrium, RA — right atrium, LAA — left atrial appendage, RAA — right atrial appendage.

Table 2

Characteristics of patients after thoracoscopic ablation

	Patients after thoracoscopic ablation	Patients with sinus rhythm	Patients with atrial tachycardia
Number	46	37	9
Age (years)	56,5±9,4	56,1±9,5	54,2±9,2
Sex (men/women)	38/8	31/6	7/2
BMI (kg/m^2)	29,5±3,76	28,9±3,9	30,8±3,1 (p>0,05)
AF type			
paroxysmal	21,7% (10)	24,3% (9)	11,1% (1)
persistent	15,2% (7)	8,1% (3)	44,4% (4)
long-standing persistent	63,04% (29)	67,5% (25)	44,4% (4)
Patients with a history of RFA	30,4% (14)	27,1% (10)	44,4% (4)
LA volume (ml)	162,6±38,6	158,34±38,5	180,2±35,6 (p>0,05)

Abbreviations: BMI — body mass index, LA — left atrium, RFA — radiofrequency ablation, AF — atrial fibrillation, p — level of statistical significance.

conduction block and the absence of electrical activity.

This study was performed in accordance with the Helsinki declaration and Good Clinical Practice standards. The local medical ethics committee approved this study. All patients signed informed consent.

Statistical processing included descriptive statistics methods with calculating mean values, standard deviations. The statistical significance of the differences between groups was assessed using the Student's t-test.

Results

Complete isolation of the PV was established in 55,5% (n=5), residual fragmented spike activity without conduction in the LA during PV stimulation — in 44,4% (n=4): 3 — right superior PV, 2 — left superior PV. In all cases, additional antral PV isolation was performed until the potentials disappeared (Figure 1B).

In 22,2% (n=2) of patients, we revealed typical isthmus-dependent atrial flutter, which was eliminated by RFA of the cavo-tricuspid isthmus (CTI). In the majority of patients with tachyarrhythmias (77,7%; n=7), atypical left atrial flutter was revealed.

In 66,6% (n=6) of patients, a zone of inadequate thoracoscopic ablation in LA roof was established. In these cases, additional linear ablation was performed, closing the upper line between the superior PVs. There was a restoration of sinus rhythm or an activation front change from left atrial to right atrial (Figure 2).

Perimitral atrial flutter with zone of delayed conduction along the LA anterior wall was detected in 11,1% (n=1) of patients. Linear RFA was performed from the LA roof to the mitral valve with restoration of sinus rhythm (Figure 3).

Analysis of the clinical data of patients after thoracoscopic ablation with atrial arrhythmias and sinus rhythm, two main factors affecting the occurrence of arrhythmias were identified. In the group with arrhythmias, the LA volume and body mass

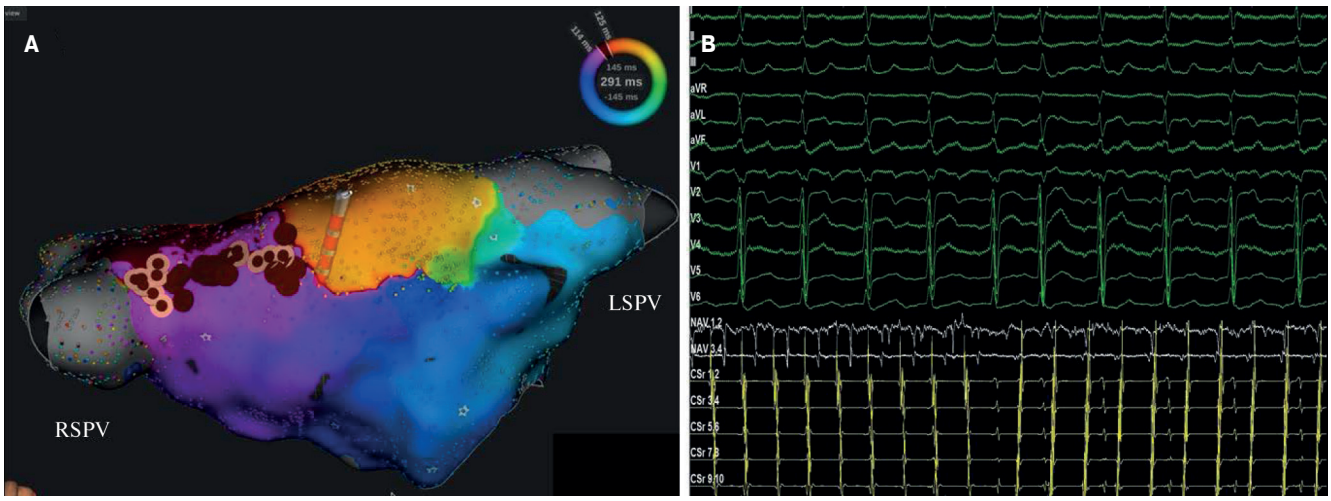


Figure 2. Elimination of left atrial flutter with a cycle length of 299 ms in a patient after thoracoscopic ablation. **A**. High-density map of LA activation, created using the Orion lead. Gaps within LA roof line, where RF exposure was performed. **B.** Transition of left atrial flutter into right atrial flutter under LA roof ablation. I-III, aVL, aVR, aVF, V1-V6 — ECG leads, CS 1-10 — recording from a 10-pole diagnostic lead in the coronary sinus, NAV 1-4 — electrogram from the ablation lead.
Abbreviations: RSPV — right superior pulmonary vein, LSPV — left superior pulmonary vein, LA — left atrium, ECG — electrocardiogram.

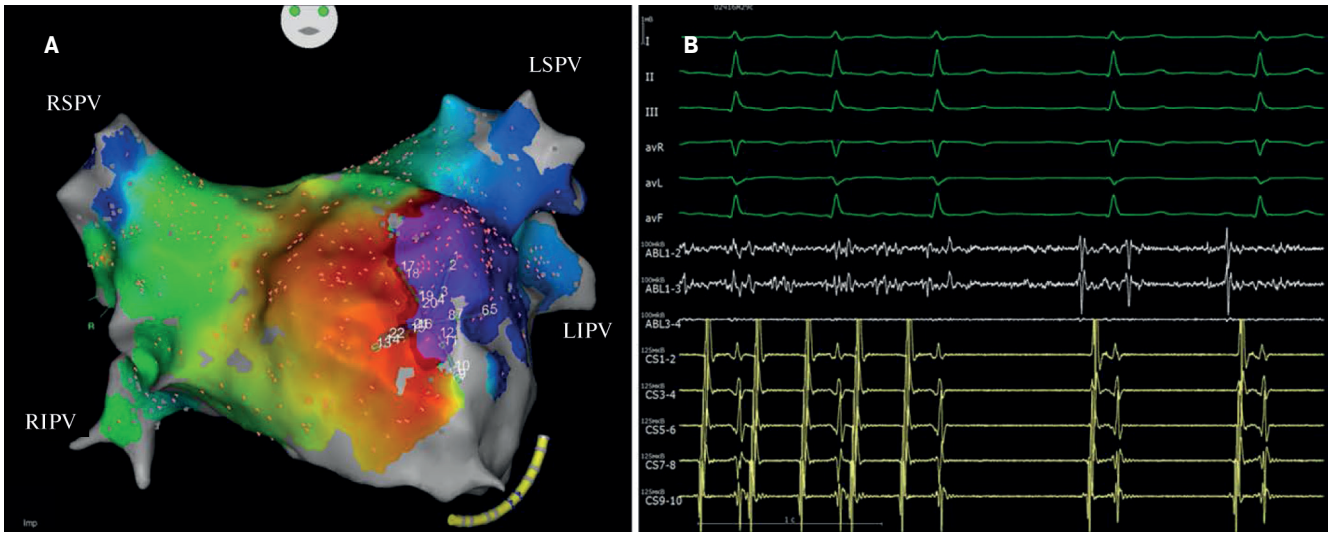


Figure 3. Elimination of left atrial perimitral atrial flutter in a patient after thoracoscopic ablation. **A.** High-density map of LA activation, created using the PentaRay lead. Gap along the LA anterior wall. **B.** Restoration of sinus rhythm with LA anterior wall ablation. I-III, aVL, aVR, aVF, V1-V6 — ECG leads, CS 1-10 — recording from a 10-pole diagnostic lead in the coronary sinus. ABL 1-4 — recording from the ablation lead.
Abbreviations: RSPV — right superior pulmonary vein, LSPV — left superior pulmonary vein, LA — left atrium, RIPV — right inferior pulmonary vein, LIPV — left inferior pulmonary vein, ECG — electrocardiogram.

index (BMI) were 180,2±35,6 ml vs 158,34±38,5 ml (p>0,05) and 30,8±3,1 kg/m^2 vs 28,9±3,9 kg/m^2 (p>0,05), respectively (Table 2).

The average follow-up period was 9,8±2,7 months. All patients after catheter ablation maintained a stable sinus rhythm.

Discussion

The first radical surgery of AF was performed by J. Cox in the 80s of the last century [7]. The cut-and-sew technique provided good effect and long-term freedom from AF, but the surgical injury limited its use. Subsequently, the technique was significantly modified, mainly due to the use of alternative energy sources [8]. However, in some cases, despite the method's effectiveness, atrial tachycardia may occur in the postoperative period, requiring detailed atrial high-density mapping [9-12].

Cases of tachycardia after thoracoscopic ablation (n=8) are described in the study by Liu X and Dong

J (2009) [13]. A recurrence of AF was registered in 3 patients, and typical atrial flutter was observed in the rest. Activation and voltage mapping revealed pulmonary vein gaps and inadequacy of the LA roofline. Gaps were localized in the upper and lower PV segments. With catheter ablation, electrical activity in these areas disappeared quite quickly. The authors associate the inadequacy of ablation with the lack of radio frequency energy at the ends and at the junction of leads. The study by Hye Bin Gwag, et al. (2019) [14] included 154 patients after thoracoscopic ablation. In the postoperative period, AF recurrence was registered in 11 patients, and atypical atrial flutter in 11 patients. In 13 patients, PV gap zones were identified, most of which were in the posterior PV segments. During the follow-up period (9,1±1,4 months), 76,7% of patients maintained a stable sinus rhythm after the catheter procedure.

Study by Beukema RJ, et al. (2016) described catheter ablation of atrial tachycardia, which occurred in 23 of 41 patients after thoracoscopic ablation [15]. Recurrence of paroxysmal AF was diagnosed in 20 patients. Recurrence of AF in combination with atrial tachycardia was noted in 2 patients, and an AF in combination with type 1 atrial flutter was diagnosed in 1 patient. Electrophysiological testing revealed PV gaps in all 23 patients. Most often, electrical activity was recorded in the ridge area, as well as in the lower segment of the right inferior PV. RFA were performed in these areas. The patient with typical atrial flutter underwent additional ablation at the CTI. The authors conclude that in this category of patients, the effects were not initially transmural. The reasons may be tactical and technical issues such as insufficient RF applications or uneven energy distribution. The authors also suggest that transmurality during thoracoscopic ablation was not achieved due to overweight (83% of patients had a BMI >25 kg/m^2). Therefore, a significant part of the RF energy may be consumed by the epicardial adipose tissue, which leads to the RFA failure.

Conclusion

Patients after thoracoscopic ablation may have atrial tachyarrhythmias despite effective PV isolation. The major causes of arrhythmias are inadequate ablation lines in areas of increased epicardial fat. This creates zones of myocardial heterogeneity, and, as a consequence, areas of delayed conduction and prerequisites for the re-entry.

According to our data, the main predictors of ablation failure and arrhythmia recurrence are large LA volume and high BMI of patients. The use of high-density mapping allows to accurately verify the zones of delayed conduction and block and increase the efficiency of tachycardia elimination.

CTI plays a role in the development of typical atrial flutter, since this area is inaccessible for thoracoscopic ablation, and endocardial treatment makes it possible to radically cure these patients.

In this study, all 9 patients maintained a stable sinus rhythm. The effectiveness of the procedure was 100% with a follow-up period of 9,8±2,7 months.

Thus, a combination of epi- and endocardial techniques is the most effective approach to the surgical treatment of persistent AF.

Relationships and Activities: none.

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

Romanov A. B., Minin S. N., Nikitin N. A., Losik D. V., Stenin I. G., Yelesin D. A., Zhizhov R. E., Filippenko A. G., Mikheenko I. L., Artemenko S. N., Fisher E. V., Baranova V. V., Shirokova N. V., Shabanov V. V.

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

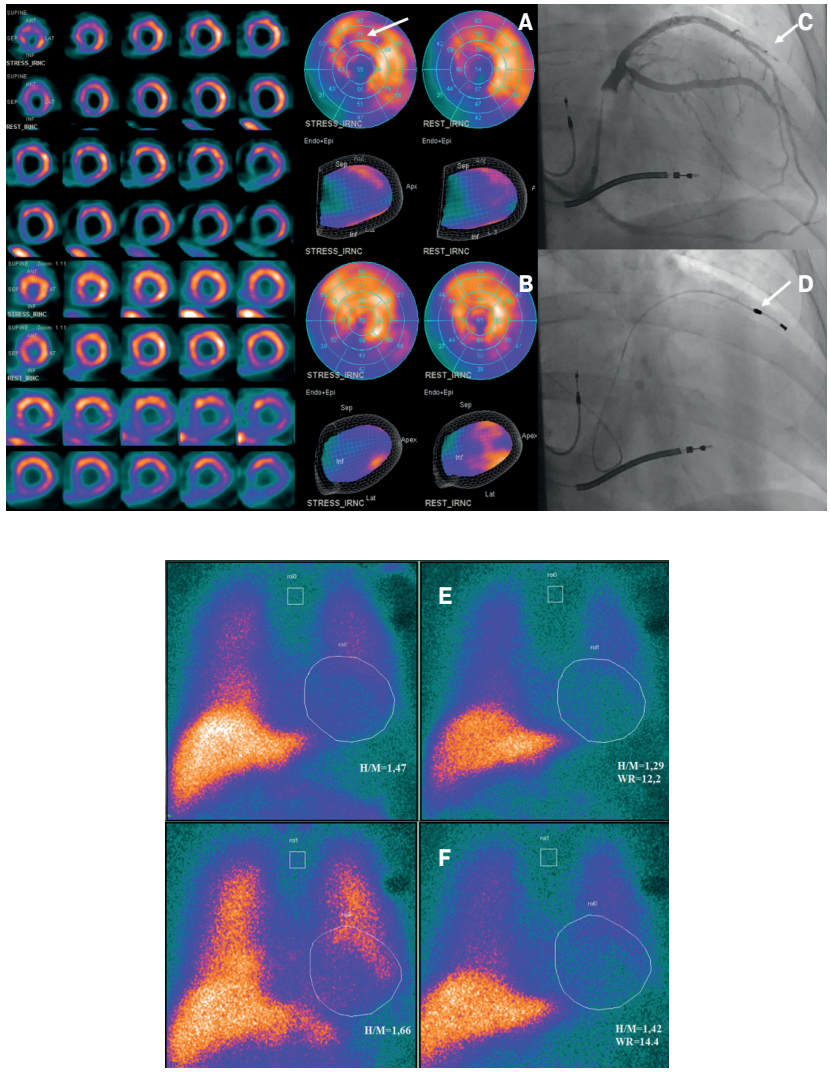

Figure 1. Assessment of myocardial perfusion and cardiac sympathetic neural activity before and after CRT.
Note: A — data of myocardial perfusion scintigraphy before CRT device implantation. There are signs of hypoperfusion in the apical, inferior and inferior septal areas of the LV (indicated by the 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

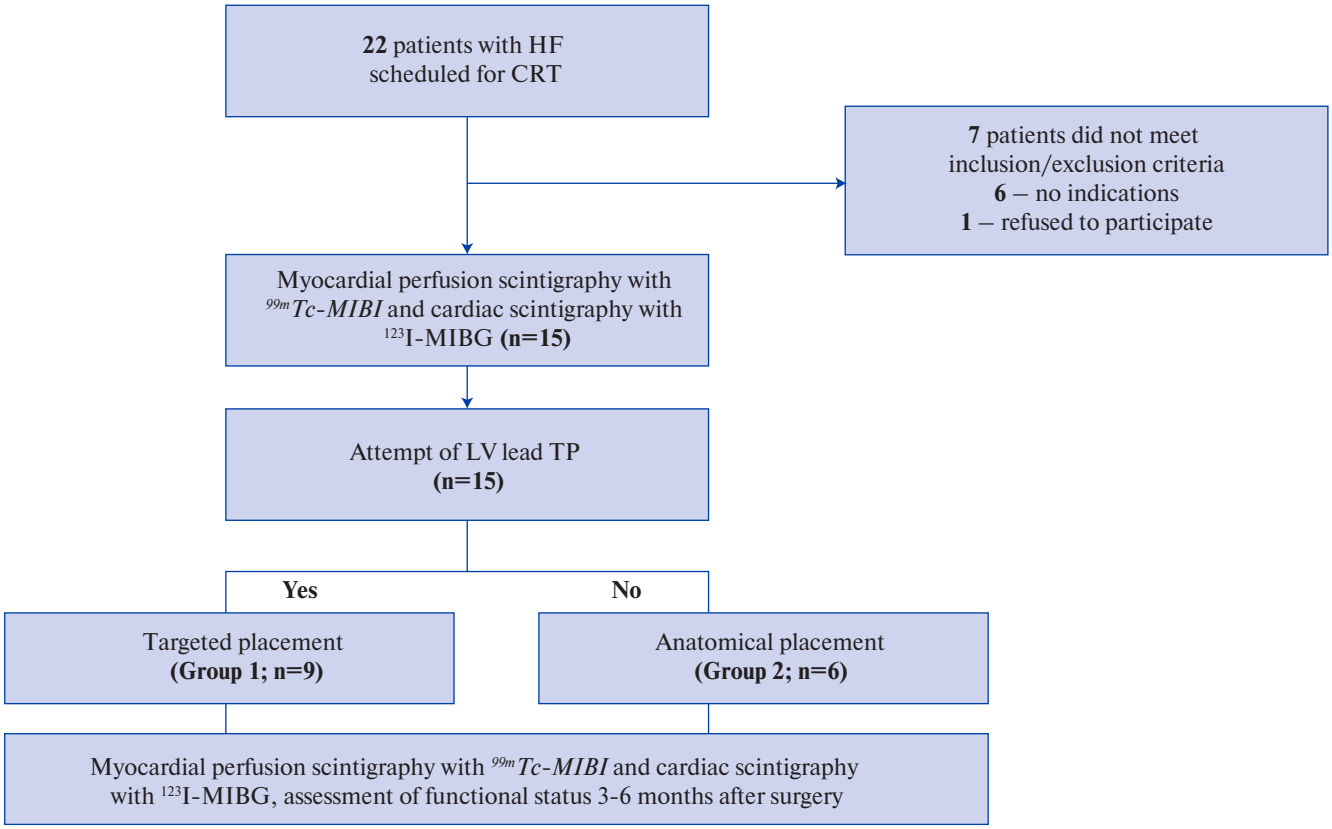

Figure 2. Study design.
Abbreviations: HF — heart failure, CRT — cardiac resynchronization therapy, LV — left ventricle.

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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Two-year follow-up of patients with heart failure with reduced ejection fraction receiving cardiac contractility modulation

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Aim. To assess the 2-year prognosis of patients with heart failure with reduced ejection fraction (HFrEF) receiving cardiac contractility modulation (CCM).

Methods. This single-center observational study included 55 patients (46 men, mean age 53±11 years) with NYHA class II-III HFrEF receiving optimal medical therapy, with sinus rhythm, QRS <130 ms or QRS <150 ms with nonspecific intraventricular conduction delay. NYHA class II and III were established in 76% and 24% of patients, respectively. All patients were implanted with CCM devices between October 2016 and September 2017. Follow-up visits were carried out every 3 months during the 1st year and every 6 months during the 2nd year of observation. The primary composite endpoint was mortality and heart transplantation. Secondary composite endpoints included death, heart transplantation, paroxysmal ventricular tachycardia/ventricular fibrillation, hospitalizations due decompensated HF.

Results. The one-year and two-year survival rate was 95% and 80%, respectively. Primary endpoint was observed in 20% of patients. NYHA class III and higher levels of N-terminal pro-brain natriuretic peptide (NTproBNP) were associated with unfavorable prognosis (p=0,014 and p=0,026, respectively). NTproBNP was an independent predictor of survival (p=0,018). CCM contributed to a significant decrease in hospitalizations due to decompensated HF (p<0,0001). The secondary endpoint was observed in 18 (33%) of patients during the 1st year. The predictor for the secondary composite endpoint was NTproBNP (p=0,047).

Conclusion. CCM is associated with a significant decrease in hospitalization rate due to decompensated HF. The 2-year survival rate of patients with NYHA class II-III HF receiving CCM was 80%. The NTproBNP level was an independent predictor of survival in patients receiving CMM for 2 years. Further longer-term studies of the CCM efficacy are required.

Key words: cardiac contractility modulation, heart failure, reduced ejection fraction, long-term results, prognosis.

Relationships and Activities: none.

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Over the past decades, new electrophysiological methods of treating patients with heart failure with reduced ejection fraction (HFrEF) have been actively developed and introduced into clinical practice. Previous studies have proven the effectiveness of cardiac resynchronization therapy (CRT) in the management of patients with HFrEF and electrical desynchrony in presence of complete left bundle branch block with QRS >130 ms and patients with nonspecific intraventricular block with QRS >150 ms. However, most patients with HFrEF have QRS ⩽130 ms and cannot be considered CRT candidates. In addition, in patients with complete right bundle branch block and nonspecific intraventricular block with QRS <150 ms, a positive response to CRT is questionable [1]. In this regard, a new method for management of HFrEF, cardiac contractility modulation (CCM), is of great interest [2]. In CCM, the application of high-amplitude electrical impulses occurs during the absolute refractory period. These impulses do not cause myocardial contraction, do not change the sequence of cardiomyocyte contraction during ventricular systole, but increase the strength and duration of cardiomyocyte action potential, which in some cases leads to reverse remodeling and improvement of the heart's pumping function [3, 4]. The implantation of the CCM system is similar to conventional permanent pacemakers, but with CCM, two ventricular leads are placed in the middle third of interventricular septum at a distance of >2 cm from each other. From these leads, during the absolute refractory period, electrical impulses of high amplitude (>7,5 V) and duration (5,14 ms) are simultaneously applied. Randomized clinical trials demonstrate the safety and the positive effect of CCM on exercise tolerance and quality of life in patients with HFrEF [5, 6]. Data on long-term efficacy and prognosis in patients receiving CCM are limited and continue to be studied [7-9]. The aim of our study was to assess the 2-year prognosis of patients with HFrEF receiving CCM.

Material and methods

From October 2016 to September 2017 at the Almazov National Medical Research Center, 55 patients were implanted with 50 CCM Optimizer IVs systems and 5 Optimizer Smart systems (Impulse Dynamics, Germany). The inclusion criteria were NYHA class II and III HFrEF, sinus rhythm, QRS <130 ms or nonspecific intraventricular block with QRS <150 ms, optimal medication therapy for heart failure (HF) for at least 3 months, signed informed consent. The exclusion criteria were a permanent atrial fibrillation, high-grade premature ventricular contractions; acute myocardial infarction or major heart surgery, percutaneous coronary intervention, valvuloplasty within 12 months and hospitalization due to decompensated HF within 3 months prior to inclusion in the study. The ethics committee of Almazov National Medical Research Center approved this study.

Initially, all patients underwent a physical examination, six-minute walk test, routine blood tests, determination of serum N-terminal pro-brain natriuretic peptide (NTproBNP), electrocardiography, 24-hour Holter monitoring, treadmill cardiopulmonary exercise test (Ochuson Pro, Jaeger, Germany). Echocardiography was performed by one researcher using a VIVID 9 ultrasound system (GE, USA). At the inclusion, the projected survival was assessed in all patients using the Seattle Heart Failure Model (SHFM).

The technique of CCM device implantation and settings were described in earlier publications [2, 4].

After implantation of the CCM system, patients were followed up by specialists in management of HF and patients with implanted devices. Follow-up visits for examination and programming of the CCM were carried out every 3 months during the first year and every 6 months during the second year of observation. The total number and average number of hospitalizations for each control point were assessed over the previous 6-month time interval.

Mortality and heart transplantation (HT) were considered as the primary composite endpoint (CEP). The secondary endpoint included a combination of the following events: death, HT, actuation of implantable cardioverter-defibrillator (ICD) due to paroxysmal ventricular tachycardia/ventricular fibrillation, hospitalization due to decompensated HF.

Changes in HF class and echocardiography parameters in this part of the study was not assessed.

Statistical analysis. The database included >200 parameters. All primary indicators were analyzed using the software packages IBM SPSS Statistic 23 and STASTICA 10. Categorical data were presented by frequencies and percentages of the total number. The contingency tables and Fisher's exact test were used for the analysis. Normally distributed data are presented as mean ± standard deviation (M±SD); medians (Me), 25% and 75% quartiles; minimum and maximum values. To compare the deceased and the survivors according to quantitative data, independent-samples Student's t-test (normally distributed data) or the nonparametric Mann-Whitney test were used. Nonnormally distributed data was assessed using the Wilcoxon test (2 time points) and the Friedman test (3 or more time points). Survival analysis was performed using the Kaplan-Meier estimator. For comparative analysis of individual factors that could potentially affect survival

and death time, we used the log-rank test and regression models. The likelihood of a secondary CEP was assessed by the binary logistic regression. The predictive assessment was performed using ROC analysis. The differences were considered significant at p<0,05.

Clinical characteristics of patients. The study group consist of 46 men (84%) and 9 women (16%) aged 27-73 years. Their clinical characteristics are presented in Table 1. Left ventricle ejection fraction (LVEF) was 14-38%. Class II and III HF were diagnosed in 76% and 24% of cases, respectively. In the group of patients with coronary artery disease, 30% had class II angina, 55% had previously undergone myocardial revascularization. Initially, ICD was recorded in 22% of patients. Other patients were assessed for indications for ICD insertion for primary prevention of sudden cardiac death (SCD). All patients received standard HF therapy: 96% — angiotensin-converting enzyme inhibitors or angiotensin type 1 receptor antagonists, 100% — β-blockers, 93% — mineralocorticoid receptor antagonists, 100% — diuretics. Angiotensin receptor neprilysin inhibitors were not used in this group of patients. Low values of the cardiopulmonary exercise test (peakVO_2 <13 ml/kg/min) were found in 15% of patients with class III HF, but due to age and comorbidities, they were not considered HT candidates. ICD insertion for the primary prevention of SCD was performed in 21 (38%) patients during the first year and in 3 (4%) patients during the second year of follow-up. The target percentage of therapeutic stimulation at baseline and during the two-year follow-up period was 92-94%.

Results

Adverse events associated with device implantation

There were no intraoperative complications during CCM insertion. In the early postoperative period, 1 patient pocket infection of device, which required explantation on the 6th day. By 3 months after implantation, CCM pocket stimulation due to ventricular lead insulation failure. In the period from 12 to 18 months, the need to cut off one of the ventricular leads was in 48% of patients. In 11 (20%) patients, revision and replacement of both ventricular leads were performed.

Endpoint analysis

Two-year follow-up revealed that 44 (80%) patients survived. Primary CEP (death and HT) were noted in 11 (20%) patients (91% — men): 5 (9,1%) deaths were recorded due to decompensated HF, 4 (7,3%) — due to SCD (patients without an implanted ICD); 1 (1,8%) patient underwent HT, 1 (1,8%) patient died due to cancer detected 6 months after implantation of the CCM device (Figure 1).

Significant factors effecting mortality were the class III HF in comparison with class II HF (p=0,014) and NTproBNP value (p=0,026). The distribution of groups depending on HF class and NTproBNP is presented in Table 2.

Survival analysis using the log-rank test revealed that patients differed depending on the initial HF class (p=0,007). Patients with class IIICHF had the worst prognosis. During 2 years, in patients with initial class II and III HF, mortality rate was 12% and 46%, respectively (Figure 2, Table 3).

To analyze the predictive value of HF class and NTproBNP values, ROC analysis was performed (Figure 3). The area under the curve was 0,69 (sensitivity — 55%; specificity — 84%) and 0,73 (sensitivity — 91%; specificity — 50%) for models based on HF class and NTproBNP, respectively, which indicates fair and good quality of models [10].

To assess the relationship between survival and predictors, which showed their significance in univariate analysis (p<0,001 for NTproBNP and p=0,009 for HF class), Cox multivariate regression was used (Table 4).

It was shown that the baseline concentration of NTproBNP was a significant independent predictor of survival, and with an increase in baseline NTproBNP by an additional 100 units, the risk of death in HFrEF patients receiving CCM increased by 2% within 2 years (p=0,018).

The prognosis of an unfavorable outcome in patients receiving CCM did not depend on such parameters as sex (p=0,67), age (p=0,14), causation of disease (p=0,25), LVEF (p=0,91). Thus, the survival rate did not differ in the subgroups of patients who had LVEF >25% and LVEF ⩽25% (p=0,99). Cut-off of one of the ventricular leads also did not affect mortality and/or hospitalizations during the two-year follow-up period (p=0,31 and p=0,44, 12 and 24 months, respectively).

Secondary CEP during 24-month follow-up reached 18 (33%) patients. Hospitalizations due to decompensated HF in the first 6 months after device implantation were registered in 5 (9%) patients compared with 38 (69%) patients before implantation (p<0,0001). This effect was maintained during 2 years of follow up. Each subsequent 6 months the number of hospitalized patients due to decompensated HF did not increase and amounted to 8%, 10% and 9% for the period of 12, 18 and 24 months, respectively (Figure 4, Table 5).

Ventricular arrhythmias were not recorded during 2 years of follow-up.

To assess the likelihood of secondary CEP, the stepwise binary logistic regression was used. NTproBNP concentration was associated with secondary CEP. Chi-square distribution with 1

Table 1

Clinical characteristics of patients before device implantation

Parameter	
Sex (men/women), n (%)	46/9 (84/16%)
Age, years, Me [Q1; Q3]	55 [45;61]
Minimum/maximum, years	27-73
Body mass index, kg/m^2, Me [Q1; Q3]	29 [25;32]
Office systolic blood pressure, mm Hg, Me [Q1; Q3]	110 [105;120]
Orthostatic systolic blood pressure, mm Hg, Me [Q1; Q3]	110 [100;120]
Resting heart rate, bpm, Me [Q1; Q3]	67 [61;73]
Coronary artery disease, old myocardial infarction, n (%)	40 (73%)
Myocardial revascularization, n (%)	30 (55%)
Nonischemic cardiomyopathy, n (%)	15 (27%)
Diabetes, n (%)	8 (14%)
Implanted cardioverter-defibrillator at baseline, n (%)	12 (22%)
Paroxysmal atrial fibrillation, n (%)	8 (14%)
Chronic obstructive pulmonary disease, n (%)	5 (9%)
Smoking, n (%)	12 (22%)
Number of patients hospitalized 6 months before implantation, n (%)	38 (69%)
Number of hospitalizations 6 months before implantation, Me [Q1; Q3]	1 [0;1]
Minimum/maximum number of hospitalizations, n	0-4
NYHA class of HF, Me [Q1; Q3]	2 [2;3]
Six-minute walk test, m, Me [Q1; Q3]	385,00 [346,00;450,00]
Glomerular filtration rate (MDRD), ml/min/1,73 m^2, Me [Q1; Q3]	79 [62;92]
Hemoglobin, g/l, Me [Q1; Q3]	149 [135;154]
Sodium, mol/l, Me [Q1; Q3]	140 [138;142]
Maximal oxygen uptake, ml/kg/min, Me [Q1; Q3]	16,5 [12,4;18,4]
NTproBNP, pg/ml, Me [Q1; Q3]	1094 [569;1749]
LVEF, %, Me [Q1; Q3]	26,00 [21,00;31,00]
LV end-diastolic volume, ml, Me [Q1; Q3]	249,00 [206,00;315,00]
LV end-systolic volume, ml, Me [Q1; Q3]	185,00 [136,00;230,00]
QRS, ms, Me [Q1; Q3]	106 [100;121]
Target therapeutic stimulation, initially, after 6, 12, 18, 24 months of follow-up, %, M±SD	92±13,9, 94±9, 94±10, 91±14,5, 92±11
Beta blockers, n (%)	55 (100%)
ACE inhibitors/ARBs, n (%)	52 (96%)
Mineralocorticoid receptor antagonists, n (%)	51 (93%)
Loop diuretics, n (%)	53 (96%)
Amiodarone, n (%)	7 (13%)

Notes: data are presented: 1) n — absolute number of patients, (%); 2) Me [Q1; Q3] — median and quartiles; 3) M±SD — mean±standard deviation.

Abbreviations: ACE — angiotensin-converting enzyme, ARBs — angiotensin II receptor blockers.

degree of freedom was 7,3 (p=0,007), which means that the predictor is associated with secondary CEP. Odds ratio of 1,001 means that the risk of secondary CEP increases by 0,1% with an increase in NTproBNP by 1 unit (Table 6).

To assess the predictive value of NTproBNP and find the optimal classification threshold, a ROC analysis was performed. The area under the curve was 0,716, which is defined as good on the AUC expert scale (Figure 5). ROC-curve revealed the optimal

Table 2

HF class and NTproBNP values in the groups of survivors and deceased HF patients receiving CCM: 2-year follow-up

Parameter	Survivors n=44 (80%)	Deceased n=11 (20%)
NYHA class II	37 (84,09%)	5 (45,45%)
NYHA class III	7 (15,91%)	6 (54,55%)
p=0,014		
NTproBNP, пг/мл M±SD Me [Q1;Q3]	 1184,35±927,36 987,90 [526,75;1449,00]	 3576,45±4213,27 1200,00 [1094,00;4670,00]
p=0,026		

Note: n — absolute number of patients.
Abbreviations: NTproBNP — N-terminal pro-brain natriuretic peptide, NYHA — New York Heart Association.

Table 3

Number of patients with a risk of primary endpoint

Follow-up period Patient group	Days of follow-up								
	100	200	300	400	500	600	700	800	900
NYHA class II (n)	42	42	41	41	41	40	39	37	37
NYHA class III (n)	13	11	11	10	10	8	7	6	6

Abbreviation: NYHA — New York Heart Association.

Table 4

Multivariate survival analysis

Parameter	B value	P value	RR	95% CI	
NTproBNP	0,0002	0,018	1,0002	1,000037	1,00040
HF class	1,11	0,11	3,03	0,78	11,78

Abbreviations: CI — confidence interval, RR — relative risk, HF — heart failure, NTproBNP — N-terminal pro-brain natriuretic peptide.

classification threshold (p=0,302), at which the sensitivity was 73,7% and the specificity was 65,7%.

Prior to CCM implantation, the prognosis of survival was assessed in all patients using the SHFM. The mean 1-year and 2-year survival rates were 97,7±1,2% and 93,8±11,9%, respectively. The actual — year and 2-year survival was 94,5% and 80%, respectively (with the exclusion of the patient who died due to cancer). The SHFM overestimated survival rates by 3,2% and 13,8%, respectively.

Logistic regression with factors included in SHFM (sex; age; weight; HF class; causation of disease; initial LVEF; systolic blood pressure; taking angiotensin-converting enzyme inhibitors, angiotensin type 1 receptor antagonists, β-blockers, mineralocorticoid receptor antagonists, statins, allopurinol, diuretics; presence of ICD; levels of hemoglobin, lymphocytes, uric acid, total cholesterol, serum sodium) provided a significant predictive model (p<0,001, specificity — 95,5%, sensitivity — 81,8%). Four factors associated with an unfavorable outcome were identified: male sex (p=0,045), HF class (p=0,002), orthostatic systolic blood pressure (p=0,017), serum cholesterol (p=0,010). Separately, only HF class was significantly associated with a poor prognosis (p=0,012).

Discussion

The survival rate of patients with class II-III HFrEF, sinus rhythm and implanted CMM devices

Table 5

Hospitalizations due to decompensated HF depending on HF class at baseline: 2-year follow-up

Parameter \ Follow-up period	Before implantation	Follow-up			
	(-) 6 months	6 months	12 months	18 months	24 months
NYHA class II					
Number of hospitalizations, n	32	4	2	2	5
Number of hospitalized patients, % (n)	64% (27)	7% (3)	5% (2)	5% (2)	8% (3)
NYHA class III					
Number of hospitalizations, n	19	2	2	7	3
Number of hospitalized patients, % (n)	100% (11)	18% (2)	20% (2)	38% (3)	16% (1)

Abbreviation: NYHA — New York Heart Association.

Table 6

Relationship between the secondary CEP and the initial data

Parameter	Multiple regression coefficient	p	Odds ratio	CI (95%)
LV ESV	0,017	0,019	1,017	1,001-1,034
NTproBNP	0,00049	0,046	1,0005	1,000-1,001

Abbreviations: LV ESV — left ventricular end-systolic volume, NTproBNP — N-terminal pro-brain natriuretic peptide.

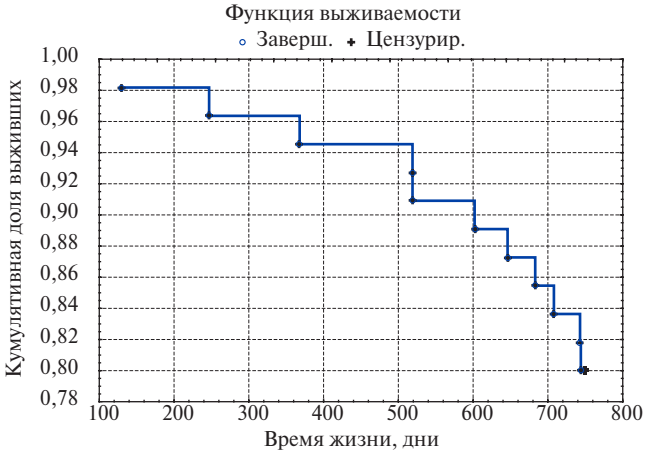


Figure 1. Kaplan-Meier survival curve for all-cause mortality and HT in all patients.

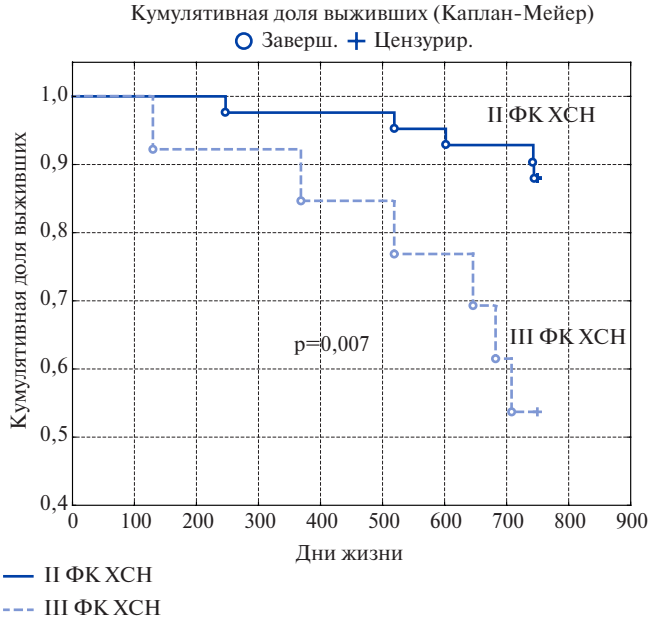
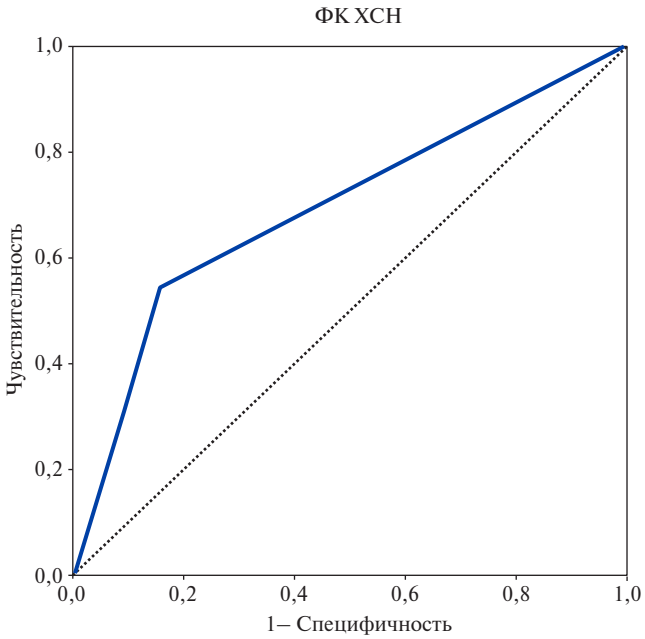


Figure 2. Kaplan-Meier survival curves for all-cause mortality and HT depending on HF class before implantation.

in the presented single-center prospective nonrandomized observational study for the first and second years was 95% and 80%, respectively. Third of patients reached secondary CEP in 2 years. With CCM, from the 6th month, there was a significant decrease in the number of hospitalizations and no life-threatening ventricular arrhythmias were detected.

Randomized and register studies demonstrate a positive effect of CCM on quality of life and exercise tolerance, assessed by ventilatory threshold and/or maximal oxygen uptake. At the same time, the data



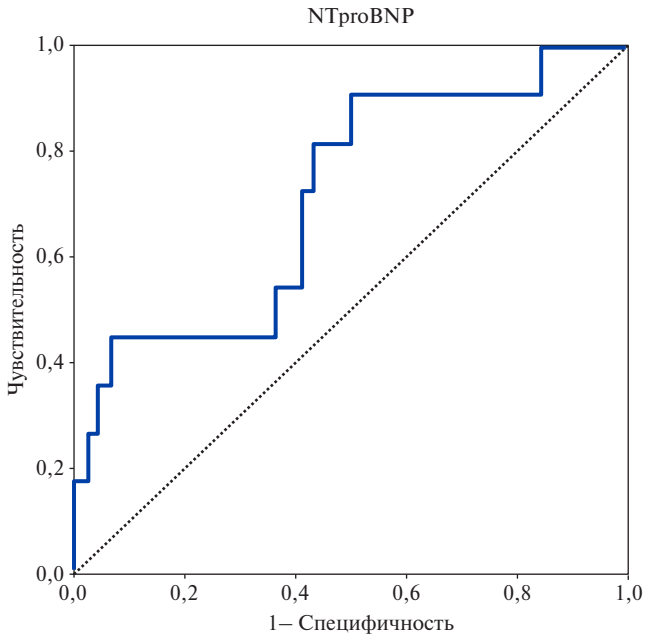


Figure 3. ROC curves for HF class and NTproBNP.

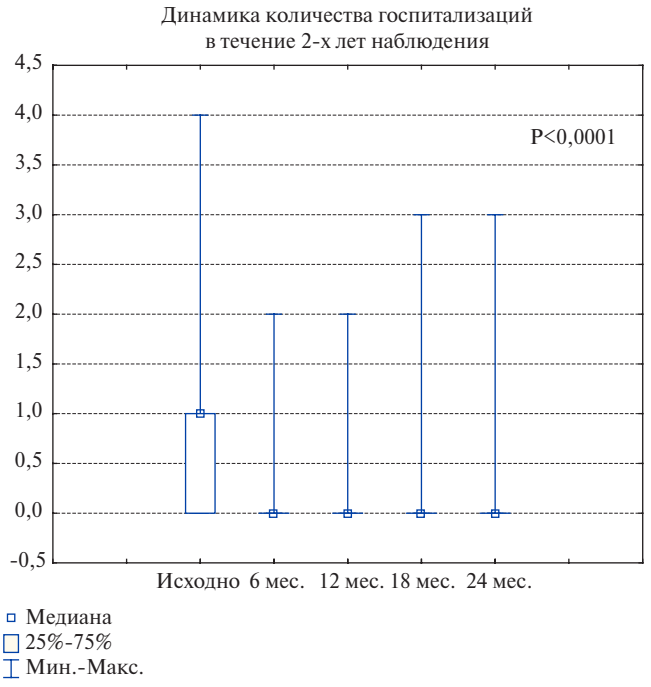


Figure 4. Changes in hospitalization rate during the 2-year follow-up.

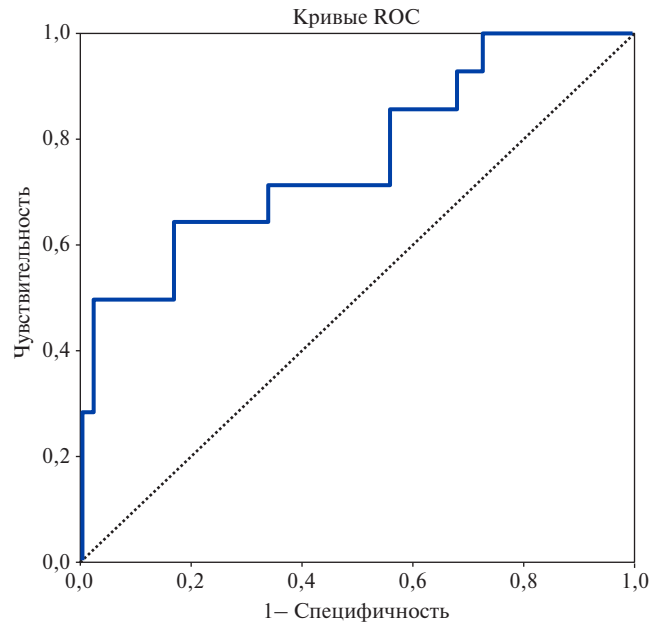


Figure 5. ROC-curve for the CEP risk.

on the effect of CCM on hard endpoint is ambiguous. It should be noted that the FIX-HF randomized clinical trials were limited to short follow-up periods of 3 to 12 months [5, 6]. In the FIX-FH-5C study, the composite endpoint (cardiovascular mortality and hospitalizations due to HF) by 24 weeks of follow-up was significantly lower in the group of CCM and optimal drug therapy compared with patients receiving only HF medication therapy: 2,9% vs 10,8%, respectively (p=0,048) [6]. Similar data were obtained in the European CCM-REG registry, which included 140 patients with class III-IV HF and LVEF of 25-45% [11]. Within 24 months, the all-cause hospitalization rate and due to HF significantly decreased both in the entire group and in the subgroup of patients with LVEF of 25-34% (n=83). The

survival rate for 1, 2 and 3 years in this subgroup was 89,6%, 82% and 79,4%, respectively, and did not differ significantly from the predicted survival rate according to the SHFM (91,8%, 84,6% and 78%, respectively). In the CCM-REG subgroup with LVEF of 35-45%, 3-year mortality was significantly less than predicted, amounting to 94,5% and 91,7% and 88,0%. Moreover, as in our study, the causation of disease and LVEF in the CCM-REG registry did not affect the prognosis of patients, and the SHFM overestimated the survival rate in the group of patients with LVEF <35%, without reaching the significance level. No influence of ischemic HF on outcomes during a two-year follow-up period is probably due to the high percentage of revascularization and the lack of indications for this procedure at the time of CCM implantation. According to Kloppe A, et al. (2016), the SHFM significantly underestimated the survival rate in patients with class II-III HFrEF [9]. The SHFM was developed with the American population and is based on simple clinical, laboratory and therapeutic characteristics for use in outpatients. In our protocol, the NTproBNP level was an important independent predictor influencing the prognosis. Along with this indicator, the severity of HF significantly affected the actual and predicted survival in the study group. Thus, it was previously shown that the most unfavorable prognosis is for patients with class III HF [12]. Obviously, such patients require closer observation and timely referral to other types of high-tech medical care, including HT.

In a meta-analysis of 4 FIX-HF randomized clinical trials, Mando R, et al. (2019) did not find a significant difference in hospitalization and mortality rates between the groups of HFrEF patients receiving and not receiving CCM [13]. It should be noted that there were no differences in arrhythmias between the comparison groups, including ventricular arrhythmias requiring intervention. In our study cohort, there was more than 7% of SCD cases in patients without ICD and previous decompensated HF, which justifies the use of ICD in combination with CCM in this category of patients.

NTproBNP was independently associated with secondary CEP within 2 years in patients receiving CCM. Interestingly, the cut-off of one of the leads did not affect mortality and hospitalization. This is consistent with the study by Röger S, et al. (2017), where single-lead stimulation did not have a significant effect on HF class, maximal oxygen uptake and 6-month mortality, compared to stimulation with 2 leads [14].

Study limitations. This study was observational and did not have a comparison group. In some patients, ICD was not implanted, and in cases of out-hospital death, the contribution of cardiac arrhythmias is not excluded. The drug therapy of HF for 2 years underwent changes in accordance with status of patients and the analysis of its effect on the endpoints was not carried out.

Conclusion

CCM is associated with a significant decrease in the number of hospitalizations due to decompensated HF. In patients with class II and III HF, the one- and two-year survival rate was 95% and 80%, respectively. The predictors of an unfavorable prognosis within 2 years (death/HT) were NYHA class III HF and a higher level of NTproBNP before CCM. The only independent predictor of survival, as well as the of the secondary CEP within 2-year follow-up, was the NTproBNP level.

Relationships and Activities: none.

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Drug-induced bradycardia as a medical and social problem: data from the Cardiac Drug Overdoses Hospital Registry (STORM)

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Aim. To analyze hospitalizations due to drug-induced bradyarrhythmia (DIB) over a 5-year period (2014-2018), its clinical characteristics, causes and outcomes.

Material and methods. The analysis included all hospitalizations due to DIB at the Ryazan Regional Vascular Center in 2017 and 2018 and retrospectively in 2014.

Results. A total of 325 cases of DIB were included in the analysis (age 76,0 [68,0; 82,0] years; men — 26,1%). The proportion of DIB as a hospitalization cause in 2017 increased by 4,3 times compared to 2014 (p<0,001), in 2018 compared to 2014 — by 6,3 times (p<0,001) and compared to 2017 — by 46,2% (p=0,001). We recorded the following manifestations of DIB: bradycardia (<40 bpm — 51,4%), atrioventricular (31,7%) and sinoatrial (29,2%) block, syncope (36,0%), Frederick's syndrome (8,6%), pauses >3 s (5,9%). Management in intensive care was required in 42,2% of patients, temporary cardiac pacing — in 7,7%, permanent pacemaker — in 6,2%. Mortality rate was 6,2%. Before hospitalization, patients took beta-blockers (65,1%), antiarrhythmic agents (39,6%), cardiac glycosides (23,0%), I_1-imidazoline receptor agonist moxonidine (13,5%, its prescription rate increased 8,9 times over 5 years, p=0,004), nondihydropyridine calcium channel blockers (7,9%), and other drugs (15,4%). In 60,1% of patients, ⩾2 drugs with bradycardic action were used, in 22,0% — ⩾3, in 8,1% — ⩾4, in 10,6% — with an excessive single/daily dose.

Conclusion. The medical and social significance of DIB have been demonstrated. DIB due to exceeding the recommended dose was associated with independent try of patients to manage the deterioration. In other cases, DIB was due to the summation/potentiation of several drugs' action, the comorbidities contributing to the development of bradyarrhythmia and/or changes in pharmacokinetic properties of drugs.

Key words: drug-induced bradycardia, bradyarrhythmia, adverse drug reaction, overdose.

Relationships and Activities: none.

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The term "bradyarrhythmias" (BA) unites a heterogeneous group of cardiac arrhythmias characterized by a delayed production of electrical impulses or a slowed ventricular rhythm associated with a conduction block [1]. The main etiological factors of BA are degeneration, ischemia, inflammation, trauma and etc. Pharmaceuticals, of course, may be also such a factor, but they do not occupy leading positions [2]. There are publications devoted to overdose of nondihydropyridine calcium channel blockers (CCB) [3, 4], beta-blockers (BB) [4] and cardiac glycosides [5, 6]. It should be noted that for the listed drugs, the bradycardic effect is a direct pharmacodynamic action, well studied and well known to physicians.

In recent years, the list of drugs with bradycardic effect has expanded significantly [2, 7]. Moreover, some drugs (for example, psychoactive drugs, muscle relaxants [2]) are prescribed even by non-cardiologists/therapists. We did not find any data for an increase in the relevance of drug-induced bradyarrhythmia (DIB) in the literature, but in our clinical practice we encountered a significant increase in hospitalizations due to DIB. The pilot study (18 months) confirmed this data and justified the need for further study of DIB [8].

Thus, the purpose of this work was to analyze hospitalizations due to DIB over a 5-year period (2014-2018), its clinical characteristics, causes and outcomes.

Material and methods

This study was performed in accordance with the Helsinki declaration and Good Clinical Practice standard at the Ryazan Regional Vascular Center. The medical ethics committee approved this study.

The analysis included all hospitalizations with verified DIB in 2017 and 2018, as well as retrospectively in 2014. Inclusion criteria were age ⩾18, verified DIB, signed informed consent. Exclusion criterion was BA due to acute coronary syndrome and other *severe* diseases. No additional interventions in the diagnostics or treatment of patients were performed within the registry.

Statistical processing was performed using the software packages Excel 2010 (Microsoft Corporation, USA) and Statistica 10.0 (Stat Soft Inc., USA). The Shapiro-Wilk test was used to determine the normality of distribution. The prevalence of a trait/event is presented as absolute and relative values (n and %). Nonnormally distributed quantitative variables are presented as median and interquartile range: Me [Q1; Q3]. To compare the relative qualitative traits in two independent groups, we used the Pearson's chi-squared test or Fisher's exact test in the case of the lowest expected value <5. Quantitative characteristics was compared using the Mann-Whitney test. Differences were considered significant at $p<0,05$.

Results

In total, 325 clinical cases of DIB were included in the analysis, which amounted to 1,0% of all hospitalizations to the cardiology departments. Most of them were persons of older age groups (76,0 [68,0; 82,0] years; ⩾65 — 83,7%, ⩾75 — 57,9%). The proportion of men was 26,1%.

At the same time, only 13,5% of the analyzed cases was in 2014. In 2017, the absolute number of hospitalizations for DIB increased by 2,6 times compared to 2014, in 2018 — by 3,8 times compared to 2014 and by 46,5% compared to 2017. This was accompanied by an increase in the proportion of DIB among the hospitalization causes: in 2017 compared to 2014 by 4,3 times ($p<0,001$), in 2018 compared to 2014 by 6,3 times ($p<0,001$) and compared to 2017 by 46,2% ($p=0,001$). There were severe clinical manifestations, a significant number of patients requiring intensive care, artificial pacing and a significant level of hospital mortality (11,4% in 2014). A decrease in the glomerular filtration rate (GFR) <45 ml/min*1,73 m^2 was recorded in more than half (57,0%) of patients, <30 ml/min*1,73 m^2 — in every third case (31,7%), <15 ml/min*1,73 m^2 — in every tenth case (10,4%, Table 1).

At the next stage of the study, the analysis of drug therapy before hospitalization was carried out. All drugs with the same international nonproprietary name were regarded as one and the same medicinal product. First of all, attention is drawn to the high frequency of taking (60,1%) several drugs with bradycardic effect at once. Moreover, 22,0% of patients took ⩾3 of these drugs at once. There were even patients (8,1%), which took ⩾4 drugs with bradycardic effect. The relative frequency of therapy with several drugs with bradycardic effect among DIB cases did not change significantly over a 5-year period (except for an increase in the frequency of four-drug therapy in 2017-2018), but the absolute number of such cases increased (Table 2).

Among the groups of drugs with bradycardic effect taken by the patient before hospitalization, the following were most often recorded:

– BB (65,1%, no significant change in prescription rate),

– antiarrhythmic agents (39,6%, no change in prescription rate),

– cardiac glycosides (23.0%, no change in prescription rate),

– I_1-imidazoline receptor agonist moxonidine (13,5%, prescription rate increased 8,9 times over 5 years, $p=0,004$; in 2018, moxonidine was registered in every fifth case of hospitalization with DIB),

Table 1

Clinical and demographic characteristics of patients hospitalized with drug-induced bradycardia in 2014-2018

Parameter	Year of follow-up			Total	p_{1-2}	p_{1-3}	p_{2-3}
	2014	2017	2018				
	1	2	3				
n	44	114	167	325	-	-	-
Proportion of all hospitalizations to therapy departments,%	0,3	1,3	1,9	1,0	<0,001	<0,001	0,001
Age, years, Me [Q1; Q3]	73,5 [67,0; 82,0]	77,0 [70,0; 81,0]	77,0 [68,0; 82,0]	76,0 [68,0; 82,0]	1,000	1,000	1,000
Proportion of men, % of n	22,7	27,2	30,5	26,1	0,566	0,309	0,545
Clinical manifestations							
Bradycardia <40 bpm, % of n	47,7	53,5	50,9	51,4	0,514	0,708	0,667
SA block, % v	45,5	29,0	25,2	29,2	0,049	0,009	0,480
Frederick's syndrome, % of n	2,3	14,0	6,6	8,6	0,042	0,307	0,038
Heart pause >3 sec, % of n	4,6	3,5	7,8	5,9	0,760	0,457	0,140
Syncope, Adams-Stokes syndrome, % of n	31,8	36,8	36,5	36,0	0,554	0,562	0,957
First-degree AV block, % of n	9,1	7,0	10,2	8,9	0,659	0,830	0,361
Second-degree AV block, % of n	6,8	10,5	9,0	9,2	0,476	0,030	0,666
Third-degree AV block, % of n	4,6	16,7	14,4	13,6	0,044	0,078	0,567
Renal filtration function							
Known initial creatinine level, n1 (% of n)	43 (97,7)	111 (97,4)	155 (92,8)	309 (95,1)	0,898	0,228	0,095
GFR <60 ml/min*1,73 m^2, % of n1	83,7	82,0	73,0	77,7	0,799	0,146	0,084
GFR <45 ml/min*1,73 m^2, % of n1	65,1	56,8	54,8	57,0	0,344	0,228	0,756
GFR <30 ml/min*1,73 m^2, % of n1	32,6	31,5	31,6	31,7	0,902	0,906	0,989
GFR <15 ml/min*1,73 m^2, % of n1	9,30	9,9	11,0	10,4	0,909	0,754	0,782
Treatment and outcome							
Hospitalization by EMS, % of n	84,1	92,0	96,4	93,5	<0,001	<0,001	0,189
Management in intensive care unit, % of n	50,0	42,1	40,1	42,2	0,371	0,238	0,740
Temporary pacing, % of n	6,8	5,3	9,6	7,7	0,705	0,569	0,186
Permanent pacing, % of n	2,3	3,5	9,0	6,2	0,691	0,135	0,073
Death, % of n	11,4	7,0	4,2	6,2	0,373	0,068	0,301

Abbreviations: SA — sinoatrial, AV — atrioventricular, GFR — glomerular filtration rate, EMS — emergency medical service.

– nondihydropyridine CCB (7,9%, prescription rate decreased from 19,5% to 4,9%, p=0,002),

– other drugs with bradycardic effect (15,4%, prescription rate in 2018 increased by 2,1 times compared to 2017, p=0,021).

Of the 325 analyzed cases, the dose of drugs taken before hospitalization was known in 227 patients (69,8%), which made it possible in these cases to analyze the adequacy of treatment regimen. Excess of the recommended single and/or daily dose was observed only in every tenth (10,6%) case.

Discussion

The results obtained demonstrated the high medical and social significance of DIB: an increase over the analyzed 5-year period in the absolute

Table 2

Drug therapy before hospitalization

Parameter	Year of follow-up			Total	p_{1-2}	p_{1-3}	p_{2-3}
	2014	2017	2018				
	1	2	3				
n	44	114	167	325	-	-	-
Drugs with bradycardic effect							
BB, % of n	68,3	69,0	61,6	65,1	0,931	0,426	0,203
Antiarrhythmic agents, % of n	43,9	43,4	36,0	39,6	0,952	0,349	0,215
Cardiac glycosides, % of n	17,1	25,6	22,6	23,0	0,266	0,945	0,551
I_1-imidazoline receptor agonist, % of n	2,4	6,2	21,3	13,5	0,353	0,004	<0,001
Nondihydropyridine CCB, % of n	19,5	8,0	4,9	7,9	0,043	0,002	0,293
Other drugs with bradycardic effect, % of n	19,5	8,9	18,9	15,4	0,069	0,929	0,021
Number of drugs taken							
⩾2, % of n	73,2	55,8	59,8	60,1	0,051	0,113	0,507
⩾3, % of n	24,4	18,6	23,8	22,0	0,427	0,935	0,302
⩾4, % of n	7,3	4,4	9,8	8,1	0,475	0,630	0,010
Analysis of treatment regimen							
Dose is known, n_1 (% of n)	21 (47,7)	79 (69,3)	127 (76,0)	227 (69,8)	0,012	<0,001	0,209
Proportion of cases exceeding thee recommended dose, % of n_1	14,3	12,7	9,4	10,6	0,844	0,496	0,468

Abbreviations: BB — beta-blockers, CCB — calcium channel blockers.

number of hospitalizations, an increase in the proportion of DIB in the hospitalization structure and the high level of in-hospital mortality. Such a pronounced changes, in our opinion, cannot be explained by any changes in the health care organization. We believe that the prevalence of DIB may be even higher, and the prognosis even more unfavorable, since the register did not include prehospital deaths. At the same time, postmortem verification of the relationship between a death and inadequate treatment regimen in routine clinical practice seems to be difficult. Most likely, such lethal cases are registered under the guise of other, more often chronic, diseases [9, 10].

The majority of patients hospitalized for DIB were elderly and senile persons. On the one hand, this corresponds to the age structure of cardiovascular morbidity [11-13]. On the other hand, such patients have a high risk of DIB due to pharmacokinetic changes of drugs, multimorbidity, polypharmacy, and drug interactions associated with it. Also, a risk factor for inadequate treatment regimen is the cognitive impairment at this age. There is experience in limiting the use of bradycardic drugs in elderly and senile age (STOPP criteria, Beers List, etc.) [14].

It also relevant to draw the attention to DIB problem due to the inclusion of a combination of BB with nondihydropyridine CCB in the 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes [15] without specifying clear criteria for monitoring the safety and restrictions in elderly and senile people.

Drug overdose as a cause of DIB was quite expected. DIB due to exceeding the recommended dose was associated with independent try of patients to manage the deterioration (hypertensive crisis, episode of angina and/or atrial fibrillation). At the same time, patients increased the dose of the drug due to non-achievement of the expected effect, not taking into account the bradycardic effect. It should be emphasized that the proportion of moxonidine prescription in patients with DIB increased significantly over the observed period (2014-2018). At the same time, some patients used moxonidine as a chronic therapy, others — for treatment of hypertensive crisis, and others — in combination.

The high prevalence of clinical manifestations of bradycardic drug overdose without exceeding the therapeutic dose was quite unexpected for the researchers. The main reason (54,1%) of this is the summation/potentiation of several drugs' action. The second reason, in our opinion, should be considered the development/progression of cardiac disease, which itself contributes to BA [2]. In such cases, previously optimal doses of drugs with bradycardic effect become excessive. In this group, permanent pacing with an implantable pacemaker was required in 9,4% of cases. Timely identification of indications for permanent pacing would allow avoiding DIB and, if necessary, safely continuing therapy with bradycardic drugs.

Finally, a significant role, in our opinion, was played by a decrease in the renal filtration function. The influence of other reasons (multimorbidity, drug interactions), which could lead to a change in the pharmacokinetics of the drug, cannot be ruled out.

Conclusion

The medical and social significance of DIB have been demonstrated. It has been demonstrated that DIB due to exceeding the recommended dose occurs only in every tenth case and is associated, most often, with independent try of patients to manage the deterioration. The majority of analyzed DIB cases were associated not with a violation of treatment regimen, but with the lack of a comprehensive assessment of therapy safety in general.

Relationships and Activities: none.

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