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Research article

Disease-Modifying Therapy of Chronic Heart Failure on the Background of Heart Rhythm and Conductivity Disorders (Clinical Case)

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The article presents a clinical case of the development and progression of chronic heart failure (CHF) in a patient with postinfarction cardiosclerosis after implantation of a permanent pacemaker due to binodal dysfunction. The progression of CHF was exacerbated by the patient's transition to a permanent form of atrial fibrillation. Complex therapy for CHF, including cardiac resynchronization therapy, drug therapy with valsartan + sacubitril, empagliflozin, eplerenone, metoprolol succinate (quadrotherapy) led to a complete recovery of the ejection fraction (EF) of the left ventricle. After the patient stopped taking one of the components of quadrotherapy (valsartan + sacubitril), there was a tendency to decrease in EF. The clinical case emphasizes the importance of the timely transformation of traditional permanent pacing into cardiac resynchronization therapy and the appointment of complex modern drug therapy for CHF. When an improvement or restoration of EF is achieved, it is advisable to continue the therapy against which the improvement was obtained in order to avoid the negative consequences that are possible when the components of the quadrotherapy are cancelled.

Keywords: schronic heart failure; atrial fibrillation; permanent pacing; cardiac resynchronization therapy; valsartan + sacubitril; rivaroxaban.

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Научная статья

Болезнь-модифицирующая терапия при хронической сердечной недостаточности на фоне нарушений ритма сердца и проводимости (клинический случай)

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В статье представлен клинический случай развития и прогрессирования хронической сердечной недостаточности (ХСН) у пациента с постинфарктным кардиосклерозом после имплантации постоянного электрокардиостимулятора по поводу бинодальной слабости. Переход пациента на постоянную форму фибрилляции предсердий усугубил прогрессирование ХСН. Комплексная терапия ХСН, включающая сердечную ресинхронизирующую терапию, медикаментозную терапию валсартаном+сакубитрил, эмпаглифлозином, эплереноном, метопролола сукцинатом (квадротерапия) привела к полному восстановлению фракции выброса (ФВ) левого желудочка. После прекращения пациентом приема одного из компонентов квадротерапии (валсартана+сакубитрил) наметилась тенденция к снижению ФВ. Клинический случай подчеркивает важность своевременного преобразования традиционной постоянной электрокардиостимуляции в сердечную ресинхронизирующую терапию и назначения комплексной современной медикаментозной терапии ХСН. При достижении улучшения или восстановлении ФВ целесообразно продолжить терапию, на фоне которой получено улучшение, чтобы избежать негативных последствий, возможных при отмене

Ключевые слова: хроническая сердечная недостаточность; фибрилляция предсердий; постоянная электрокардиостимуляция; сердечная ресинхронизирующая терапия; валсартан+сакубитрил; ривароксабан.

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ЭКО•ВЕКТОР

INTRODUCTION

The incidence of chronic heart failure (CHF) in European countries reaches 1–2% in the adult population [1]. In Russia, according to epidemiological studies, the prevalence of CHF in the general population is 7% [2]. CHF is a syndrome resulting from many diseases and conditions accompanied by myocardial damage. One of the most common causes of CHF is coronary heart disease, primarily myocardial damage during acute myocardial infarction. Cardiac arrhythmias and conduction disturbances can also contribute to the development of CHF. Atrial fibrillation (AF), especially its permanent form, is associated with the onset and progression of CHF. Violation of the physiological sequence of electrical activation of the left ventricle (LV) myocardium against the background of a complete blockade of the left branch of the bundle of His or against the background of constant pacing of the apex of the right ventricle (RV) can lead to CHF. When CHF symptoms appear and LV EF decreases against the background of traditional permament RV apical pacing, the implanted device should be upgraded to a resynchronizing device in a timely manner [1, 2].

Among the causes of CHF that are not related to cardiovascular diseases, type 2 diabetes mellitus occupies a special place. First of all, against the background of type 2 diabetes mellitus, coronary artery disease (CAD) develops and progresses. In addition, diabetes mellitus, even in the absence of CAD, can be complicated by diabetic cardiomyopathy, leading not only to CHF with preserved EF, but also to CHF with low EF [2, 3].

Modern complex drug therapy for CHF with reduced EF stops the processes of negative heart remodeling, favorably affects the prognosis, leads to an increase and even normalization of EF [4].

CLINICAL CASE

Patient S., 68, came to the clinic due to the deterioration of exercise tolerance, the appearance of shortness of breath. At the age of 51 (2001) he suffered a myocardial infarction in the basin of the anterior interventricular artery. During hospitalization for myocardial infarction, type 2 diabetes mellitus was diagnosed. Myocardial infarction led to an asymptomatic decrease in LV EF to 42%. A year after myocardial infarction, coronary bypass grafting was performed due to multivessel coronary disease and the presence of asymptomatic LV dysfunction: mammary bypass to the anterior interventricular artery, autoarterial coronary bypass grafting (grafts from the radial artery to the 1st and 2nd diagonal arteries). The patient regularly took ramipril, metoprolol succinate, atorvastatin, acetylsalicylic acid, glimepiride. Against the background of the therapy, indicators of the components of the lipid spectrum and glycemia were achieved the target level. After complete revascularization against the background of optimal, relevant for that time, therapy, EF returned to normal and reached 59% according to Echocardiography (ECHOCG) data from 2009 (Table 1). The patient felt good before 2010. In 2010, at the age of 60, there were arrhythmia. 22.574 monomorphic ventricular extrasystoles per day,

Table 1. Dynamics of echocardiographic parameters

Year	EF (%)	End-diastolic volume index EDVI (ml/m^2)	Left atrial volume index LAVI (ml/m^2)	Mitral regurgitation
2001 (Acute Myocardial Infarction)	42	No data	No data	Absent
2002 year – complete revascularization + optimal medication				
2009	59	No data	No data	Absent
2010	58	No data	No data	Absent
2012 year – permanent conventional pacing due to binodal dysfunction 2013 year – permanent form of AF				
2017	49	86	40	1st degree
2018	47	81	49	1st degree
2019 August	33	85	No data	2nd degree
2019 September	25	97	54	3rd degree
Therapy with valsartan + sacubitril, empagliflozin in addition to β-adrenergic blocker and AMPR was started, CRT-D implantation				
2020 September	60	54	No data	Absent
2021 – stopped taking valsartan + sacubitril				
2021 December	40	73	No data	1st degree

Note: AF — atrial fibrillation; AMR — mineralocorticoid receptor antagonist; CRT-D — cardiac resynchronization therapy- defibrillator; EF — ejection fraction

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37 episodes of non-sustained ventricular tachycardia were registered during 24-hour ECG monitoring (Fig. 1).

Coronary angiografy was performed to rule out coronary shuntes stenosis as the cause of ventricular arrhythmias: the shuntes were patent, and no hemodynamically significant stenoses were detected outside the bypass areas of the coronary arteries. An echocardiographic (ECHO) examination revealed cicatricial changes in the myocardium of the left ventricle (LV), with a lesion area of 31% and a local contractility index of 1.6, LV diastolic dysfunction, dilatation of the left atrium (LA), LV EF 58%. Due to the lack of indications for implantation of a cardioverter-defibrillator, a catheter procedure was performed for ventricular arrhythmias. A year later, in 2011, the patient developed paroxysmal AF against the background of binodal dysfunction that had developed by that time. Instead of acetylsalicylic acid, anticoagulant therapy was prescribed (warfarin under the control of INR with a transition to rivaroxaban 20 mg per day). Due to binodal dysfunction, complicated not only by AF, but also by syncope, in 2012 a permanent dual-chamber pacemaker (PM) was implanted. During 24-hour ECG monitoring after PM implantation it was observed an alternation of A-V sequential pacing with ventricular pacing after atrial tracking, a decrease in the number of ventricular extrasystoles to 100 per day (as compared to the year 2010), episodes of unstable ventricular tachycardia to two per day (Fig. 2). As expected, the catheter procedure for ventricular arrhythmias associated with postinfarction cardiosclerosis gave a "cosmetic effect", reducing, but not completely eliminating ventricular arrhythmias. Amiodarone was added to therapy.

A year later, in 2013, despite taking amiodarone, AF got a permanent form. One of the reasons for the AF transition to a permanent form was a high percentage (90%) of right ventricular stimulation against the background of subtotal atrioventricular (AV) blockade. Amiodarone was cancelled.

During the next scheduled ECHOCG examination in 2017, there was a decrease in EF to 49%, mild LV dilatation with an end-diastolic volume index (EDVI) of 86 ml/m^2, a slight increase in LA with an LA volume index (LAVI) of 40 ml/m^2 [5].

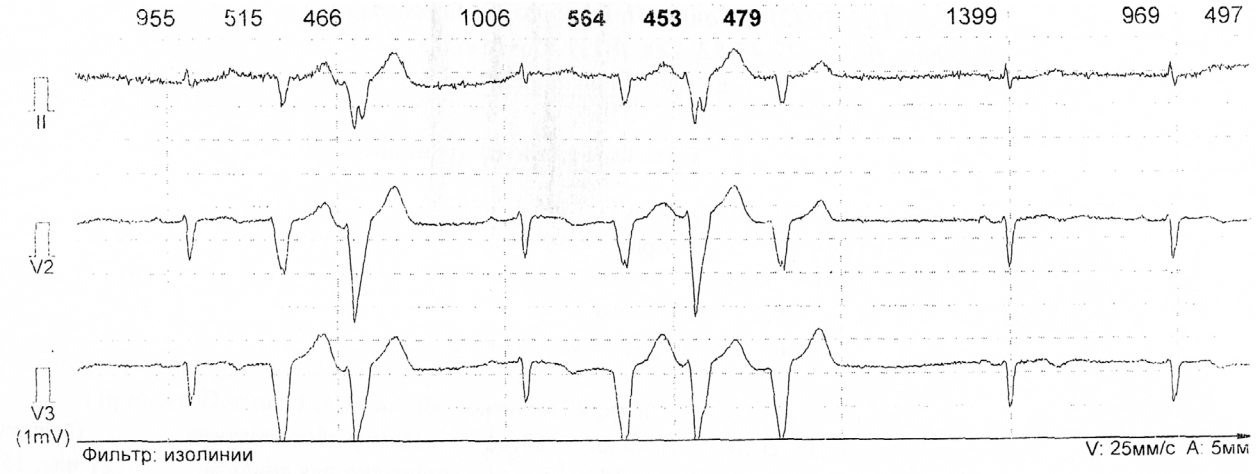

Fig. 1. Fragment of ECG monitoring. Explanation in the text

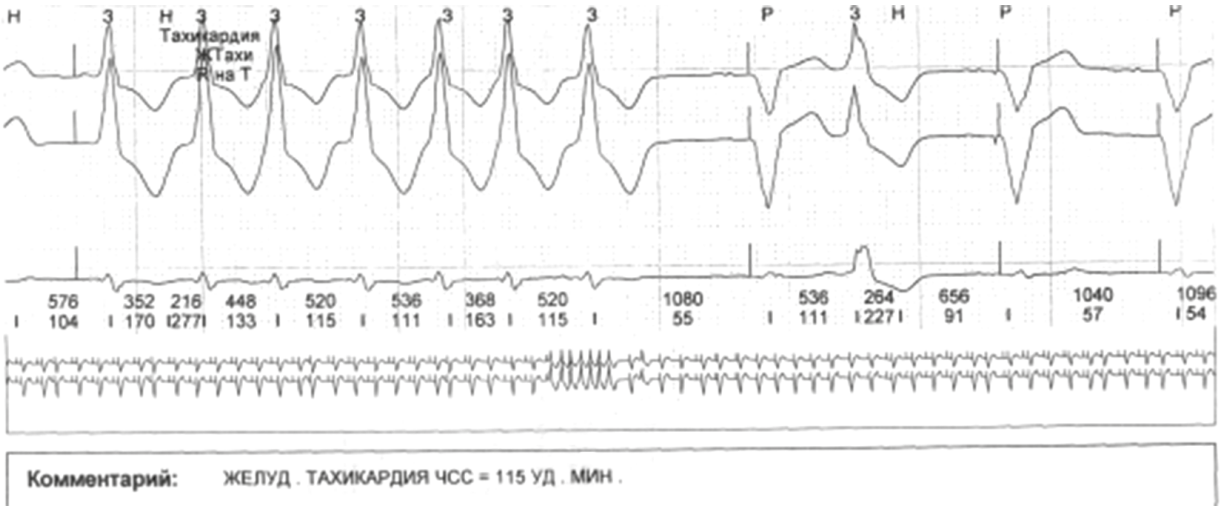

Fig. 2. Fragment of ECG monitoring after permanent pacemaker implantation. Explanation in the text

Secondary mitral regurgitation of 1 degree was also revealed. Due to the absence of complaints, the previous therapy was continued. When observed in dynamics in 2018, a decrease in EF to 47%, an increase in the LAVI to 49 ml/m^2, ECDO (81 ml/m^2) were revealed. Complaints were absent, correction of therapy was not carried out. In 2019, the patient felt a deterioration in exercise tolerance. An ECHOCG study performed in August 2019 revealed a decrease in EF to 33%, an increase in EDVI (85 ml/m^2), secondary mitral regurgitation of the 2nd degree. Correction of therapy was not carried out again.

In September 2019, the patient was admitted to our clinic for examination and selection of therapy. Clinical examination showed: satisfactory condition, no peripheral edema, height 180 cm, weight 85 kg, body mass index 26.2 kg/m^2, blood pressure 110/70 mmHg., heart rate and pulse 60 beats per 1 minute, rhythmical (PM rhythm). Borders of relative cardiac dullness: left — along the left mid-clavicular line, upper — 2nd intercostal space, right — along the right edge of the sternum. Auscultatory findings: 1st tone is muffled at the apex, the 3rd tone, a musical blowing systolic murmur at the apex. On percussion of the lungs there was pulmonary sound, on auscultation there was vesicular breathing, no wheezing. The liver is not enlarged. An ECHO study revealed a decrease in EF up to 25%, a global longitudinal strain of the left ventricular myocardium went down up to — 5.7%, an increase in EDVI up to 97 ml/m^2 (significant deviation), and an LAVI up to 54 ml/m^2 (sharp deviation) [5]. LV diastolic dysfunction of the 2nd degree was registered: the speed of movement of the lateral segment of the mitral annulus (Em) was 7 cm/sec (normal value ⩾ 10 cm/sec), the speed of movement of the septal segment was 4 cm/sec (normal value ⩾ 7 cm/sec), ratio E/Em reached off 13.6 (E is the peak velocity of the transmitral blood flow in the phase of rapid filling of the left ventricle, normal value ⩽ 13), tricuspid regurgitation was absent [6]. The volume of mitral regurgitation was 34 ml, the area of the effective regurgitation orifice was 0.25 cm^2, which corresponded to a severe degree of secondary mitral regurgitation [7]. The function of the RV was not impaired. Dyssynchrony of mechanical movement of the LV myocardium with a maximum delay in movement of the myocardium against the background of permament right ventricular stimulation outside the zone of scar tissue was found: in the area of the interventricular septum, mainly its inferior parts, the inferior wall, the posteriolateral and anterolateral walls at the basal and mid levels (Fig. 3).

When programming PM there was a permanent form of AF, pacing in the VVIR mode for 100% of the time despite taking metoprolol succinate in the dose of 50 mg per day. It diagnosed chronic heart failure (CHF) with reduced EF. During the 6-minute walk test, the patient walked 417 m, which corresponded to the II functional class of CHF. To exclude coronary shunts stenosis as the cause of a significant decrease in EF, coronary shuntography was performed. It demonstrated the following: the right type of coronary blood supply; main left coronary artery showed no stenosis; anterior interventricular artery had an occlusion at the border of the proximal and middle third, filled from a functioning shunt of the left internal mammary artery; 1st diagonal branch was occluded at the mouth, filled in a retrograde way from the basin of the right coronary artery, the shunt is not visualized; 2nd diagonal branch was occluded at the mouth, filled from a functioning shunt;

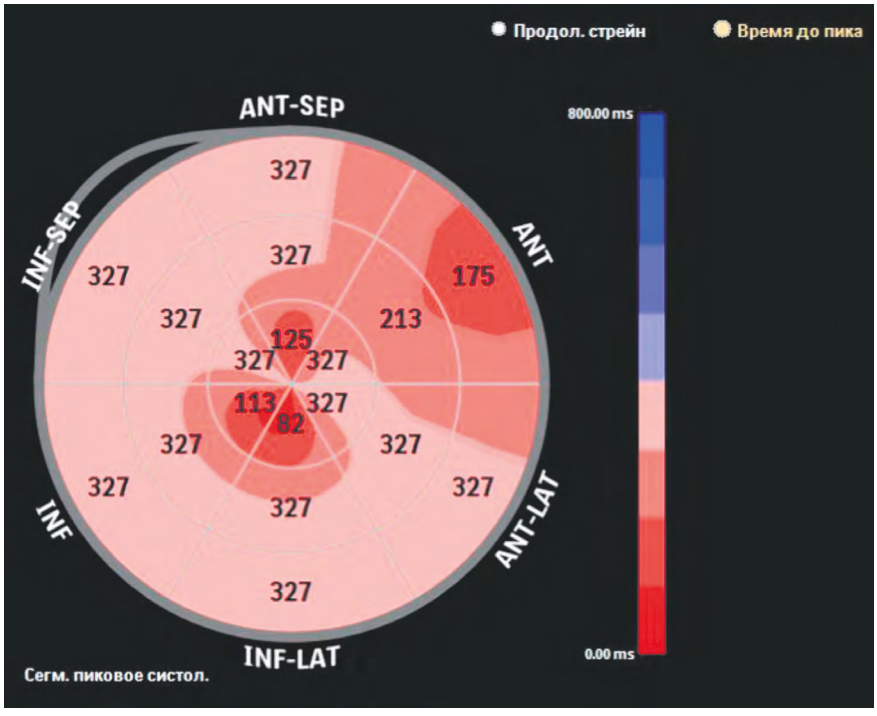

Fig. 3. Assessment of myocardial dyssynchrony. Explanation in the text

circumflex branch had no significant stenosis; 1st marginal branch was moderately altered in the proximal third with 70–75% stenosis (fractional flow reserve — FFR > 0.8), the periphery is satisfactory, 2nd marginal branch was less than 1.5 mm in diameter, diffusely changed from the mouth, the periphery is poor; the right coronary artery had no significant stenoses.

Thus, it was not possible to link the decrease in EF with the progressive pathology of the coronary arteries. The decrease in EF was associated with LV mechanical dyssynchrony that developed against the background of permament pacing of the right ventricular apex and retrograde propagation of electrical excitation to the LV. The transition of the patient to a permanent form of AF with the loss in this connection of mechanical atrial systole, which compensated for the violations of diastolic function that had taken place, also contributed to a decrease in EF. According to national and European recommendations for the diagnosis and treatment of CHF, patients with LV EF ⩽ 35%, in whom the course of heart failure worsens against the background of a traditionally implanted PM with a significant proportion of right ventricular pacing (despite optimal drug therapy) should consider the possibility of "updating" the implanted device to the resynchronizing one [1, 2]. The patient underwent PM replacement with a cardiac resynchronization therapy-defibrillator (CRT-D). The drug therapy was adjusted. Ramipril was changed to valsartan + sacubitril after a 36 hour break from ramipril. Due to the low dose of ramipril and the patient's tendency to hypotension, the starting dose of valsartan + sacubitril was 50 mg 2 times a day, followed by a slow dose titration to 200 mg 2 times a day. Glimepiride was replaced by empagliflozin at a dose of 10 mg daily. Eplerenone 25 mg per day was added to therapy, followed by dose incrising thtoughout a month to 50 mg per day under the control of potassium and serum creatinine. The glomerular filtration rate (GFR) was determined using the CKD-EPI formula. The resulting result was 46 ml/min/1.73 m^2, which corresponded to stage 3a chronic kidney disease (CKD). To assess the correctness of the dose of rivaroxaban, creatinine clearance (CC) was calculated using the Cockcroft-Gault formula without standardization to body surface area (it was this formula that was used in randomized clinical trials comparing direct oral anticoagulants with warfarin in AF). The resulting result was 55 ml/min. The dose of rivaroxaban remained the same — 20 mg per day, dose adjustment to 15 mg per day is required only with a creatinine clearance of 15–49 ml/min.

Against the background of complex therapy for CHF, including cardiac resynchronization therapy, drug quadrotherapy (valsartan + sacubitril, empagliflozin, eplerenone, beta-blocker), a year later, by September 2020, EF increased to 60%, EDVI decreased to 54 ml/m^2, LV diastolic function performance improved: velocity of movement of the lateral segment of the mitral valve anulus (10 cm/sec), of the septal segment (11 cm/sec), E/Em ratio (7.1). Mitral regurgitation was not determined. The symptoms of CHF disappeared. Since the implantation of the CRT-D, there have been no cardioverter-defibrillator shocks. When programming a resynchronization device with a cardioversion-defibrillation function, it was found that the proportion of biventricular stimulation was 90%. During the period from the moment of CRT-D implantation until December 2020, only one episode of non-sustained ventricular tachycardia was recorded, which lasted 3 seconds and spontaneously stopped. In the spring of 2021, due to low blood pressure (down to 80/60 mmHg), the patient stopped taking valsartan + sacubitril. At the next ECHO examination after discontinuation of valsartan + sacubitril in December 2021, an asymptomatic decrease in EF to 40%, an increase in EDVI to 73 ml/m^2, mitral regurgitation of the 1st degree reappeared. The patient was warned about the need to take all recommended drugs and resume titration of the dose of valsartan + sacubitril with systolic blood pressure (SBP) ⩾ 100 mm Hg to optimal well-tolerated (according to the PARADIGM HF study design) [8]. During the period of titration of the dose of valsatran + sacubitril, temporary discontinuation of the drug is recommended only when the SBP decreases < 95 mmHg with the resumption of titration when the SBP stabilizes at the level of ⩾ 100 mmHg. In addition, the dose of metoprolol succinate was increased to 75 mg with further titration to an optimal well-tolerated dose in order to better control AV conduction and achieve at least 95% biventricular pacing.

DISCUSSION

One of the most important aspects of the prevention, development and progression of CHF in patients with structural heart disease is the timely correction of rhythm and conduction disturbances. In particular, a catheter procedure for AF is recommended to eliminate LV dysfunction in AF in patients with a high likelihood of CHF being associated with a tachyarrhythmia, regardless of the presence or absence of symptoms [9, 10]. In the described clinical case, performing a catheter procedure to restore sinus rhythm was problematic due to a long history of permanent AF (about 7 years) and severe LA dilatation (LA volume 111 ml, LAVI 54 ml/m^2).

In 2012, the patient was implanted with a conventional two-chamber PM due to common indications (the presence of binodal dysfunction complicated by syncopal conditions). Due to the AV blockade that took place, the percentage of right ventricular pacing was high. There was a clear relationship between the fall in EF and permament right ventricular pacing. In accordance with national and European recommendations, the patient underwent a replacement

of a conventional pacing with a CRT-D [2, 10]. Against the background of the initial AV blockade, metoprolol succinate therapy provided control of AV conduction of supraventricular impulses and 90% biventricular stimulation. If it is not possible to control AV conduction with medication and the total duration of biventricular stimulation is less than 90–95%, the procedure of catheter modification of the AV node is resorted to [10].

Cardiac resynchronization therapy should be accompanied by optimal medical therapy. At the time of contacting our clinic, the patient had functional class II CHF with an unfavorable prognosis due to a sharp decrease in EF and needed effective life-saving therapy. Currently, two new classes of drugs, along with β-blockers and mineralocorticoid receptor antagonists (MRAs), are successfully used to treat CHF with reduced EF. These are, first of all, angiotensin II of type 1 receptors and neprilysin inhibitors, represented by valsartan + sacubitril. In the randomized controlled registration clinical trial PARADIGM HF, the addition of valsartan + sacubitril to optimal medical therapy for CHF with reduced EF reduced the relative risk of achieving the combined primary endpoint (death due to cardiovascular causes or first hospitalization due to heart failure) by 20% compared with enalapril, a well-studied drug for CHF [11]. During therapy with valsartan + sacubitril, the relative risk of individual components of the primary endpoint was statistically significantly reduced: the risk of cardiovascular death went down by 20%, the risk of first hospitalization due to heart failure decreased by 21%. In addition, a statistically significant reduction of 16% in the relative risk of such an important secondary endpoint as death from all causes was obtained. A statistically significant 20% reduction in the relative risk of sudden cardiac death deserves special attention [12]. Accumulated experience of real clinical practice confirms the results of the randomized controlled registration clinical trial PARADIGM HF [13, 14, 15].

Sodium-glucose co-transporter type 2 inhibitors (iSGLT2) represent the second innovative class of drugs for the treatment of CHF with reduced EF. Only two representatives of iSGLT2 (dapagliflozin and empagliflozin) successfully completed randomized controlled registration clinical trials on the basis of which the following indication was registered: treatment of CHF with reduced EF independent of etiology (both against the background of diabetes mellitus and in patients without diabetes) [16, 17] .

In combination with β-blockers and MRAs, the angiotensin II of type 1 receptors and neprilysin inhibitors and SGLT2 form a disease-modifying quadrotherapy [4]. In our patient, on the background of disease-modifying quadrotherapy, there was a complete recovery of EF and a positive, reverse remodeling of the heart chambers. Positive LV remodeling led to the disappearance of secondary mitral regurgitation. In a randomized clinical trial of D-H. Kang et al demonstrated pharmacological correction of the degree of functional mitral regurgitation with valsartan + sacubitril [13]. The disappearance of mitral regurgitation against the background of complex therapy for CHF in our patient confirms the results of the study by D-H. Kang et al.

Disease-modifying therapy contributs to a decrease in the number of ventricular arrhythmias. From December 2020 to November 2021, the built-in CRT-D monitoring features recorded only one episode of nonsustained ventricular tachycardia in the patient. In a study by C. de Diego et al. in patients suffering from CHF with reduced EF and implanted cardioverter-defibrillators without resynchronization function in patients with an initially narrow QRS complex or CRT/CRT-D in patients with a wide QRS, therapy with valsartan + sacubitril in combination with β-blockers and MRAs resulted in a statistically significant reduction in the number of non-sustained and sustained ventricular tachycardias compared with conventional therapy with angiotensin-converting enzyme inhibitors/angiotensin II receptor type 1 antagonists, β-blockers, and MRAs [14].

Our case demonstrated the positive effect of disease-modifying quadrotherapy. At the same time, it is obvious that not all patients suffering from CHF with reduced EF can use quadrotherapy, primarily due to the fact that the side effect in the form of hypotension is given by all four drugs included in it. Disease-modifying therapy for the treatment of CHF still requires the development of schemes and algorithms for the use of drugs [18].

Another issue requires discussion: the issue of anticoagulant therapy and the choice of a specific drug. In this case, in a patient with a polymorbid pathology, including coronary artery disease, rivaroxaban turned out to be the optimal drug with a unique evidence base to protect a patient with AF not only from stroke, but also from acute coronary events [19]. When prescribing an anticoagulant to a patient with CKD, GFR and CC should be carefully monitored and a drug without a negative effect on renal function should be preferred. A more favorable effect of rivaroxaban on renal function compared to warfarin has been demonstrated both in registration randomized controlled clinical trial and in studies performed in real clinical practice [20].

CONCLUSIONS

The case we presented illustrates the negative remodeling effect of traditional long-term pacing of the right ventricular apex in combination with a permanent form of AF in a patient with postinfarction cardiosclerosis. Complex therapy for CHF, including cardiac resynchronization therapy, drug therapy with valsartan + sacubitril with dose titration to optimal, empagliflozin, eplerenone, metoprolol succinate, made it possible to stop the processes of negative remodeling and to restore myocardial contractility. The clinical case emphasizes

the importance of converting traditional permanent pacing into cardiac resynchronization therapy in the development of CHF with reduced EF, as well as the advisability of continuing drug therapy after improvement and even recovery of EF. A negative effect on EF of the withdrawal of such an important component of quadrotherapy as sacubitril + valsartan was demonstrated.

ADDITIONAL INFORMATION

Conflict of interest. There is no conflict of interest.

Consent and anonymity of the patient. The patient provided consent for anonymous use and publication of his medical data.

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