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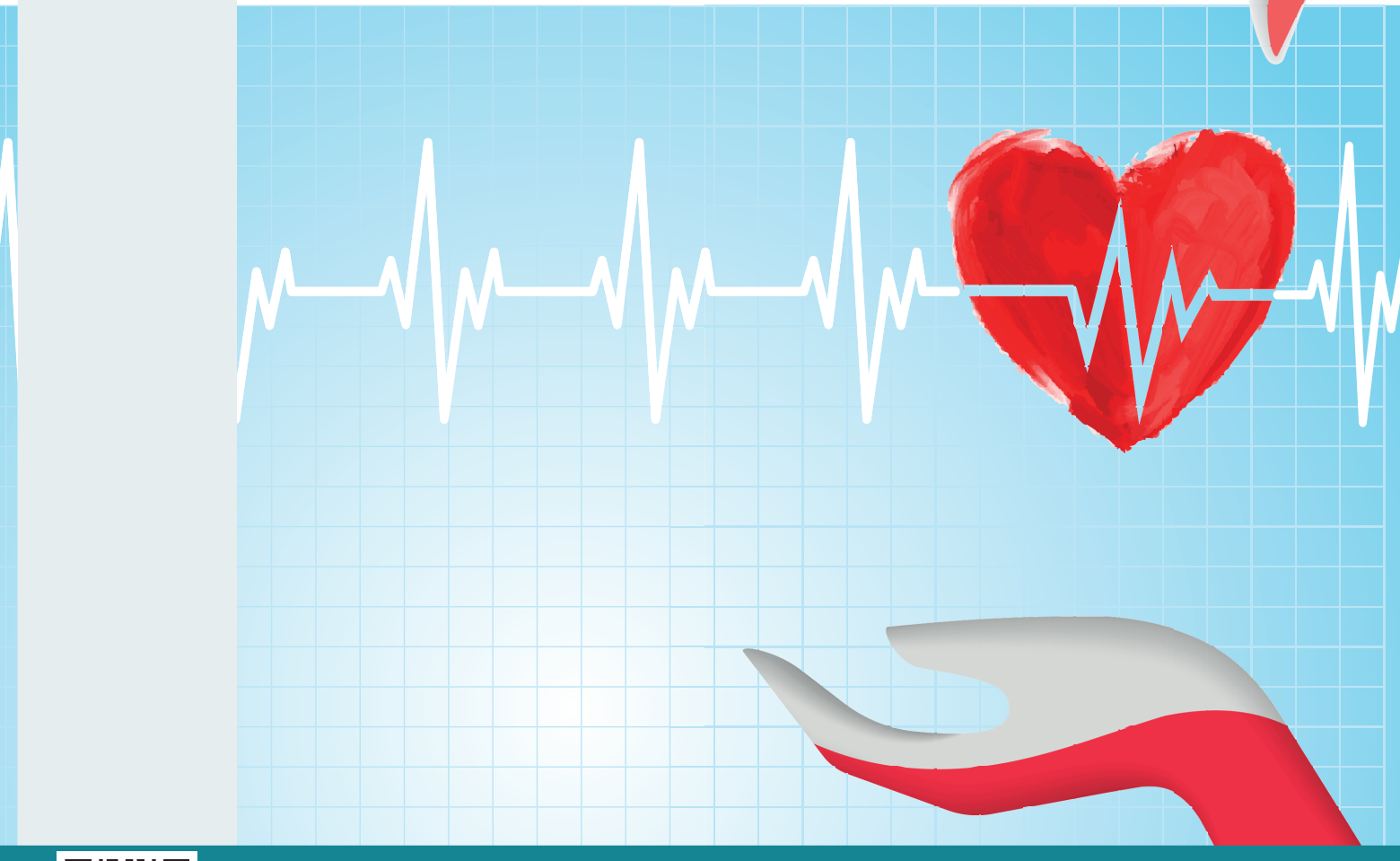

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Research article

Prognostic value of N-terminal Brain Natriuretic Peptide (NT-proBNP) in Risk Assessment of Adverse Cardiovascular Events in Patients with Atrial Fibrillation and Heart Failure with Reduced Left Ventricular Systolic Function

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According to Russian epidemiological studies, the incidence of chronic heart failure (HF) in the general population is approximately 7%, increasing from 0.3% in the group aged 20–29 years to 70% in patients aged > 90 years [1]. In the general population, the incidence of atrial fibrillation (AF) ranges from 1% to 2%, which increases with age, that is, from 0.5% at the age of 40–50 years to 5%–15% at the age of 80 years [2]. HF and AF aggravate significantly each other's course and mutually increase the risk of adverse outcomes [3, 4]. Moreover, the incidence of AF in patients with HF increases with increasing New York Heart Association (NYHA) grade; that is, among patients with HF of NYHA grade I, the incidence of AF is < 5%, whereas among patients with HF NYHA grade IV, the AF incidence in > 50% [5].

Chronic HF is a syndrome with complex pathophysiology, which is characterized by the activation of neurohumoral systems, namely, the renin–angiotensin–aldosterone system (RAAS), sympathetic nervous system (SNS), and insufficient activity of the natriuretic peptide (NUP) system. In the early stage of HF, i.e. asymptomatic dysfunction of the left ventricle, the activation of the SNS and RAAS plays a compensatory role aimed at maintaining cardiac output and circulatory homeostasis [6]. Moreover, the NUP system has a counter-regulatory function in relation to the RAAS and SNS, and with prolonged and excessive activation of the SNS and RAAS or with insufficient NUP system activity, imbalance occurs and HF progresses [7].

The brain natriuretic peptide (BNP) and biologically inactive N-terminal fragment of BNP (NT-proBNP) are the most studied and significant in clinical practice representatives of the NUP system. BNP and NT-proBNP are secreted by cardiomyocytes of the left ventricular (LV) myocardium in response to an increase in the mechanical load and stress of the LV myocardium. NT-proBNP is widely used as a test to rule out HF in patients with dyspnea. The NUP level also correlates with the severity and prognosis in patients with an established diagnosis of HF, and studies have reported that the NUP level acts as a criterion for treatment efficiency in patients with HF [8]. NT-proBNP is a biomarker not only for HF but also for several other conditions, such as acute coronary syndrome and myocardial infarction (MI), because it is associated with an increased risk of death from all causes, regardless of age, stable effort angina grade, myocardial infarction history, and LV ejection fraction (LVEF) [9].

NT-proBNP levels can be influenced by several additional factors such as age, obesity, or glomerular filtration rate. The prognostic value of NT-proBNP is relevant in comorbid patients with AF associated HF because AF can increase NT-proBNP levels independently [10]. Given that NUP secretion depends on intracardiac hemodynamics, the NT-proBNP levels may also depend on the approach to managing AF. Tachycardia is associated with high NT-proBNP levels [11].

The rhythm control approach has advantages over the heart rate control approach in patients with HF and LVEF < 50% to reduce mortality and the number of unplanned hospitalizations due to HF progression [12].

To date, the prognostic significance of NT-proBNP levels in relation to the risk of adverse events in patients with HF and reduced LV systolic function associated with AF, depending on the approach of AF management, remains unresolved.

This study aimed to assess the predictive value of NT-proBNP in relation to the development of adverse cardiovascular events in patients with permanent or persistent AF associated with HF and LVEF < 50%.

Keywords: atrial fibrillation; heart failure; NT-proBNP; prognostic value.

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Научная статья

Прогностическая значимость N-терминального фрагмента мозгового натрийуретического пептида (NT-proBNP) в оценке риска развития неблагоприятных событий у пациентов с фибрилляцией предсердий в сочетании с сердечной недостаточностью со сниженной систолической функцией левого желудочка

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Актуальность. Наиболее значимым в клинической практике биомаркером сердечной недостаточности (СН) является N-терминальный фрагмент мозгового натрийуретического пептида (NT-proBNP). NT-proBNP также является прогностическим маркером развития тяжелых клинических исходов у пациентов с фибрилляцией предсердий (ФП) без диагностированной СН. Прогностическая значимость NT-proBNP в отношении риска развития неблагоприятных событий у пациентов с ФП и СН с фракцией выброса левого желудочка (ФВ ЛЖ) < 50 %, в зависимости от тактики ведения ФП, не достаточно изучена.

Цель. Оценить прогностическую ценность NT-proBNP в отношении развития неблагоприятных сердечно-сосудистых событий у пациентов с постоянной или персистирующей формой ФП в сочетании с СН с ФВ ЛЖ < 50 %.

Материалы и методы. Обследовано 152 пациента с ФП в сочетании с СН с ФВ ЛЖ < 50 %. Всем пациентам были выполнены: ЭХО КГ, 24-часовое мониторирование ЭКГ, определение уровня NT-proBNP. Конечная точка для оценки прогноза течения СН — декомпенсация СН и связанная с этим госпитализация, конечная точка для оценки прогноза течения ФП — рецидив ФП после успешной электрической кардиоверсии (ЭКВ). Определение предикторов неблагоприятного исхода проведено методом многофакторного регрессионного анализа.

Результаты. Период наблюдения составил в среднем 12,4 [от 11 до 14,5] месяца. Пациенты с персистирующей формой ФП и СН с ФВ ЛЖ < 50 %, имеющие уровень NT-proBNP ⩾ 1096 пг/мл перед ЭКВ, имели более высокий риск рецидива ФП, ОШ = 2,12 [95 % ДИ от 1,48 до 4,1]. Уровень NT-proBNP ⩾ 1184 пг/мл ассоциирован с повышенным риском декомпенсации СН и связанной с этим госпитализации у пациентов с постоянной формой ФП и диагностированной СН с ФВ ЛЖ < 50 %, ОШ = 2,61 [95 % ДИ от 1,15 до 5,85].

Выводы. Повышенный уровень NT-proBNP сохраняет свою прогностическую значимость в отношении риска развития неблагоприятных событий у пациентов с ФП и СН с ФВ ЛЖ < 50 %. Эти результаты демонстрируют универсальность и высокую информативность определения уровня NT-proBNP и позволяют адекватно оценивать как тяжесть и прогноз течения СН у пациентов на фоне ФП, так и риск рецидива ФП у пациентов с СН с ФВ ЛЖ < 50 %.

Ключевые слова: фибрилляция предсердий; сердечная недостаточность; NT-proBNP; прогностическая значимость.

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MATERIALS AND METHODS

The study included 152 patients with AF associated with ischemic heart disease (IHD) that was associated with HF and LVEF < 50% (LVEF 42.0% [39; 45.5]). The inclusion criteria were as follows: persistent or permanent AF, age 35–70 years, and documented manifestation of HF with LVEF < 50% for at least 3 months before inclusion in the study. The exclusion criteria were as follows: paroxysmal AF, AF associated with organic valvular heart disease, acute myocardial infarction (MI) or MI < 6 months old, progressive exertional angina, acute myocarditis, operated valvular disease of any localization, hemodynamically significant stenosis of the coronary arteries, complete block of one of His bundle branches, severe renal failure (glomerular filtration rate [GFR] < 30 mL/min/m^2), changes in the levels of thyroid hormones, and electrolyte disorders. At the time of study inclusion, all patients underwent standard general clinical laboratory tests, transthoracic echocardiography (LVEF was assessed using the Simpson method in the B-mode), and 24-h ECG monitoring.

The NYHA grade was determined using a 6-min walk test. The HF phenotype was determined based on the LVEF according to the classification [13], where LVEF < 40% indicates heart failure with reduced left ventricular ejection fraction (HFrEF) and LVEF of 41%–49% indicates heart failure with a moderately reduced left ventricular ejection fraction (HFmrEF).

The NT-proBNP level was determined by enzyme immunoassay in the venous blood serum. The technique was performed according to the manufacturer's instructions, and the expected normal levels for NT-proBNP range from 0 to 125 pg/mL.

The primary endpoints of the study were AF recurrence (in patients with persistent AF) after successful electrical cardioversion (ECV) and hospitalization due to AF progression in patients with persistent AF. The criteria for recurrent AF include a documented episode of AF lasting ⩾30 s. The criteria for HF progression are an increase in clinical signs/symptoms of HF, a decline in the NYHA grade, and an increase in NT-proBNP levels.

Statistical data processing was performed using the STATISTICA 10 software package (StatSoft Inc.) and StatTech v. 2.6.6 (Stattech, Russia). Quantitative indicators were assessed for compliance with the normal distribution using the Shapiro–Wilk test (< 50 subjects). Levels of indicators between the two groups were compared using the non-parametric Mann–Whitney U-test. Descriptive statistics of numerical indicators were presented as Me [Lq; Uq], where Me is the median, Lq is the 25th percentile, and Uq is the 75th percentile. Qualitative indicators in the groups were described using absolute and relative frequencies of occurrence (percentage). Percentages in the analysis of four-field contingency tables were compared using Pearson's χ^2-squared test. To assess the diagnostic significance of the combinations of quantitative and qualitative attributes in predicting a certain outcome, direct enumeration and filtering of binary logistic regression models were employed. The threshold value of the level of statistical significance was taken as equal to 0.05.

All participants were informed about their inclusion in the study and signed an informed consent to participate. The study complies with the Declaration of Helsinki and was approved by the local ethics committee (Protocol No. 1 dated January 26, 2020).

RESULTS

Depending on the AF form, all patients were initially distributed into two groups. Group 1 included 60 patients with persistent AF and HF with LVEF < 50% (mean age, 57 [54; 61] years, 85% men), and group 2 included 92 patients with persistent AF and HF with LVEF <50% (mean age 56 [52; 65.5] years, 85.7% men).

The average follow-up duration was 12.4 [11–14.5] months. By the end of the follow-up period, 26 (43.3%) patients in group 1 maintained sinus rhythm (subgroup 1a), and 34 (56.7%) patients had an AF recurrence (subgroup 1b). The median sinus rhythm maintenance in the group with recurrent AF was 2.4 [1.3; 5.3] months. The compared subgroups did not differ in the regimens and doses of antiarrhythmic therapy at the time of inclusion in the study. Patients in both subgroups were comparable in terms of sex, age, major risk factors, and structure of cardiovascular diseases (CVDs). Individuals having their first episode of arrhythmia and those having a lower NYHA grade were more common in the group without AF recurrence. The characteristics of the studied subgroups are presented in Table 1.

Both subgroups initially did not differ in general laboratory parameters. However, at the time of study enrollment, patients with recurrent AF had significantly higher NT-proBNP levels. The NT-proBNP levels measured before the ECV were 676 [354; 958] pg/mL in subgroup 1a and 1481 [652; 2339] pg/mL in subgroup 1b (p = 0.0001).

The evaluation of EchoCG parameters measured before ECV revealed no statistically significant differences between the studied subgroups in terms of the left atrial volume (LAV; 130.2 [109.7; 143.4] mL versus 138.9 [108.8; 148] mL), LAV index (LAVI; 48.2 [39.7; 62.4] mL/m^2 versus 53.2 [40.4; 65.8] mL/m^2), left ventricular end-systolic dimension (LV ESD; 44 [41; 51.5] mm versus 47 [43.5; 51] mm), left ventricular end-diastolic dimension (LV EDD; 59 [56; 62.5] mm versus 61 [56.5; 64] mm), end-diastolic volume index of the left ventricle (LV EDVI; 98.7 [87.2; 111.8] mL/m^2 versus 106.4 [84.4; 118.5] mL/m^2), end-systolic volume index of the left ventricle (LV ESVI; 54.2 [43.2; 66.4] mL/m^2 versus 60.7 [44.1; 70.3] mL/m^2), LVEF (45% [39%; 47.5%] versus 42% [38%; 46%]), dimension of the right ventricle (25 [22; 26] mm versus 25 [24; 26] mm), LV myocardial mass (315 [278; 352] g versus 320 [289; 374.5] g), and LV

Table 1. General characteristics of the patients.

Characteristics of patients	Subgroup 1a No AF recurrence (*n* = 26)	Subgroup 1b AF recurrence (*n* = 34)	*P*
Age, years	58 [53; 62]	59 [56; 64]	is
Male, *n* (%)	22 (84,6)	29 (85,3)	is
BMI, kg/m^2	31 [27,5; 34]	32 [29; 36]	is
GFR, mL/min/1.73 m^2	64 [51; 74]	59 [51; 69]	is
Dyslipidemia, *n* (%)	18 (69,2)	24 (70,6)	is
Duration of AF episode before ECV, months	3 [2; 5]	5 [2; 6]	is
New episode of AF, *n* (%)	19 (73.1)	14 (41.2)	0,01
Type 2 DM, *n* (%)	5 (19.2)	6 (17.6)	is
Comparative characteristics of patients according to the cardiovascular disease structure			
IHD, *n* (%)	26 (100)	34 (100)	is
SEA, *n* (%) total	21 (80.8)	27 (79.4)	is
Grade 1	6 (28.5)	5 (18.5)	is
Grade 2	11 (53.4)	13 (48.1)	is
Grade 3	4 (19.1)	9 (33.4)	is
History of MI, *n* (%)	5 (19.2)	7 (20.6)	is
CH (NYHA), *n* (%)			
Grade I	4 (15.4)	1 (2.9)	0,02
Grade II	20 (76.9)	19 (55.9)	is
Grade III	2 (7.7)	14 (41.2)	0,01
HFmrEF/HFrEF, *n* (%)	20 (76.9) 6 (23.1)	24 (70.6) 10 (29.4)	is
AH, *n* (%) total	23 (88.4)	29 (85.3)	is
Degree 1	3 (13.1)	2 (6.9)	is
Degree 2	19 (82.6)	23 (79.3)	is
Degree 3	1 (4.3)	4 (13.8)	is

Note: AH — arterial hypertension; BMI — body mass index; CVD — cardiovascular disease; GFR — glomerular filtration rate (CKD-EPI); HFmrEF — heart failure with moderately reduced left ventricular ejection fraction; HFrEF — heart failure with reduced left ventricular ejection fraction; IHD — ischemic heart disease; is — insignificant differences; MI — myocardial infarction; NYHA — New York Heart Association grade; SEA — stable effort angina.

myocardial mass index (152 [135; 177] g/m^2 versus 154 [134; 183] g/m^2). Patients with arrhythmia recurrence had a higher level of pressure in the pulmonary artery (41 [35; 47] mm Hg versus 35 [33.5; 44.5] mm Hg in subgroups 1b and 1a, respectively, $p < 0.01$).

To identify predictors of AF recurrence in patients with HF and LVEF < 50%, clinical, anamnestic, laboratory, and instrumental parameters were included in the univariate regression analysis (Table 2).

In the multivariate regression analysis, only the NT-proBNP level retained its predictive value for AF recurrence (OR = 1.35 [95% CI 1.14–3.04]). According to the ROC analysis results, the level of NT-proBNP of ⩾ 1096 pg/mL with a sensitivity of 86.0% and a specificity of 84.3% is associated with recurrent AF (area under the ROC curve, 0.89; 95% CI 0.81–0.95). Patients with persistent AF and HF with an LVEF < 50%, who have an NT-proBNP level of ⩾ 1096 pg/mL before ECV have an increased risk of recurrent AF (OR = 2.12 [95% CI 1.48–4.1]).

Patients with permanent AF and HF with LVEF < 50%, who were hospitalized during the follow-up period due to HF progression, were included in subgroup 2a, and 67 (72.8%) patients with permanent AF and HF with LVEF < 50%, who were not hospitalized during the follow-up period, were included in subgroup 2b. During the follow-up, both subgroups were taking the main groups of drugs

Table 2. Data included in univariate regression analysis

Characteristics of patients	*p*-value	RR	CI –95%	CI +95%
Age	0.54	0.98	0.92	1.05
Sex	0.07	2.62	0.92	7.48
Cardiovascular disease heredity	0.69	0.83	0.33	2.09
AF heredity	0.83	1.13	0.37	3.44
Smoking	0.05	1.02	0.92	1.48
New AF episode	**0.03**	**1.03**	**1.002**	**1.14**
Age of AF, months	0.77	0.99	0.85	1.13
Body mass index, g/m^2	0.55	1.03	0.93	1.14
Type II diabetes mellitus	0.89	0.95	0.72	1.24
GFR, mL/min	0.4	0.99	0.97	1.01
NT-proBNP, pg/mL	**0.0003**	**1.53**	**1.19**	**4.64**
Average daily HR (before ECV), beats/min	**0.02**	**1.02**	**1.003**	**1.24**
LA volume, mL	0.87	1.12	0.91	1.49
LAVI, mL/m^2	0.23	1.08	0.96	1.18
LV EDD, mm	0.93	1.004	0.92	1.1
LV ESD, mm	0.33	1.04	0.96	1.12
LV EDVI, mL/m^2	0.71	1.012	0.91	1.1
LV ESVI, mL/m^2	0.44	1.03	0.89	1.05
LV SV, mL	0.26	0.98	0.96	1.01
LVEF, %	0.17	0.97	0.93	1.01
LV MM, g	0.87	0.98	0.75	1.27
LVMI, g/m^2	0.75	0.99	0.98	1.02
Systolic PAP, mm Hg	**0.001**	**1.15**	**1.09**	**1.65**

Note: AF — atrial fibrillation; EDD — end-diastolic dimension; EDVI — end-diastolic volume index; ESD — end-systolic dimension; ESVI — end-systolic volume index; GFR — glomerular filtration rate (CKD–EPI); LA — left atrium; LAVI — left atrial volume index; LV — left ventricle; LVMI — left ventricular mass index; HR — heart rate; MM — mass of the left ventricular myocardium; NT-proBNP — N-terminal fragment of brain natriuretic peptide; PAP — pulmonary artery pressure; SV — stroke volume.

indicated for HF, such as angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers/angiotensin receptor and neprilysin inhibitors, beta-adrenergic blocking agents, mineralocorticoid antagonist receptors, and diuretics. Groups 2a and 2b received comparable therapy in groups and doses of drugs taken.

In a retrospective analysis, both subgroups were comparable in terms of sex, age, major risk factors, and CVD structure. However, subgroup 2a included a significantly smaller number of patients with HFmrEF than subgroup 2b (10 patients [40%] versus 47 patients [70%]; p = 0.02), and subgroup 2a also had significantly more patients who had one or more episodes of hospitalization associated with HF progression (14 patients [56%] versus 19 [28%]; p = 0.03) (Table 3).

In a retrospective analysis, both subgroups did not differ in general laboratory parameters. However, in a retrospective analysis, subgroup 2a had significantly higher NT-proBNP levels at the time of study enrollment. The NT-proBNP level in the subgroup with repeated hospitalizations was 2293 [1300; 4675] pg/mL, and in the subgroup without hospitalizations, it was 989 [758; 1600] pg/mL (p < 0.0005).

At the time of study inclusion, groups 2a and 2b were comparable in terms of the level of systolic pressure in the pulmonary artery; however, compared with group 2b, group 2a was characterized by significantly higher values

Table 3. General characteristics of the patients.

Characteristics of patients	Subgroup 2a AF + HF Hospitalized due to HF progression (*n* = 25)	Subgroup 2b AF + HF Not hospitalized due to HF progression (*n* = 67)	*p*
Age, years	56 [50; 65]	61 [53; 66]	is
Male, *n* (%)	21 (84)	58 (86)	is
BMI, kg/m^2	31 [26,4; 35]	30 [27; 34,7]	is
GFR, mL/min/1.73 m^2	59 [49; 73]	68 [53; 74]	is
Dyslipidemia, *n* (%)	15 (60)	39 (58)	is
AF duration, months	17 [12; 62]	23 [12; 44]	is
1 or more episodes of hospitalization due to HF progression in history, *n* (%)	14 (56)	19 (28)	0,03
Comparative characteristics of patients according to the structure of cardiovascular disease			
IHD, *n* (%)	24 (96)	67 (100)	is
SEA, *n* (%) total	11 (44)	19 (28)	is
Grade 1	2 (8)	3 (4)	is
Grade 2	5 (20)	6 (9)	is
Grade 3	4 (16)	10 (15)	is
History of MI, *n* (%)	4 (16)	20 (30)	is
HF (NYHA), *n* (%)			
Grade I	1 (4)	3 (5)	is
Grade II	15 (60)	43 (64)	is
Grade III	9 (36)	21 (31)	is
HFmrEF/HFrEF, *n* (%)	10 (40)/15 (60)	47 (70)/20 (30)	0,02
AH, *n* (%) total	23 (92)	61 (91)	is
Degree 1	3 (12)	4 (6)	is
Degree 2	19 (76)	49 (73)	is
Degree 3	1 (4)	5 (7)	is
Type II DM, *n* (%)	5 (20)	16 (24)	is

Note: AH — arterial hypertension; BMI — body mass index; CVD — cardiovascular disease; DM — diabetes mellitus; GFR — glomerular filtration rate (CKD–EPI); HFmrEF — heart failure with moderately reduced left ventricular ejection fraction; HFrEF — heart failure with reduced left ventricular ejection fraction; IHD — ischemic heart disease; is — insignificant differences; MI — myocardial infarction; NYHA grade — New York Heart Association grade; SEA — stable effort angina.

of the LAV (138.8 [119.7; 151.4] mL versus 119.3 [99.5; 135.1] mL/m^2, p = 0.02), LAVI (74.2 [51.9; 87.5] mL/m^2 versus 59.9 [43; 75.5] mL/m^2, p = 0.015), higher LV EDD (64 [60; 65] mm versus 59.5 [55; 63] mm, p = 0.002), LV ESD (49 [47; 53] mm versus 44 [41; 52] mm, p = 0.01), LV EDVI (106.9 [100; 122.7] mL/m^2 versus 94.4 [79.6; 104.4] mL/m^2, p = 0.01), and LV ESVI (68 [51.7; 75.8] mL/m^2 versus 51.9 [43.2; 66.2] mL/m^2, p = 0.01). In group 2a, a tendency toward a lower LVEF was found; however, the level of statistical significance was not reached (39 [34; 45]% versus 42 [38; 46]%, p = 0.09).

To identify predictors of readmissions due to HF progression among patients with AF and HF with reduced LV systolic function, a univariate regression analysis was

Table 4. Data included in the univariate regression analysis.

Characteristics of patients	*p*-value	RR	CI – 95%	CI + 95%
Age	0.57	0.98	0.90	1.08
Sex	0.05	2.12	0.92	6.88
Heredity for cardiovascular diseases	0.75	0.88	0.42	1.09
Smoking	0.05	0.99	0.87	1.18
Age of AF, months	0.80	2.08	0.85	4.43
Body mass index, g/m^2	0.72	1.89	0.97	2.24
Type 2 diabetes mellitus	0.03	2.07	0.82	1.14
GFR, mL/min	0.4	0.93	0.99	1.88
NT-proBNP, pg/mL	**0.0001**	**2.83**	**1.29**	**3.24**
Average daily HR, beats/min	0.62	1.02	0.93	1.14
LA volume, mL	0.055	1.13	0.99	1.38
LAVI, mL/m^2	**0.04**	**1.21**	**1.02**	**1.27**
LV EDD, mm	**0.03**	**1.34**	**1.02**	**1.17**
LV ESD, mm	0.06	1.04	0.98	1.72
LV EDVI, mL/m^2	**0.04**	**1.21**	**1.04**	**3.92**
LV ESVI, mL/m^2	0.06	1.13	0.98	1.21
LVEF, %	0.81	1.36	0.85	1.47
LV MM, g	0.02	1.06	1.009	1.14
LVMI, g/m^2	0.75	0.99	0.98	1.02
Systolic pressure in PA, mm Hg	0.65	1.15	0.96	1.05

Note: GFR — glomerular filtration rate; LA — left atrium; LAVI — left atrial volume index; LV EDD — left ventricular end-diastolic dimension; LV EDVI — left ventricular end-diastolic volume index; LV ESD — left ventricular end-systolic dimension; LV ESVI — left ventricular end-systolic volume index; LV MM — mass of the left ventricular myocardium; LVEF — left ventricular ejection fraction; LVMI — left ventricular mass index; PA — pulmonary artery.

performed, including clinical anamnestic, laboratory, and instrumental parameters (Table 4).

In the multivariate regression analysis, NT-proBNP levels retained their predictive value for the progression of HF symptoms, with an OR of 1.28 [95% CI 1.12–4.16]. According to the results of the ROC analysis, the level of NT-proBNP of ⩾ 1184 pg/mL with a sensitivity of 79.7% and a specificity of 65.3% is associated with HF progression in patients with permanent AF and diagnosed HF with LVEF < 50% (area under the ROC curve, 0.714 [95% CI 0.573–0.854]). Patients with persistent AF and HF with an LVEF < 50%, who had NT-proBNP levels of ⩾1184 pg/ml, had a 2.61-fold increased risk of progression of HF symptoms [95% CI 1.15–5.85].

DISCUSSION

As the prevalence of AF increases, the prevention of its complications has important public health and economic benefits. Despite significant progress in the prevention of thromboembolic complications, particularly ischemic stroke, less attention has been paid to methods for preventing the adverse course of HF. The chronology of HF and AF development is of practical interest because it can affect the prognosis. It is assumed that AF development in the presence of HF is associated with an unfavorable outcome. Conversely, AF may contribute to HF development [14]. HF decompensation develops, and 20%–30% of all patients with AF need hospitalization [15]. Generally, AF development increases significantly the risk of lethal outcomes from CVD and common causes in patients with HF, both with reduced LVEF and in patients with preserved LVEF. The presence of AF presages a greater risk of mortality, especially among individuals with HFrEF (OR 2.72; 95% CI 2.12–3.48) compared with HF with preserved LVEF (OR 1.83; 95% CI 1.41–2.37) [16, 17].

When assessing the risk of HF progression and hospitalization in patients with AF and HF with an

LVEF < 50%, depending on the chosen approach for AF management, patients with HF and persistent AF had a lower risk of hospitalization because of HF progression, who could maintain sinus rhythm throughout the follow-up period compared with patients with persistent AF who had AF recurrence and compared with patients with permanent AF.

AF and atrial flutter are associated with higher blood levels of BNP/NT-proBNP, with NT-proBNP levels in patients with AF typically above diagnostic thresholds for HF. To assess the prognosis of the HF course, due to the uncertainty of the threshold value of the NT-proBNP level in the presence of AF, randomized controlled trials in patients with HF traditionally focus on higher threshold values of NT-proBNP [18]. Despite attempts at developing models for predicting the risk of HF in patients with AF, none of these models included the BNP/NT-proBNP levels [19].

Regardless of the chosen approach of AF management, in patients with AF associated with HF with LVEF < 50%, the NT-proBNP level retains prognostic significance. This can be due to the pathophysiological relationship between HF and AF, which consists of the development and progression of pathological myocardial remodeling. Despite the reversibility of LV dysfunction, after the restoration of sinus rhythm, factors for the development of arrhythmia and adverse outcomes of HF persist [20]. Neurohumoral activation, structural and functional remodeling of the atrial and ventricular myocardium, endothelial dysfunction, inflammation, and activation of the prothrombotic system do not ensure a reduction in the risk of acute cardiovascular events even after the restoration of sinus rhythm and reversible LV dysfunction [21, 22]. Based on our results, an elevated NT-proBNP level is associated with an increased risk of adverse outcomes in patients with HF-associated AF, both in patients with permanent AF and patients with successfully restored sinus rhythm. In both patients with recurrent AF and with developed HF decompensation, comparative analysis revealed a tendency to larger LA sizes, indicators of LV volumes and sizes, and tendency to a lower LVEF value. However, these widely used markers of the adverse clinical course of both AF and HF have not been revealed to be predictive in the multivariate analysis.

The results of our study are consistent with those of Brady et al. [23], who stated that in patients with HF and LVEF < 35%, higher NT-proBNP levels are associated with hospitalization due to HF or death from CVD, both in patients with AF and patients without a history of AF episodes.

In this study, we also assessed the predictive value of NT-proBNP levels in relation to the risk of AF recurrence after successful ECV, associated with HF with an LVEF < 50%, while a high NT-proBNP level, determined immediately on the day before ECV, was considered a predictor of AF recurrence. Clinical manifestations of AF, in particular heart rate, correlate significantly with NT-proBNP levels. This was confirmed by Kuroda et al. [24], who reported that the BNP levels decreased significantly immediately after the restoration of sinus rhythm in comparison with the level measured immediately before cardioversion. A decrease in the BNP level may be associated with both a decrease in AF severity and a slowdown in the processes of LV myocardial remodeling, which is associated with the sinus rhythm. However, the development of reverse myocardial remodeling is a long-term process, and a rapid decrease in BNP levels after cardioversion indicates a decrease in hemodynamic load and a positive effect on sinus rhythm. Patients with more hemodynamically significant AF showed a more pronounced decrease in BNP levels after cardioversion.

The most beneficial approach to managing patients with HF-associated AF is rhythm control. Routine determination of the NT-proBNP levels before the restoration of sinus rhythm will enable assessment of the level of LV myocardial stress and optimization of the methods of management and monitoring in the short and long-term follow-up period to increase the probability of maintaining sinus rhythm.

In their recent study, Hamatani et al. [25] established that BNP/NT-proBNP is a significant prognostic marker for severe clinical outcomes, including stroke, all-cause death, and hospitalization associated with HF progression in patients with AF without HF. In this study, in patients with HF-associated AF with LVEF < 50%, both of these diseases can distort the possibility of interpreting the NT-proBNP level. According to our results, an elevated NT-proBNP level retains its prognostic value in relation to the risk of adverse events in patients with HF-associated AF with LVEF < 50%. These results demonstrate the universality and high informative value of NT-proBNP levels, which enables adequate assessment of both HF severity and prognosis in patients with AF and the risk of AF recurrence in patients with HF and reduced LV systolic function.

CONCLUSIONS

1. NT-proBNP level of ⩾1184 pg/mL is associated with an increased risk of HF decompensation and associated hospitalization in patients with permanent AF and HF with LVEF < 50% by 2.5 [95% CI 1.15–5.85] times.

2. NT-proBNP level of ⩾1096 pg/ml is associated with an increased risk of arrhythmia recurrence in patients with HF-associated AF with LVEF <50% after successful ECV by 2.12 [95% CI 1.48–4.1] times.

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Research article

Significance of the N-terminal Fragment of Brain Natriuretic Peptides in Predicting Ventricular Arrhythmias in Young and Middle-Aged Patients with Diabetes and Myocardial Infarction

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ABSTRACT. Fatal ventricular arrhythmias in patients with diabetes mellitus (DM) in the acute stage of myocardial infarction (MI) and postinfarction period often cause adverse outcomes. Therefore, the search for new reliable biomarkers in predicting ventricular arrhythmias in the long term is necessary.

AIM: This study aimed to evaluate the value of N-terminal-pro hormone BNP (NT-proBNP) in predicting ventricular arrhythmias in young and middle-aged patients with MI and DM-associated ST-segment elevation.

MATERIALS AND METHODS: Seventy-six patients (59 men and 17 women) with DM and MI with ST-segment elevation (aged 36–59 years; mean 53 ± 5 years) were examined. Anterior MI was diagnosed in 35 patients, and non-anterior MI was detected in 41 patients. The DM duration was up to 1 year in 16 patients, 1–5 years in 24, and 5–12 years in 36. Patients were examined on day 1 after percutaneous coronary intervention (PCI) with implantation of 1–3 stents in the coronary arteries (CA) and again after 12 months. Holter monitoring, echocardiography, and blood tests for NT-proBNP were performed.

RESULTS: After PCI, ventricular extrasystole (VES) of grades III–V according to Lown and Wolf was detected in 21 of 37 (56.7%) patients with DM. The left ventricular ejection fraction (LVEF) was 42% (27%–45%), and the NT-proBNP level was 1127 (790–2530) at a rate of up to 125 pg/mL. After 12 months, VES was noted in 9 of 37 (24.3%) patients. The LVEF was 33% (28%–35%), and the NT-proBNP level was 938 (497–1294) pg/mL. A positive correlation was found between the blood serum level of NT-proBNP on day 1 after PCI and the number of grade III–V VES 12 months later. At an NT-proBNP level of > 898 pg/mL on day 1 after PCI, the sensitivity of this biomarker in predicting high-grade VES 12 months after MI in patients with DM was 100%.

CONCLUSIONS: The NT-proBNP level after PCI in patients with DM and MI is a reliable predictor of ventricular arrhythmias over the next 12 months.

Keywords: myocardial infarction; diabetes mellitus; percutaneous coronary intervention; N-terminal fragment of brain natriuretic peptide; ventricular extrasystole.

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Научная статья

Значение N-терминального фрагмента мозгового натрийуретического пептида в прогнозировании желудочковых нарушений ритма у больных сахарным диабетом молодого и среднего возраста с инфарктами миокарда

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Актуальность. Фатальные желудочковые нарушения ритма у больных сахарным диабетом (СД) в острой стадии инфаркта миокарда (ИМ) и в постинфарктном периоде часто являются причиной неблагоприятных исходов. Этим обусловлен поиск новых надежных биомаркеров в прогнозирования желудочковых аритмий в долгосрочной перспективе.

Цель — оценить значение NT-proBNP в прогнозировании желудочковых аритмий у больных молодого и среднего возраста с ИМ с подъемом сегмента *ST* на фоне СД.

Материалы и методы. Обследовано 76 больных СД (59 мужчин и 17 женщин) с ИМ с подъемом сегмента *ST* в возрасте 36–59 лет (средний 53 ± 5 года). У 35 больных диагностированы передние ИМ, у 41 — непередние ИМ. Длительность СД до 1-го года — у 16; от 1-го до 5 лет — у 24; от 5 до 12 лет — у 36. Больные обследовались в 1-е сутки после чрескожного коронарного вмешательства (ЧКВ) с имплантацией 1–3 стентов в коронарные артерии (КА) и повторно через 12 месяцев. Выполнялись холтеровское мониторирование (ХМ), ЭхоКГ, анализы крови на NT-proBNP.

Результаты. После ЧКВ желудочковая экстрасистолия (ЖЭС) III–V градаций по Лауну — Вольфу выявлялась у 21 из 37 (56,7 %) больных СД. Фракция выброса левого желудочка (ФВ ЛЖ) составила 42 % (27–45 %); уровень NT-proBNP — 1127 (790–2530) при норме до 125 пг/мл. Через 12 месяцев ЖЭС отмечалась у 9 из 37 (24,3 %) пациентов. ФВ ЛЖ составила 33 % (28–35 %); уровень NT-proBNP — 938 пг/мл (497–1294). Была выявлена положительная корреляционная зависимость между содержанием в сыворотке крови NT-proBNP в 1-е сутки после ЧКВ и количеством ЖЭС III–V градаций через 12 месяцев. При уровне NT-proBNP > 898 пг/мл в 1-е сутки после ЧКВ чувствительность данного биомаркера в прогнозировании ЖЭС высоких градаций через 12 месяцев после ИМ у больных СД составляет 100 %.

Заключение. Уровень NT-proBNP после ЧКВ у больных СД с ИМ является надежным предиктором желудочковых аритмий в течение ближайших 12 месяцев.

Ключевые слова: инфаркт миокарда; сахарный диабет; чрескожное коронарной вмешательство; N-терминальный фрагмент мозгового натрийуретического пептида; желудочковая экстрасистола.

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ЭКО•ВЕКТОР

LIST OF ABBREVIATIONS

ESC — European Society of Cardiology
ACS — acute coronary syndrome
CA — coronary artery
CCF — chronic cardiac failure
DM — diabetes mellitus
EchoCG — echocardiography
EF — left ventricle ejection fraction
HF — heart failure
HM — Holter monitoring
LV — left ventricle
MI — myocardial infarction
NT-proBNP — N-terminal fragment of brain natriuretic peptide
PCI — percutaneous coronary intervention
ROC — receiver operating characteristic
VES — ventricular extrasystole
VT — ventricular tachycardia

INTRODUCTION

As knowledge is obtained, the level of understanding of factors that can predict the risk of fatal ventricular arrhythmias, sudden death, and progression of heart failure (HF) changes. This concept refers to young and middle-aged patients with diabetes mellitus (DM) because atherosclerotic lesions of large- and medium-sized CAs occur in this group 8–10 years earlier than that in the DM group [1], and the incidence of myocardial infarction (MI) is 3–5 times higher [2, 3]. Moreover, the 30-day mortality rate reaches 11.3% and 5.9% and the 1-year mortality rate is 14.5% and 8.9% in the non-DM group with MI [4].

Natriuretic peptides were discovered in the 1950s–1970s, among which type B natriuretic peptide (BNP) and its N-terminal fragment (NT-proBNP) proved to be the most discussed in cardiology [5]. They are secreted in the heart ventricles in response to increased myocardial tension and increased blood volume or pressure and are the most sensitive markers in diagnosing chronic cardiac failure (CCF) [6]. The BNP level measured on day 1 after acute coronary syndrome can be used as a marker of long-term mortality prognosis [7]. Moreover, only single reports have revealed that NT-proBNP concentrations are significantly higher in patients with ventricular arrhythmias than in those without ventricular arrhythmias [8]. In young and middle-aged patients with DM and MI, these issues are not covered enough.

AIM

This study aimed to estimate the NT-proBNP level that can predict ventricular arrhythmias in young and middle-aged patients with MI and DM-associated ST-segment elevation.

MATERIALS AND METHODS

A prospective, controlled, non-randomized cohort study was performed. We examined 76 patients with DM (59 men and 17 women) aged 36–59 (mean 53 ± 5) years (Table 1).

DM duration of up to 1 year was determined in 16 patients, 1–5 years in 24, and 5–12 years in 36. Moreover, 31.6% of the patients had a history of MI, and all patients had grade 1–3 AH. Anterior MI was diagnosed in 35 patients with DM admitted with a diagnosis of acute coronary syndrome (ACS) with ST elevation on echocardiography (ECG), and non-anterior MI in 41 patients. Patients were examined on day 1 after percutaneous coronary intervention (PCI) with implantation of 1–3 stents in the CA and again after 12 months. As the control group, 115 young, and middle-aged patients with MI and ST elevation without DM were examined. The DM and non-DM groups were completely comparable in terms of age, sex, and comorbid diseases.

Echocardiography was performed using Philips EnVisor (Philips Electronics N.V.), Toshiba Artida (Toshiba Medical Systems), and Vivid 7 Pro series (General Electric Company) devices on day 1 after PCI and 12 months later. The study was conducted according to the standard method using (B) and (M) scanning modes, pulsed wave and continuous wave modes, and color Doppler mapping. The left ventricular ejection fraction (LVEF) was calculated according to the Simpson method. To quantify local contractility disorders, the wall motion score index (WMSI) of the left ventricle was calculated [9, 10].

In the dynamics of the examination, LVEF was assessed according to the recommendations of the European Society of Cardiology for the diagnostics and treatment of chronic HF (2021), namely, (1) CCF with preserved EF (⩾ 50%) (HFpEF), (2) CCF with moderately reduced EF (40%–49%) (HFmrEF), and (3) CCF with low EF (⩽ 40%) (HFlEF) [11].

For Holter monitoring (HM), we used a portable HM "Kardiotekhnika 4000" (Inkart, St. Petersburg) with a multi-channel recorder, digital recording of information, and subsequent automatic data processing according to the attached software package KT-4000. HM analysis was performed using the Incardio Result v2.0 program (St. Guidelines for HM in clinical practice [12]. The daily dynamics of the heart rate was assessed, and ventricular ectopic activity was evaluated using the VES classification according to Lown and Wolf (1971) [13] and changes in repolarization according to the ECG with the calculated ischemia index and ischemia duration during the day. The eligibility of patients for HM was determined by the severity of their condition (classes II–III according to Killip and Kimballe) [14].

The blood serum NT-proBNP level was measured on the Cobas device using the Elecsys platform (Roche Diagnostics, USA). The normal value is < 125 pg/mL.

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Table 1. Characteristics of the patients with myocardial infarction

Parameters	DM group *n* = 76	Non-DM group *n* = 115	*p*
Age, years M (SD)	53 ± 5	52 ± 5	0.2822
Sex, m/f, *n*	59 / 17	101 / 14	no data
BMI kg/m^2, M (SD)	29.1 ± 4.6	27.7 ± 4.7	0.0855
DM duration, *n* (%) up to 12 months 1–5 years > 5 years	 16 (21.1%) 24 (31.6%) 36 (47.4%)		no data
History of MI, *n* (%)	24 (31.6%)	20 (17.4%)	0.3829
Anterior MI, *n* (%)	35 (46%)	56 (48.7%)	no data
Non-anterior MI, *n*. (%)	41 (54%)	59 (51.3%)	no data
Arterial hypertension, *n* (%) Grade 1 Grade 2 Grade 3	 32 (42.0%) 10 (13.3%) 34 (44.7%)	 72 (62.6%) 25 (21.7%) 18 (15.7%)	no data
Acute cardiac failure by Killip classification, *n* (%) Class I Class II Class III	 48 (63.2 %) 27 (35.5 %) 1 (1.3 %)	 85 (73.9 %) 28 (24.3 %) 2 (1.8 %)	no data
Troponin I, pg/mL, *Me* (IQR)	73.0 (4.0 – 50000)	67.0 (3.0 – 50000)	0.0015
Total cholesterol, mmol/l, (*M* ± *m*)	5.58 ± 1.53	5.03 ± 1.45	0.0141
Triglycerides, mmol/l, (*M* ± *m*)	2.18 ± 1.31	1.71 ± 1.01	0.0012
High-density lipoprotein cholesterol mmol/L, (*M* ± *m*)	1.30 ± 0.42	1.15 ± 0.32	0.0046
Low-density lipoprotein cholesterol mmol/L, (*M* ± *m*)	4.14 ± 1.45	3.66 ± 1.26	0.0334
Glycated hemoglobin, % (*M* ± *m*)	7.9 ± 1.78	5.26 ± 0.56	0.0001
Creatinine, μmol/L, (*M* ± *m*)	90.7 ± 14.5	89.5 ± 16.7	0.5158
GFR by MDRD mL/min/1.73 m^2, (*M* ± *m*)	66.0 ± 15.0	78.0 ± 18.0	0.0001

Differences between groups were assessed by the Mann–Whitney *U*-test, and a *p* value lower than 0.05 was considered significant. Spearman's coefficient was used to assess the correlation between NT-proBNP values and HM parameters.

Receiver operating characteristic (ROC) analysis indicating the area under the ROC curve (AUC) was performed to obtain the operational characteristics of event predictors. Based on the median of the initial NT-proBNP levels obtained on day 1 after PCI, the maximum sensitivity, and specificity of the biomarker were determined after 12 months.

RESULTS

HM parameters were analyzed in 37 patients with LVEF of 42% (27%–45%) in the DM group and 42 patients with LVEF of 46% (37%–49%) in the non-DM group (Table 2).

Furthermore, 3 of 37 patients in the DM group and 17 of 42 patients in the non-DM group did not have ventricular ectopic activity on day 1 after PCI. Ten patients in the DM group and five in the non-DM group had grade I ventricular extrasystole (VES) (< 30/h). In three patients in the DM group, VES grade II (> 30/h) was detected.

Most often, in patients with MI in the DM group on day 1 after PCI, VES grades III–V were detected in 21 of 37 (56.7%) patients. In 12 of 37 patients in the DM group and 17 of 42 patients in the non-DM group, single polytopic VESs of ⩾ 3 morphological types were recorded. In five patients in the DM group and three patients in the non-DM group, paired monomorphic (grade IVa) and paired polymorphic (grade IVb) VES with a shortening coupling interval were detected. Moreover, four DM patients in the DM group had unstable paroxysms of monomorphic ventricular tachycardia (VT) (< 30 s). In the non-DM group, no paroxysms, and runs of VT were recorded. In general,

Table 2. Dynamics of Holter monitoring indicators in patients with myocardial infarction on day 1 after PCI and after 12 months.

Me indicator (IQR)	Day 1 after PCI			After 12 months		
	DM group *n* = 37	Non-DM group *n* = 42	*p*	DM group *n* = 37	Non-DM group *n* = 42	*p*
Daytime heart rate, bpm	72 (68–76)	69 (62–74)	p_1 = 0.0705	64 (58–71)	69 (62–74)	p_2 = 0.2286
HR at night, bpm	66 (62–73)	62 (56–67)	p_1 = 0.0235	55 (50–65)	64 (59–66)	p_2 = 0.2281
VES grade III	*n* = 12 38 (11–730)	*n* = 17 12 (5–19)		*n* = 6 1770 (4-10890)	*n* = 4 38 (20-77)	
VES grade IV	*n* = 5 19 (13–57)	*n* = 3 1 (1.1)		*n* = 2 539 (5–1073)	*n* = 3 1 (1–1)	
VES grade V	*n* = 4 4 (1–41)			*n* = 1 59 (59–59)		
Ischemia index, μV · min	33 775 (20210–94475)	17 317 (10185–55712)		32 078 (8144–40782)	3041 (1358–30075)	p_2 = 0.0196 p_3 = 0.0050 p_4 = 0.0329
Ischemia duration, min	417 (228–942)	305 (203–705)		355 (271–503)	57 (9–189)	p_2 = 0.0111 p_3 = 0.0050 p_4 = 0.0033

Note: p_1 — is the significance of differences between groups on day 1 after PCI; p_2 — is the significance of differences between groups after 12 months; p_3 — is the significance of differences between the indicator on day 1 and after 12 months in the DM group, and p_4 — is the significance of differences between the indicator on day 1 and after 12 months in the non-DM group.

Таблица 3. Динамика эхокардиографических показателей и содержания в крови NT-proBNP у больных с инфарктами миокарда и желудочковой экстрасистолией III–V градаций

Parameters	Day 1 after PCI		After 12 months		*p*
	DM group *n* = 37	Non-DM group *n* = 42	DM group *n* = 37	Non-DM group *n* = 42	
NT-proBNP pg/mL, Me (IQR)	1127 (790–2530)	614 (421–1397)	938 (497–1294)	517 (118–989)	p_1 = 0,0010 p_2 = 0,0054 p_3 = 0,0004 p_4 = 0,0001
LVEF, % Me (IQR)	42 (27–45)	46 (37–49)	33 (28–35)	49 (44–58)	p_1 = 0,0014 p_2 = 0,0001 p_3 = 0,0227 p_4 = 0,0184
WMSI Me (IQR)	1,65 (1,56–2,0)	1,34 (1,25–1,80)	1,75 (1,63–1,93)	1,31 (1,13–1,81)	p_1 = 0,0008 p_2 = 0,0003 p_3 = 0,1687 p_4 = 0,0072

20 of 42 (47.6%) patients in the non-DM group had high-grade VESs.

The ischemia index, that is, an indicator of the depth of the ST segment depression in patients with DM ranged from 20 210 to 94 475 μV·min (on average, 33 775 μV · min), which was almost twice as high as in patients with MI in the non-DM group (17 317, 10 185–55 712 μV · min).

On day 1 after stenting of the infarct-associated CA in the DM group, myocardial ischemia persisted, whereas the ischemia duration ranged from 228 to 942 (average, 417)

min. In the non-DM group, the ischemia duration after PCI was shorter and averaged 305 (203–705) min.

The NT-proBNP level in the blood serum of the DM group was two times higher than that in the non-DM group (p_1 = 0.0010). WMSI in the DM group was high, that is, 1.65 (1.56–2.0) in patients with grade 3–4 lesions, whereas in the non-DM group, the WMSI was 1.34 (1.25–1.80) in those with grades 2–3 lesions (p_1 = 0.0008). In patients of the DM group with VES grades III–V, the LVEF was significantly lower than that in patients without diabetes (p_1 = 0.0014) (Table 3).

In the DM group, in young, and middle-aged patients with MI, large lesion area, and persistent myocardial ischemia after PCI, high NT-proBNP levels, and VES grades III–V were recorded. In the non-DM group, in the presence of WMSI grades 2–3, persistent myocardial ischemia, but of a shorter duration, VES grades III–V were registered less frequently and NT-proBNP levels were significantly lower.

After 12 months, the number of high-grade VESs in the DM group decreased and was recorded in 9 of 37 (24.3%) patients. Thus, in 6 of 37 patients, single polytopic polymorphic VES were recorded, with 4–10 890 (average, 1770) per day. Two patients had a paired polymorphic VES with a shortening coupling interval, with 5–1073 (average, 529) per day. Unsustainable (< 30 s) and sustained (⩾ 30 s) VT paroxysms of 59 per day were recorded in one patient, whereas the ventricular contraction rate reached 160–196 beats/min (grade V).

The duration of ischemic displacement of the ST segment decreased from 417 to 355 min (p_3 = 0.0050) and the ischemia index from 33775 to 32 078 μV · min (p_3 = 0.0050).

After 12 months, 7 of 42 patients in the non-DM group (16.7%) also showed an improvement. Of 42 patients, 4 had grade III VESs with a frequency of 38 (20–77) per day. Three patients had VES grade IV. Unlike the DM group, no VT paroxysms were recorded in this group. The ischemia duration was 57 (9–189) min (p_4 = 0.0033), and the ischemia index decreased by more than five times (3041, 1358–30075, μV · min) (p_4 = 0.0329).

In general, after 12 months, the ischemia index in the DM group was 10.5 times higher than that in the non-DM group (p_2 = 0.0196), and the duration of myocardial ischemia was six times longer than that in the non-DM group (p_2 = 0.0111). Probably, prolonged postinfarction myocardial ischemia in patients with low LVEF in the DM group was the cause of life-threatening ventricular arrhythmias.

After 12 months in the DM group, LVEF decreased to 33% (28%–35%) (p_3 = 0.0227), whereas in the non-DM group, the EF increased to 49% (44%–58%) (p_4 = 0.0184). The blood serum levels of NT-proBNP in the DM group decreased to 938 (497–1294) pg/mL (p_3 = 0.0004), which exceeded significantly the normal value (< 125 pg/mL) and was higher than that in the non-DM group (p_2 = 0.0054). Moreover, in the non-DM group, the NT-proBNP level decreased to 517 (118–989) pg/mL (p_4 = 0.0001) and was almost normalized in some patients.

To assess the NT-proBNP level in predicting ventricular arrhythmias in patients with MI and ST-segment elevation, Spearman's rank correlation was employed. Table 4 presents the results of the correlation analysis.

In the DM group, patients with MI were found to have a high-level positive correlation between the NT-proBNP level on day 1 after PCI and the number of VESs (r = 0.5796; p = 0.0117),

Table 4. Correlation dependence of NT-proBNP levels on day 1 of myocardial infarction after PCI with Holter monitoring indicators after 12 months

Parameters	DM group		Non-DM group	
	r	*p*	*r*	*p*
Number of VES grades III–V	0.5796	0.0117	0.6010	0.0051
Ischemia index (μV · min)	0.5814	0.0003	0.5235	0.0004
Ischemia duration (min)	0.6101	0.0001	0.6458	0.0001

Table 5. Correlation dependence of NT-proBNP levels taken 12 months after myocardial infarction with Holter monitoring indicators after 12 months

Parameters	DM group		Non-DM group	
	r	*p*	*r*	*p*
Number of VES grades III–V	0.7685	0.0001	0.5149	0.0084
Ischemia index (μV · min)	0.8108	0.0001	0.3946	0.0097
Ischemia duration (min)	0.8681	0.0001	0.6901	0.0001

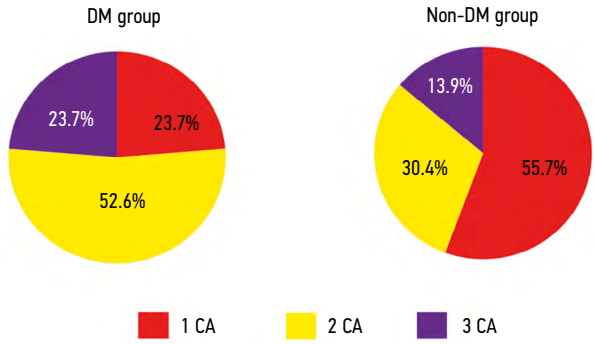

Fig. 1. Incidence of atherosclerotic coronary arteries in young and middle-aged patients with myocardial infarction with and without DM

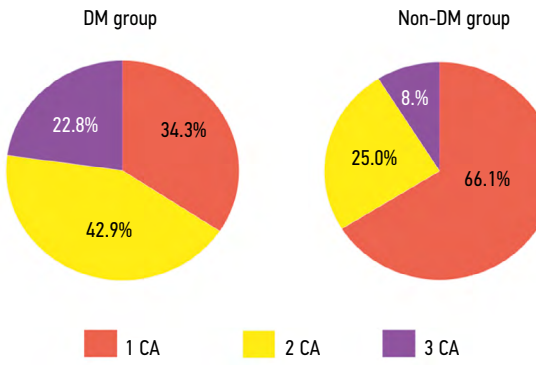

Fig. 2. Incidence of atherosclerotic lesions of the coronary arteries in patients with anterior myocardial infarction

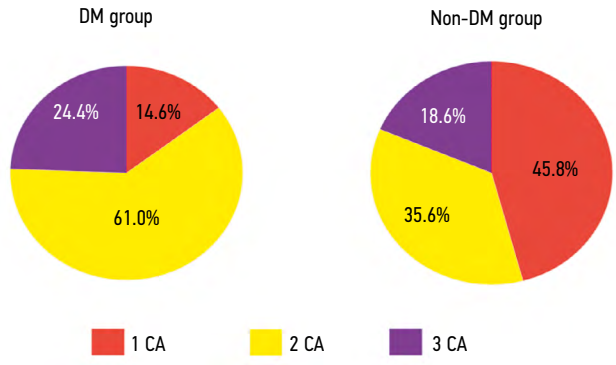

Fig. 3. Incidence of atherosclerotic lesions of the coronary arteries in patients with non-anterior myocardial infarction

ischemia index (r = 0.5814; p = 0.0003), and myocardial ischemia duration (r = 0.6101; p = 0.0001) after 12 months.

By analogy in the DM group, in patients with MI in the non-DM group, a positive correlation dependence of a high significance was also noted between the NT-proBNP level and the number of VESs (r = 0.6010; p = 0.0051), ischemia index (r = 0.5235; p = 0.0004), and myocardial ischemia duration (r = 0.6458; p = 0.0001) after 12 months.

Correlations between NT-proBNP levels taken after 12 months and HM parameters after 12 months in the DM group become comparable (Table 5). Thus, a high significantly positive dependence increased between the NT-proBNP level and VES grades III–V (r = 0.7685; p = 0.0001), ischemia index (r = 0.8108; p = 0.0001), and myocardial ischemia duration (r = 0.8681; p = 0.0001).

After 12 months in the non-DM group, the correlation between serum NT-proBNP levels and HM parameter values after 12 months, compared with an acute MI period, decreases while maintaining significance. This is most noticeable in the ratio with VES grades III–V (r = 0.5149; p = 0.0084) and ischemia index (r = 0.3946; p = 0.0097).

Probably, this recorded difference is due to numerous arrhythmias in the postinfarction period in the DM group and to deeper and more prolonged myocardial ischemia associated with the peculiarities of CA lesions in diabetes (Fig. 1).

According to the coronary angiography (CAG) results, the incidence rates of lesions of CAs 2 and 3 were 52.6% and 23.7% (73.6%) in the DM group and 30.4% and 13.9% (44.3%), respectively, in the non-DM group.

In anterior and non-anterior MI in patients with DM, the incidence rates of multivessel CA lesions were 65.7% and 85.4%, respectively (Fig. 2, 3).

In the non-DM group of patients with anterior and non-anterior MI, the incidence rates of multivessel CA lesions were 34.9% and 54.2%, respectively, which was less than that in the DM group.

Apparently, after PCI with CA stenting, young, and middle-aged patients in the DM group, low LVEF, and high-grade ventricular arrhythmias require the most complete myocardial revascularization in the postinfarction period.

To confirm the NT-proBNP levels in the DM group, taken on day 1 after PCI, the ROC analysis was used to predict ventricular arrhythmias 12 months later (Fig. 4).

In the plotted graph, the AUC value was 0.8429, which indicates that the model is effective and has high predictive power. Serum NT-proBNP levels higher than 898 pg/mL on day 1 of MI after PCI in the DM group were a predictor of high-grade VES after 12 months with a sensitivity of 100% and a specificity of 80%.

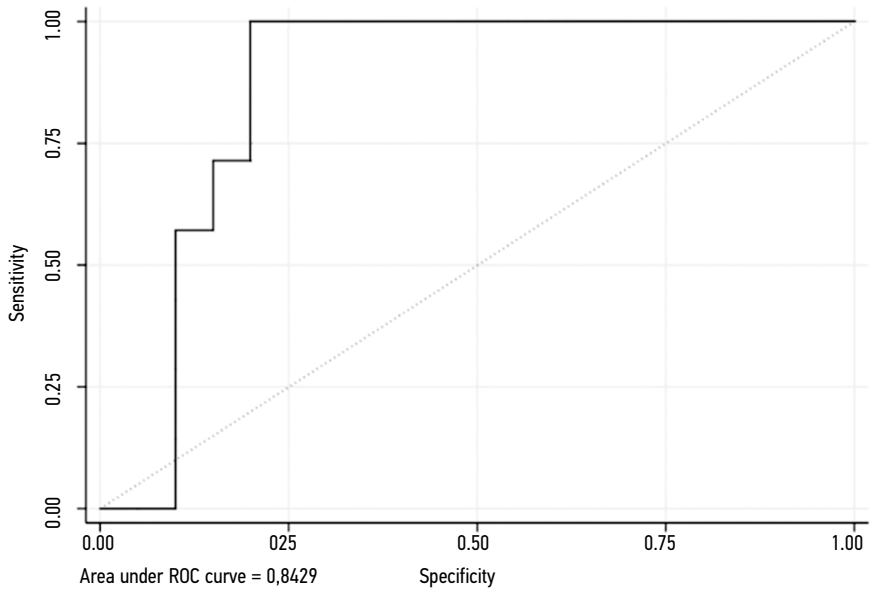

Fig. 4. ROC curve. Model of sensitivity and specificity of NT-proBNP, taken on day 1 after PCI in patients with diabetes mellitus, as a predictor of VES grades III–V in 12 months

In the non-DM group, the AUC value was 0.5000, indicating that this model is non-functional, and the predictive value of NT-proBNP is low.

DISCUSSION OF RESULTS

According to Katritsis et al. (2013), after myocardial reperfusion, and treatment with beta-blockers, runs, and unstable paroxysms of VT were detected in 56.4% of the patients with HM, which greatly increased the risk of sudden death [15]. This is consistent with the results of our study that the incidence rates of grade III–V VESs after PCI were 56.7% in the DM group and 47.6% in the non-DM group. After 12 months, the frequency of VESs decreased to 24.3% in the DM group and up to 16.7% in the non-DM group.

A study supervised by Lekston et al. (2014) proved that reperfusion is not always successful in patients with DM and ACS, compared with patients without DM. This occurred because at least two CAs are affected more often in DM; thus, repeated PCI or coronary artery bypass grafting was performed [16]. According to our data, on day 1 after reperfusion, myocardial ischemia persisted in the DM group, which duration was significantly longer than that in the non-DM group. After 12 months, both groups showed improvement as a decrease in the ischemia index and myocardial ischemia duration; however, in the DM group, the ischemia index was 10.5 times greater, and the myocardial ischemia duration was six times longer than that in the non-DM group.

The mortality analysis performed by Denisova et al. (2016) revealed that fatal arrhythmias were more common in patients with type 2 DM, who died from ACS, than in patients with normal carbohydrate metabolism [17].

Maggioni et al. (1993) followed up 8676 patients after MI for 6 months. In 64.1% of the patients, ventricular arrhythmias were recorded, and 19.7% of them had high-grade VES and 6.8% of them had VT paroxysms. Moreover, 2% of deceased patients had rhythm disorders in the postinfarction period [18]. With follow-up periods of up to 4 years, the prognosis is relatively favorable. With long follow-up periods, including the registration of VT paroxysms, LV dysfunction decreased with EF [19]. In the present study, with a follow-up period of up to 12 months, the dynamics of LVEF was multidirectional in the DM group and non-DM group with VES grades III–V. Thus, in the DM group, by the end of year 1 after MI, the LVEF decreased; in the non-DM group, normal, and moderately reduced EF values were recorded.

Ephrem et al. (2013) followed up 222 patients during the rehabilitation period after ACS for 2.3 years. According to the results of HM, 48% of the patients had VESs, which were complicated by the aggravation of HF, palpitations, and syncope in 17.6% of cases. They concluded that polymorphic VESs occurring at a frequency of < 4/h are prognostically unfavorable [20].

Structural changes in the heart in the DM group and those who died from MI were studied by Mayorova et al. (2011). In the presence of severe atherosclerosis of the CAs, postinfarction and diffuse small-focal cardiosclerosis, 17.9% of the patients have metabolic myocardial damage with the formation of diabetic cardiomyopathy, namely, an increase in heart mass, sharp dilatation of the cavities, signs of microangiopathy, cardiomyocyte damage, and

myocardial stroma [21]. According to Akhmedov et al. (2015) and Elsukov et al. (2015), diabetic autonomic cardioneuropathy is characterized by the early degeneration of nerve fibers of both the sympathetic and parasympathetic systems and may be complicated by the development of fatal ventricular arrhythmias, sudden cardiac arrest, and painless MI [22, 23].

Skranes et al. (2016), based on the analysis of 24-h HM records in 498 patients, revealed that NT-proBNP levels are significantly higher in patients with VES and complex ventricular arrhythmias than in those without ventricular arrhythmias [8]. Using multivariate regression analysis, Omland (2008) concluded that an increase in the NT-proBNP level after ACS is associated with a high risk of fatal ventricular arrhythmias (OR 1.50 [95% OR 1.07–2.12], $p = 0.020$) [24].

According to our data, on day 1 after PCI in young and middle-aged patients with DM and MI associated with a large lesion area and persistent myocardial ischemia, high levels of NT-proBNP, and grades III–V VES were recorded. In the non-DM group, after reperfusion, myocardial ischemia also persisted; however, the frequency of grades III–V VES was lower. The blood serum level of NT-proBNP was significantly lower in them.

The NT-proBNP level is a significant factor in assessing the long-term prognosis of patients with DM after ACS. Thus, Salama et al. (2011), as a result of long-term follow-up of 62 diabetic patients after ACS, proved that the blood concentration of NT-proBNP in predicting long-term mortality is more accurate than other markers [25].

In patients with MI in the DM group, we revealed a high-significance positive correlation between the NT-proBNP level taken on day 1 after PCI and the number of VESs, ischemia index, and myocardial ischemia duration after 12 months. The prediction of high-grade VESs in the early period of MI with NT-proBNP levels > 898 pg/mL is performed with a sensitivity of 100%.

CONCLUSION

The blood serum levels of NT-proBNP in young and middle-aged patients with DM, and MI on day 1 after PCI is a reliable prognostic biomarker of ventricular arrhythmias over the next 12 months. To finally resolve the issue of which parameters, in addition to myocardial ischemia and LVEF, are closely associated with a high NT-proBNP prediction, and require additional studies in the context of groups of revascularized and non-operated patients.

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Research Article

Remodeling of the Left Atrium and the Possibility of Predicting Recurrences of Atrial Fibrillation in Various Variants of Sinus Rhythm Restoration

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OBJECTIVE: to compare the dynamics of left atrial remodeling in patients with AF with various CP recovery options and to identify the most reliable predictors of AF recurrence.

MATERIALS AND METHODS: 153 patients with non-valvular AF lasting from 24 hours to 6 months were examined. All patients were divided into 3 groups depending on the type of cardioversion: the 1st group included 49 patients whose CP was restored against the background of drug therapy; the 2nd group included 57 patients after electro-pulse therapy (EIT); the 3rd group included 47 patients who underwent radiofrequency isolation of the pulmonary veins (RFI LV). All patients underwent ECHO-cardiographic examination (ECHO KG) at the time of AF, as well as on 1, 3, 5, 15 days and 6 months after CP recovery with an assessment of indexed indicators of linear left atrium size (LP), LP volume, LP function recovery time by the rate of peak A transmittal flow (TMF) and LP filling pressure in relation to E/E' with the help of a fabric Doppler imaging.

RESULTS: it was revealed that the absence of AF paroxysms in any variant of cardioversion for 2 weeks is a reliable predictor of maintaining CP after 6 months ($p < 0.001$) and reducing the number of AF paroxysms for 6 months ($p < 0.001$). Accordingly, relapses of AF during the first 2 weeks indicate an increase in their probability within 6 months [OR (risk ratio) = 15.37]. A significant relationship was found between the timing of recovery of LP function (peak A > 0.5 m/sec) and recurrence of AF during 2 weeks and 6 months of follow-up ($p < 0.05$). In patients after LV RF, the linear size and volume of LP significantly decreased in dynamics while maintaining CP in comparison with those who had AF relapses for 6 months ($p < 0.05$). In patients after conservative cardioversion and RF ILV, LP filling pressure (E/E') significantly decreased after 14 days ($p < 0.05$) in the absence of AF relapses and did not change significantly by 6 months of follow-up ($p < 0.05$).While in the presence of repeated paroxysms of AF, this indicator did not change significantly by 6 months of follow-up. In the EIT group, no reliable dynamics of the estimated parameters of LP remodeling was found.

CONCLUSIONS: The peak A > 0.5 m/s measured by TMF on 1 day after the rhythm restoration is a reliable predictor of CP retention for 6 months in any variant of cardioversion ($p < 0.001$). The absence of AF paroxysms within 2 weeks after CP recovery reduces the likelihood of their occurrence also within 6 months with any choice of cardioversion ($p < 0.001$). In patients with CP recovery on the background of drug therapy and after RF ILV, the absence of recurrence of arrhythmia for 6 months is associated with a significant decrease in the size of LP (ILP and IOLP), ($p < 0.05$). A decrease in LP filling pressure (E/E') 2 weeks after conservative cardioversion and LV RFI can be considered a reliable predictor of maintaining sinus rhythm by 6 months ($p < 0.05$).

Keywords: atrial fibrillation; thromboembolic complications; cardioversion; restoration of sinus rhythm.

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Научная статья

Ремоделирование левого предсердия и возможности прогнозирования рецидивов фибрилляции предсердий при различных вариантах восстановления синусового ритма

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Цель — сравнить динамику ремоделирования левого предсердия у пациентов с фибрилляцией предсердий (ФП) при различных вариантах восстановления синусового ритма (СР) и выявить наиболее достоверные предикторы рецидивирования ФП.

Материалы и методы. Обследовано 153 пациента с неклапанной формой ФП продолжительностью от 24 часов до 6 месяцев. Все пациенты делились на 3 группы в зависимости от вида кардиоверсии: в 1-ю группу вошли 49 пациентов, у которых СР восстанавливался на фоне медикаментозной терапии; во 2-ю — 57 пациентов после электроимпульсной терапии (ЭИТ); в 3-ю — 47 пациентов, которым проводилась радиочастотная изоляция легочных вен (РЧИ ЛВ). Всем пациентам проводилось ЭХО-кардиографическое исследование на момент ФП, а также на 1, 3, 5, 15-е сутки и через 6 месяцев после восстановления СР с оценкой индексированных показателей линейного размера левого предсердия (ЛП), объема ЛП, времени восстановления функции ЛП по скорости пика А трансмитрального потока (ТМП) и давления наполнения ЛП по отношению E/E' с помощью тканевой допплеровской визуализации.

Результаты. Выявлено, что отсутствие пароксизмов ФП при любом варианте кардиоверсии в течение 2 недель является достоверным предиктором сохранения СР через 6 месяцев ($p < 0,001$) и уменьшения количества пароксизмов ФП в течение 6 месяцев (< 0,001). Соответственно, рецидивы ФП в течение первых 2 недель свидетельствуют о повышении их вероятности в течение 6 месяцев [OR (отношение риска) = 15,37]. Обнаружена достоверная взаимосвязь между сроками восстановления функции ЛП (пик А > 0,5 м/с) и рецидивированием ФП в течение 2 недель и 6 месяцев наблюдения (< 0,05).

У пациентов после РЧИ ЛВ в динамике достоверно уменьшались линейный размер и объем ЛП при сохранении СР в сравнении с теми, у кого регистрировались рецидивы ФП в течение 6 месяцев ($p < 0,05$).

У пациентов после консервативной кардиоверсии и РЧИ ЛВ давление наполнения ЛП (E/E') достоверно снижалось через 14 дней ($p < 0,05$) при отсутствии рецидивов ФП и существенно не менялось к 6 месяцам наблюдения ($p < 0,05$), в то время как при наличии повторных пароксизмов ФП данный показатель существенно не менялся к 6 месяцам наблюдения. В группе ЭИТ не обнаружено достоверной динамики оцениваемых показателей ремоделирования ЛП.

Выводы. Измеренный по ТМП пик А > 0,5 м/с в 1 сутки после восстановления ритма является достоверным предиктором сохранения СР в течение 6 месяцев при любом варианте кардиоверсии ($p < 0,001$). Отсутствие пароксизмов ФП в течение 2 недель после восстановления СР снижает вероятность их возникновения так же в течение 6 месяцев при любом выборе кардиоверсии ($p < 0,001$).

У пациентов при восстановлении СР на фоне медикаментозной терапии и после РЧИ ЛВ отсутствие рецидивирования аритмии в течение 6 месяцев сопряжено с достоверным уменьшением размеров ЛП (ИЛП и ИОЛП), ($p < 0,05$). Снижение давления наполнения ЛП (E/E') через 2 недели после консервативной кардиоверсии и РЧИ ЛВ можно считать достоверным предиктором сохранения синусового ритма к 6 месяцам ($p < 0,05$).

Ключевые слова: фибрилляция предсердий; тромбоэмболические осложнения; кардиоверсия; восстановление синусового ритма.

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ЭКО•ВЕКТОР

LIST OF ABBREVIATIONS

LA — left atrium
AF — atrial fibrillation
SR — sinus rhythm
LV — left ventricle
NYHA — HF I-II FC
LV SF — systolic function of the left ventricle
AH — arterial hypertension
LAI — left atrial index
LAVI — left atrial volume index
ET — electropulse therapy
RPVI — radiofrequency pulmonary vein isolation
RFA PV — radiofrequency ablation of pulmonary veins
FR MV — fibrous ring of the mitral valve
ApD of LA — anterior-posterior dimension of the left atrium
TF — transmission flow
TEC — thromboembolic complications
AAT — antiarrhythmic therapy
LVEF — left ventricular ejection fraction
HD — hypertonic disease
DM — diabetes mellitus
DF — diastolic function
MI — myocardial infarction
EMD — electromechanical dissociation

As is known, atrial fibrillation (AF) is the most common of all arrhythmias and the most dangerous due to the high risk of hemodynamic and thromboembolic complications (TEC) [1, 2].

Recently, numerous studies have been devoted to both the probability of predicting and recurring AF, and to the assessment of the morphology of the left atrium (LA) and its dysfunction, which may determine the predisposition to TEC in certain groups of patients [3–5, 28].

Back in 1989, W. Manning et al. found that when sinus rhythm is restored, the normalization of the mechanical function of the atria does not occur immediately: in 38–80% of patients with atrial fibrillation (AF) duration of more than 7 days, the phenomenon of "stunning" of the atrial myocardium is observed [6].

This phenomenon has become the basis of the concept of electromechanical dissociation of LA and may be the reason for TEC development.

“Stunning” of LA is often observed after spontaneous, pharmacological or electrical cardioversion, as well as after radiofrequency pulmonary vein isolation of the (RPVI) [7].

As a rule, atrial mechanical function gets to be restored in the period from several hours to 4 weeks in certain groups of patients, depending on the duration of the current AF paroxysm, on the method of rhythm restoration, as well as on the initial characteristics of the LA [8, 9].

The choice of sinus repair method is not a predictor of the presence or absence of subsequent arrhythmia recurrences [10]. According to various sources, in 50–60% of patients with AF, recurrent paroxysms can occur within 4 weeks after cardioversion, and the risk of their recurrence within a year varies from 20 to 80% [11, 12].

Over the past decades, many studies have demonstrated the complex pathophysiology of AF. The main trigger for the onset of AF is the presence of ectopic foci in the pulmonary veins, whereas LA structural remodeling is identified as the main factor in the progression of arrhythmia [13, 29]. Recent studies have also demonstrated that left atrial volume correlates with the degree of atrial fibrosis [14,15].

SInce the advent of the method of Doppler tissue imaging, the algorithm for assessing LV diastolic function (DF) has included such a mandatory parameter as the calculated ratio of the maximum rate of transmitral blood flow (E) and the peak rate of early myocardial relaxation in the early LV filling phase (E/E'), which proved to correlate with the magnitude of pressure in the LA. The E/E' index > 15 is highly likely to indicate the presence of LV diastolic dysfunction and increased pressure in the left atrium [16].

According to Kusunose et al., this indicator can also be assessed in patients with AF and does not change significantly when measured over several cardiac cycles. It has also been proven that the E/E' ratio correlates well with the level of natriuretic peptide, which is a reliable predictor of heart failure. However, researchers have not confirmed the correlation of this indicator with the presence of LV diastolic dysfunction in patients with AF [17]. The work of M. Caputo et al. associates an increase in this parameter with a more frequent recurrence of AF in patients after successful electrical cardioversion [18].

However, despite a large number of studies, to date there are no reliable predictors of maintaining sinus rhythm after cardioversion, regardless of the method of restoration of SR and the choice of antiarrhythmic therapy (AAT).

The search for new opportunities to identify the risk of recurrence of AF and prevent associated AF remains extremely relevant.

The purpose of this study was to study the features of left atrial remodeling and to find the predictors of atrial fibrillation recurrence in various types of SR restoration.

SCIENTIFIC NOVELTY OF THE RESEARCH

This research demonstrates new data in the prediction of atrial fibrillation recurrence with various methods of rhythm restoration. It has been shown that the absence of atrial contractility on the first day after any type of cardioversion is associated with AF recurrence within 2 weeks and 6 months after rhythm restoration. It was also found that the absence of AF paroxysms after SR restoration for 14 days is a significant predictor of maintaining sinus rhythm up to 6 months and reducing the number of AF relapses with any type of cardioversion. It was demonstrated that a decrease in dynamics 2 weeks after reversion to sinus rhythm in such

parameters of LA remodeling as the volume index and filling pressure (E/E') turned out to be prognostically favorable in terms of maintaining of sinus rhythm for 6 months after drug cardioversion and radiofrequency ablation of pulmonary veins. In turn, the absence of dynamics of these indicators or their increase, on the contrary, may be associated with a high risk of atrial fibrillation recurrence.

The data obtained can be used in cardiology and arrhythmology for the selection of antiarrhythmic therapy, determining the duration of anticoagulant therapy in patients without a high risk of TEC and/or at high risk of bleeding in controversial clinical situations.

MATERIALS AND METHODS

The study included 153 patients, namely 83 men (54.2%) and 70 women (45.7%), mean age was 62.7 (36–81) with non-valvular AF lasting from 24 hours to 6 months with systolic function of the left ventricle (LV SF) > 40%. Distribution into 3 groups was made: the first included 49 patients in whom SR was restored in a sign of drug therapy; the second one included 57 patients who underwent electrical cardioversion; the third one encompassed 47 patients who underwent radiofrequency pulmonary vein isolation (RPVI). The exclusion criteria were LV EF < 40%, HF I-II FC (NYHA), valvular heart disease. Initially, the comparison groups did not have significant differences in age and the presence of such diseases as stable forms of coronary artery disease I-II FC, hypertension (AH), type 2 diabetes mellitus (DM) in the compensation stage, HF I-II FC (NYHA)) (Table 1).

All patients underwent a transesophageal echocardiographic study (TEECHO CG) right before rhythm restoration to rule out thrombi in the LA auricle. Patients received anticoagulants in accordance with the recommended scale CHA2DS2VASc. All patients received antiarrhythmic therapy (AAT) with Propafenone (in the absence of contraindications to class 1C) or Amiodarone before cardioversion and as maintenance therapy after effective SR restoration. The choice of AAT did not significantly affect the predictions for the presence or absence of AF relapses in the study groups (Table 2). ET was carried out according to the standard method in ICU. RPVI was performed in patients with current AF paroxysm using the CARTO electroanatomical mapping system. During the procedure, an anatomical map of the LA was constructed, followed by circular antral isolation of the left and right PVs using magnetic navigation with verification of the conduction block using a Lasso catheter.

All patients underwent an ECHO-cardiographic study (Echo-CG) on ultrasonic Vivid q, (GE) against the background of AF, on the 1st, 3rd, 5th, 15th days and 6 months after the restoration of SR. During the study, LV systolic and diastolic function, myocardial wall thickness, indexed LA dimensions, as well as LA function according to TF were evaluated. The function of the atrial myocardium was considered effective in the presence of peak A > 0.5 m/sec. LVEF was assessed in a two-dimensional mode according to the Simpson method, the analysis of LV diastolic function (DF) was performed by the traditional method of measuring the transmitral flow (TF) in pulsed wave Doppler mode (E), as well as using Doppler tissue imaging with an assessment of early peak diastolic velocity (E') and the E/E' ratio, reflecting the pressure in the LA cavity and the LV filling pressure, the LA volume index was determined by the biplane method. The frequency of AF recurrence was assessed according to the history data, using ECG at the time of control, as well as according to the data of 24-hour Holter ECG monitoring in the period from 3 to 6 months after cardioversion. Arrhythmia recurrence was

Table 1. Clinical and demographic indicators and features of anamnesis in patients in the study groups

Parameters	Cons. (*n* = 49)	ET (*n* = 57)	*R* (*n* = 47)	*p*
Men	21 (42.9%)	40 (70.2%)	22 (46.8%)	> 0.05
Women	28 (57.1%)	17 (29.8%)	25 (53.2%)	< 0.05
AH	29 (59.2%)	41 (72%)	27 (57.5%)	> 0.05
IHD	4 (13.8%)	7 (17.1%)	3 (11.1%)	> 0.05
DM	3 (10.3%)	2 (12.5%)	3 (11.1%)	> 0.05
CHF I-II FC	5 (17.2%)	2 (12.5%)	8 (29.6%)	> 0.05

Notes: Cons. — group of conservative therapy; ET — group of electropulse therapy; R — RPVI group; AH — arterial hypertension; IHD — ischemic heart disease; DM — Type II diabetes mellitus; CHF I-II FC — chronic heart failure I-II FC (NYHA).

Table 2. Antiarrhythmic therapy (AAT)

Medication	Cons. (*n* = 49)	ET (*n* = 57)	*R* (*n* = 47)	*p*
Propafenone	16 (32.7%)	11 (19.3%)	14(29.8%)	> 0.05
Cordarone	33 (67.3%)	46 (80.7%)	33 (70.2%)	> 0.05

defined as the presence of symptomatic or asymptomatic episodes of AF lasting more than 30 seconds.

The clinical results obtained during the study were processed using the STATISTICA for Windows software system (version 10 License BXXR310F964808FA-V). Comparison of the frequency characteristics of qualitative indicators was carried out using non-parametric methods 2, 2 with the Yates correction (for small groups) and the Fisher criterion. When comparing quantitative parameters, the Mann-Whitney test, median chi-square, and ANOVA were used. The evaluation of the studied parameters in dynamics after the treatment and in follow-up was carried out using the Signs criterion and the Wilcoxon criterion. Statistical significance was considered at $p < 0.05$.

RESULTS

The studied groups initially did not differ in age and comorbidities (Table 1). However, the number of women whose rhythm was restored with the help of ET turned out to be almost 2 times less than in the groups of conservative therapy and RPVI (Table 1).

When assessing echocardiographic data in patients with restored SR on conservative therapy, LVEF was significantly higher than in the groups of ET and RPVI (Table 3).

In addition, there were differences in the measurement of LA volume in the study groups. The LA volume index initially turned out to be higher in the group of patients who underwent radiofrequency PV isolation. Differences were also found in the analysis of the parameters of LV diastolic function. Thus, the initial value of the peak E TF was lower in the group of patients with RFA PV, and the peak A TF, measured on the first day after the restoration of SR, was significantly higher among patients in the group of drug cardioversion; the E' index was higher in patients in the ET group, and the E/E' ratio in the group of radiofrequency PV isolation exceeded this parameter in other groups (Table 3). The assessment of these parameters reflects a more significant impairment of LV diastolic function in patients in the RFA PV group.

A TMP peak, measured 1 day after SR restoration, was the highest in the drug cardioversion group. This makes it possible to conclude a higher LA contractility in this group and, as a result, a decrease in the frequency of AF recurrence in the long term in these patients (Table 3).

It should also be noted that the study groups did not differ in the duration of the current arrhythmia paroxysm at the time of cardioversion (Table 4).

It was found that the absence of AF paroxysms after the restoration of sinus rhythm for 2 weeks was associated

Table 3. Baseline echocardiographic parameters in the examined patients

Parameters	Cons. (*n* = 49)	ET (*n* = 57)	*R* (*n* = 47)	*p*
Age	64.12 (48; 81)	61.33 (45; 77)	63.11 (36; 80)	> 0.05
BSA	1.86 (1.48; 2.17)	2.07 (1.69; 2.72)	1.91 (1.56; 2.36)	> 0.05
LV EF (Biplan)%	66.14 (56; 75)	62.05 (43; 76)	62.78 (46; 77)	< 0.05
EDS	48.66 (38; 64)	50.18 (41; 64)	51.89 (42; 80)	> 0.05
ESS	32.21 (23; 45)	32.56 (25; 56)	35.00 (24; 64)	> 0.05
IVS	11.93 (8; 16)	12.95 (9; 18)	11.81 (9; 15)	> 0.05
WS	11.38 (8; 16)	12.69 (9; 18)	11.33 (8; 15)	> 0.05
ILS	24.85 (17.9; 30.4)	23.13 (15.6; 29.3)	25.03 (18.9; 33.3)	> 0.05
LAVI	38.23 (26.3; 62.5)	38.05 (25.7; 60.9)	45.71 (27.2; 81.7)	< 0.05
Peak E	94.06 (70; 132)	96.72 (69; 180)	79.43 (55; 120)	< 0.05
Peak A 1d	52.02 (0; 79)	34.88 (0; 104)	27.76 (0; 100)	< 0.05
DT	161.55 (99; 230)	162.85 (77; 240)	167.42 (125; 286)	> 0.05
E’	11.78 (6; 16)	12.61 (7; 19)	7.88 (4; 20)	< 0.05
E/E’	8.28 (5; 13.3)	8.10 (4; 18)	12.04 (6; 20)	< 0.05

Note: Cons. — group of conservative therapy; ET — group of electropulse therapy; R — RPVI group; BSA — body surface area; LV EF (Biplan)% — left ventricular ejection fraction; measured according to Simpson; EDS — LV end diastolic size; ESS — LV end systolic size; IVS — interventricular septum; WS — posterior wall; ILS — index of the linear size of the left atrium; LAVI — index of the volume of the left atrium; Peak E — the maximum rate of early filling of the left ventricle; Peak A 1d — the maximum rate of late filling of the left ventricle; measured on day 1; after the restoration of sinus rhythm; DT — deceleration time of early diastolic filling; E' — the maximum speed of the early diastolic wave of movement of the fibrous ring of the mitral valve (FR MV); E/E' — the ratio of the maximum speed of early filling of the LV to the maximum speed of the early diastolic wave of movement of the FR MV.

with a decrease in the likelihood of arrhythmia recurrence within 6 months in all observation groups ($p < 0.001$).

Accordingly, the occurrence of early AF paroxysms during the first 2 weeks after the restoration of SR also indicates their higher probability of their appearance within 6 months [RR (risk ratio) = 15.37].

A significant relationship was also found between the restoration time of LA contractility (peak A > 0.5 m/sec) and the frequency of AF recurrence during 6 months of follow-up. So, in the group of medical cardioversion in 39 (80%) patients, effective LA systole (peak A > 0.5 m/sec) was recorded on the first day after the restoration of sinus rhythm, and by the 15th day of observation, sinus rhythm was maintained in all patients of this group (Fig. 1). In addition, arrhythmia did not recur within 6 months of observation in most of these patients (26 (66.7%) people), and only in 13 (33.3%) patients in the long-term period 1 or more AF paroxysms were observed (Fig. 2).

Out of 10 patients in the group of drug-induced rhythm restoration with no atrial contractility on the first day after cardioversion (peak A < 0.5 m/sec), AF relapses were recorded in 2 patients by day 15. Within 6 months, arrhythmia recurred

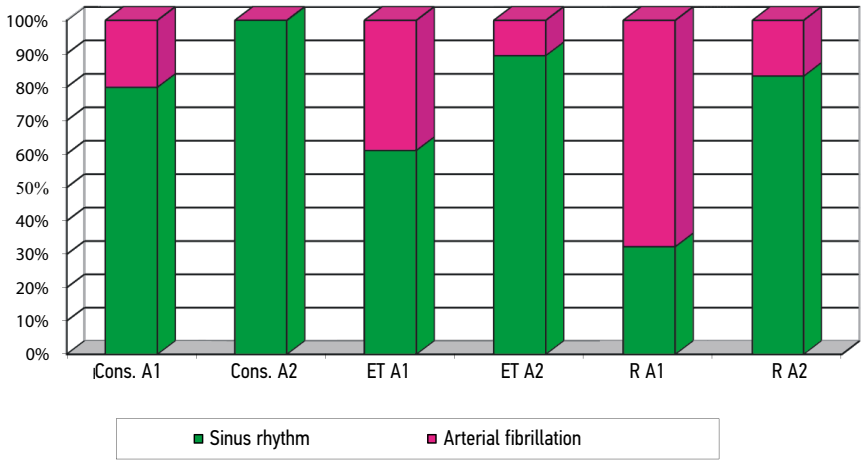

Fig. 1. The frequency of AF relapses in the observation groups for 15 days, depending on the restoration of atrial systole on the first day after cardioversion. A1 — A < 0.5 m/s; A2 — A > 0.5 m/s; Cons. — group of conservative therapy; ET — electrical cardioversion group; R — RPVI group

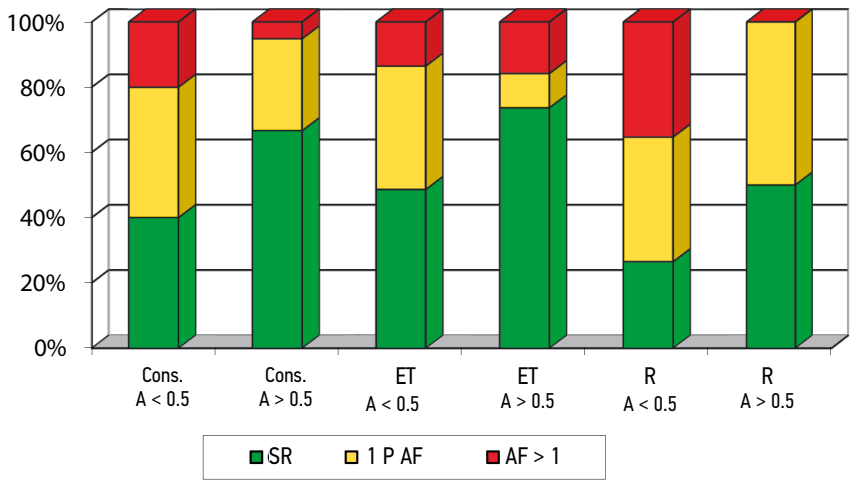

Fig. 2. The frequency of AF recurrence in groups within 6 months depending on atrial contractility on the first day after SR restoration (A > or < 0.5 m/s). SR — sinus rhythm; 1 P AF — 1 paroxysm of atrial fibrillation; AF > 1 — more than 1 paroxysm of AF; Cons. — group of conservative therapy; ET — electrical cardioversion group; R — RPVI group

Table 4. Duration of the current AF paroxysm in the study groups

Duration of AF paroxysm	Cons. (n = 49)	ET (n = 57)	R (n = 47)	p
24 h–7 days	17	15	14	> 0,05
7–30 days	20	24	18	> 0,05
30 days–6 months	12	18	15	> 0,05

in 6 patients of this subgroup (60%; significance of differences in the appearance of the sign compared with patients who restored atrial systole on the first day after cardioversion is $p < 0.005$; Fig. 2). However, after 6 months in all patients after medical restoration of SR, regardless of the timing of normalization of atrial contractility, SR was recorded.

In the ET group, peak A > 0.5 m/sec on the first day after cardioversion was recorded in 19 (34.5%) patients, of which 17 (89.5%) by the 15th day of observation maintained stable SR; relapses of AF were registered only in 2 (10.5%) people; $p < 0.05$. After 6 months, in 14 (73.7%) patients of this subgroup SR was stable, and relapses were noted only in 5 (26.3%) people.

On the first day after ET in 36 (65.5%) patients peak A was not recorded or was less than 0.5 m/sec. Of these, 14 (39%) people had AF paroxysms within 15 days after cardioversion, which was more common than in patients with good LA contractility on the first day after rhythm restoration; $p < 0.05$ (see Fig. 2).

In the group of radiofrequency PV isolation, only 12 (26%) patients had peak A > 0.5 m/sec on the first day after SR restoration. As well as in groups 1 and 2, in most of these patients (10 (83.3%)) by the 15th day of observation, SR continued, and AF relapses were observed in only 2 (16.7%) patients (see Fig. 1). Within 6 months, half of this subgroup (6 (50%)) had persistent SR, and the remaining 6 people had repeated paroxysms of AF within 6 months.

After RFA PV in most patients (34 (74%)) on the first day after the restoration of SR, peak A was not recorded or was < 0.5 m/sec, which was much more frequent than in groups 1 and 2; $p < 0.01$. At the same time, by day 15 after RFA, arrhythmia recurred in 23 (67.6%) patients, while SR continued in the remaining 11 (32.4%) patients; significance of differences in comparison with patients who had effective atrial systole on the first day after restoration of HR $p < 0.001$ (see Fig. 1). After 6 months, this subgroup also showed a greater number of patients with AF: arrhythmia recurrences were recorded in 25 (73.5%) of them; significance of differences in comparison with patients who had an effective LA systole on the first day after SR restoration was $p < 0.005$ (see Fig. 2).

DYNAMICS OF THE LINEAR SIZE OF LA

When measuring the indexed linear size of the LA, there was no significant dynamics of this indicator in the groups of medical and electrical cardioversion during the control after 6 months of observation, regardless of the presence or absence of AF relapses during this period. In the group of conservative therapy in patients without recurrence of arrhythmia for 6 months (30 people), the initial LAI was 25.1 + 2.8 ml/m^2, and after 6 months there was only a slight tendency to decrease (23.8 + 2.8 ml/m^2, $p > 0.05$). In patients with recurrent AF (19 people), LAI did not change: the initial indicator was 24.4 + 2.8 ml/m^2, after 6 months it was 24.1 + 2.1 ml/m^2, $p > 0$ .05 respectively.

In the group of patients with ET with persistent SR for 6 months (32 people), the mean values of LAI initially amounted to 23.3 + 2.1 ml/m^2 and 23.3 + 2.6 ml/m^2 by 6 months of observation ($p > 0$, 05). In patients with recurrent AF after ET (25 people), the initial LAI was 22.9 + 3.4 ml/m^2, after 6 months it did not change significantly either (23.5 + 2.7 ml/m^2; $p > 0.05$).

However, in the RPVI group, there was a significant decrease in LAI by 6 months of follow-up in patients without arrhythmia recurrence. With persistent SR after RFA PV ($n = 14$), the baseline LAI was 25 + 3.2 ml/m^2 and significantly decreased to 20.4 + 1.8 ml/m^2 after 6 months ($p < 0.001$), while in patients with recurrence of AF within 6 months ($n = 33$) the LAI was initially equal to 26 + 2.8 ml/m^2 and on average did not change after 6 months — 25.3 + 4.4 ml/m^2 (Fig. 3).

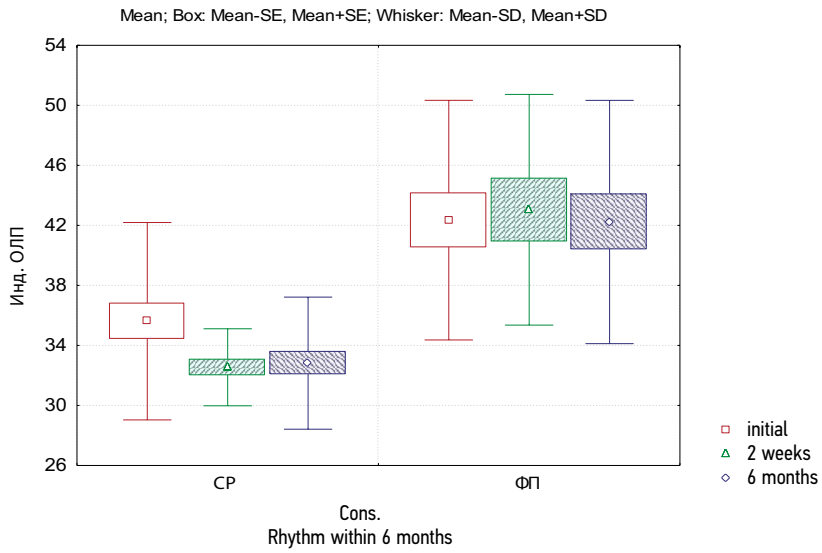

Fig. 3. Dynamics of the LA linear size index (LAI) in the RFA PV group depending on the presence or absence of AF relapses within 6 months

LP VOLUME DYNAMICS

In the group of SR drug restoration, there were initial differences in indexed LA volumes in patients depending on the presence or absence of AF paroxysms within 6 months. In the absence of recurrences of arrhythmia for 6 months in 30 patients of this group, the initial LAVI index was 35.6 + 6.6 ml/m^2, while in 19 people with subsequent recurrences of AF after SR restoration, this parameter initially turned out to be significantly higher (42.3 + 8 ml/m^2, $p < 0.05$).

After 2 weeks of observation, patients after drug cardioversion showed a slight trend towards a decrease in the LAVI to 32.5 + 2.6 ml/m^2 in the absence of arrhythmia recurrences during this period, without significant further dynamics (32.8 + 4.4 ml/m^2 after 6 months; $p > 0.05$). In patients with AF recurrence within 6 months, this indicator did not change significantly in dynamics: by the 2nd week of observation, the LAVI was 43 + 8 ml/m^2, by 6 months it was 42.2 + 8.1 ml/m^2; $p > 0.05$ (Fig. 4).

In the group of patients after ET, this parameter also did not change significantly during 6 months of observation, regardless of the presence or absence of recurrence of arrhythmia: LAVI in patients with persistent SR was 38.8 + 9.2 ml/m^2 and 40.2 + 11.9 ml/m^2 at 2 weeks and 6 months, respectively ($p > 0.05$), and in patients with recurrent AF it was 37.1 + 8.9 ml/m^2 and 34.8 + 12 ml after 2 weeks and 6 months, respectively ($p > 0.05$).

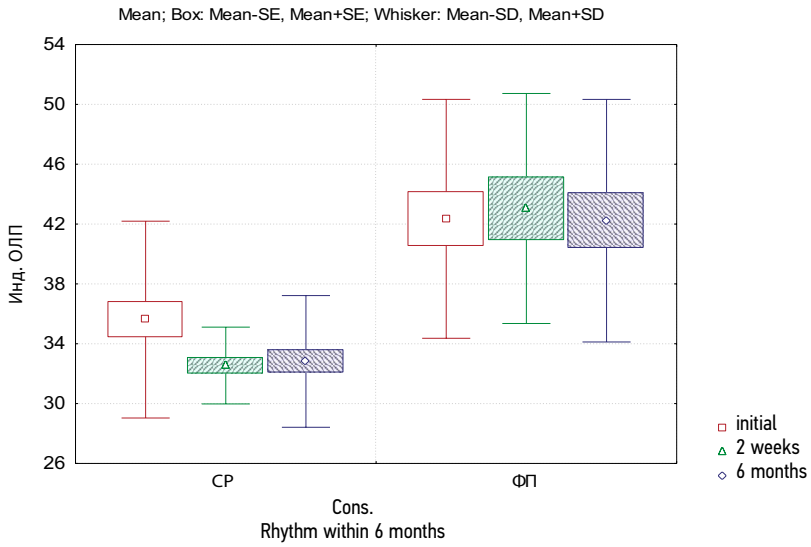

Fig. 4. Index of LA volume in the group of medical cardioversion depending on the presence or absence of AF relapses within 6 months after SR restoration

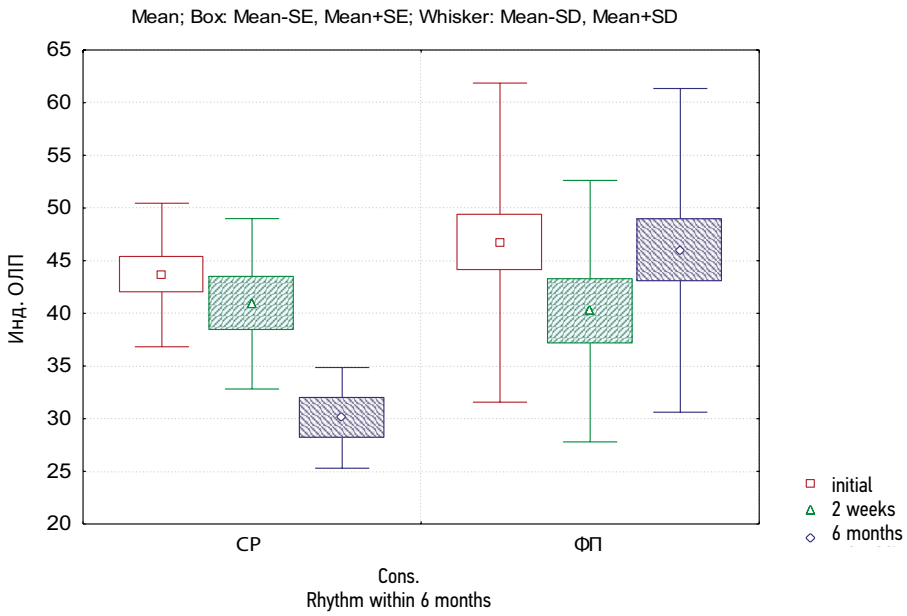

Fig. 5. Changes in the LA volume index in the RFA PV group depending on the presence or absence of recurrent AF within 6 months

However, in the group of patients after RFA PV in the absence of arrhythmia recurrence (14 people), by 6 months the LAVI decreased on average from the initial 42.9 + 7 ml/m^2 to 30.1+15.4 ml/m^2; $p < 0.001$. While in patients with recurrent AF, this indicator did not change significantly: the initial LAVI was 46.8 + 14.7 ml/m^2, and after 2 weeks and 6 months it was 41.3 + 12 and 46 + 15.4 ml/m^2, respectively; $p > 0.05$. (Fig. 5).

DYNAMICS OF E/E'

The value of the E/E' ratio in the group of patients with medical SR restoration significantly decreased after 2 weeks in the absence of arrhythmia paroxysms after cardioversion from 9.2 + 3 to 7.3 + 3 ($p < 0.05$) without further significant dynamics within 6 months (7.0 + 1.2). In patients with recurrent AF in this group, this parameter did not change significantly after 2 weeks (11.1 + 3.9 and 9.8 + 2.5, respectively; $p > 0.05$), however, it significantly decreased after 6 months (from 11.1+3.9 to 9.2+2.5; $p < 0.05$) (Fig. 6).

In the group of patients after ET, the E/E' indicator did not change significantly during 6 months of observation, regardless of the presence or absence of AF relapses during observation up to 6 months: in 32 patients without repeated paroxysms of arrhythmia, the indicator was 8.1 + 2.5 in the first days after cardioversion; 8.1 + 3.7 — after 2 weeks and 7.7 + 4.1 — after 6 months; $p > 0.05$. In patients with

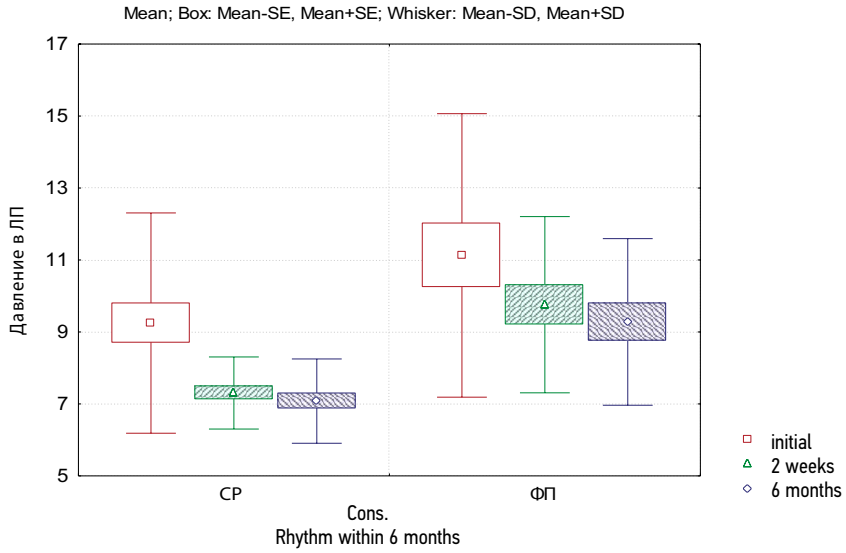

Fig. 6. E/E' indicator in the drug cardioversion group depending on the presence or absence of AF recurrence within 6 months

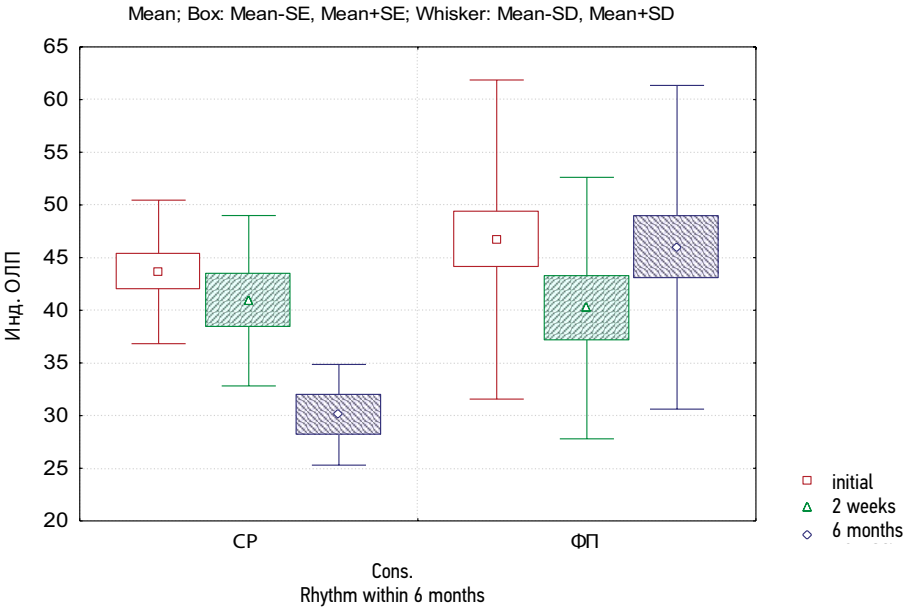

Fig. 7. Dynamics of the E/E' indicator in the group of patients after RFA PV depending on the preservation of SR or the presence of AF recurrence within 6 months

arrhythmia recurrence, no dynamics of this parameter was also found: E/E' initially amounted to 8.0 + 1.9, after 2 weeks — 8.6 + 2.2 and after 6 months — 9.5 + 2 ,8.

However, in patients after RFA PV, a statistically significant decrease in E/E' was observed in the absence of arrhythmia recurrence, both, after 2 weeks (initially, E/E' was — 20.1 + 7.6, and after 2 weeks it decreased to 14.3 + 2.8 ($p < 0.05$)), and after 6 months of observation — with a decrease in the indicator to 8.3 + 3.1; $p < 0.05$. And in patients with AF paroxysms, the E/E' ratio did not change significantly during 6 months: on the first day after RFA, the IPV and restoration of the rhythm E/E' averaged 12.5 + 7.1; after 2 weeks — 13 + 7.4; with a slight downward trend after up to 6 months of observation — 10.5 + 5 (Fig. 7).

DISCUSSION

It is known that "stunning" of the left atrium is associated with the processes of thrombosis in the LA appendage, and the longer the electromechanical dissociation of the LA persists, the higher the risk of delayed thromboembolism [13]. This must also be taken into account when deciding on the timing of anticoagulant therapy,

Some authors consider atrial systole ineffective in the complete absence of wave A of the transmural blood flow (Mahbubul A. et al., 1992), while others consider this concept with any decrease in the speed of peak A less than 0.5 m/s (Hariai K. et al., 1998). Mahbubul A. et al. (1992) also describe the dependence of the timing of restoration of atrial contractility on the linear size of the LA in patients with AF. In their opinion, an LA size of 50 mm or more is associated with the absence of an LA systole lasting more than 4 hours, and in the presence of an LA size of less than 50 mm, atrial contractility is usually restored within the first 4 hours after effective cardioversion [14]. Other studies have demonstrated that atrial systole in patients with AF can restore within seconds to weeks after cardioversion [15].

Other authors also describe the relationship between the timing of the restoration of wave A TF and the duration of arrhythmia: if the duration of paroxysm AF is less than 2 weeks, the peak A TF is restored, as a rule, within 24 hours; with paroxysm from 2 to 6 weeks, EMD persisted for about 7 days, and if the arrhythmia lasts more than 6 weeks atrial contractility could be absent for up to 1 month [16]. But at the same time, there are studies that do not confirm the relationship between the duration of EMD and the duration of AF paroxysm and the size of the LA [17].

In this issue, the work, which includes 112 patients with AF and medical restoration of SR, who were observed for 6 months in order to search for predictors of arrhythmia recurrence, deserves special attention. Atrial systole restoration was assessed based on wave A TF on days 1, 7, and 21 after cardioversion. And conclusions were drawn that the absence of a TF A peak in the first 24 hours after rhythm restoration was the most significant predictor of AF recurrence [18].

As a result of our analysis, we also concluded that the absence of wave A of the TF (or at its value less than 0.5 m/s) on the first day after cardioversion significantly correlates with the occurrence of AF paroxysms within 2 weeks and 6 months. with various methods of restoration of SR. The absence of AF paroxysms in the first 2 weeks after cardioversion in all groups in relation to reducing the likelihood of their occurrence in the period up to 6 months also turned out to be significant.

Also, in recent years, a large number of studies has been conducted aimed at finding the relationship between the size of the LA and the likelihood of recurrence of AF.

The work of F.M. Costa et al. reflects the results of a study of 809 patients with AF of various durations. The paper proved that the most significant predictors of recurrent AF paroxysms are LA volume, female sex and the duration of the current episode of arrhythmia. Moreover, the LA volume most significantly correlated with the likelihood of arrhythmia recurrence than the duration of the current episode of arrhythmia [19].

In a study by Marchese et al. data were obtained on 411 patients with AF after electrical cardioversion: after 12 months, 250 of them had repeated episodes of arrhythmia and they also had a significantly larger initial indexed volume of the left atrium compared to those who did not have arrhythmia during the year [20].

It has been proven that fibrosis is a hallmark of LA structural remodeling and is associated with an increased risk of stroke, worsening of the results of catheter ablation, and an increase in the frequency of arrhythmia recurrences [25–27].

In turn, Shin S.H. et al. studied patients with atrial fibrillation before RFA: LV dimensions, LV systolic function, and both atrial dimensions were assessed. They concluded that only the volume of the left atrium was an independent predictor of the occurrence of recurrent arrhythmia episodes during follow-up up to 6 months ($p < 0.01$) [21].

In our study, the indexed linear size and volume of the left atrium in patients after RFA PV were also independent predictors of AF recurrence for 6 months, and reverse LA remodeling after six months was associated with a decrease in the likelihood of recurrent episodes of arrhythmia during this period.

Also, relatively recently, such a parameter of LA remodeling and a criterion of LV diastolic function as E/E' began to be evaluated, including in patients with AF to assess the dynamics of LA filling pressure.

The value of this indicator is also being studied by researchers in relation to assessing the probability of predicting arrhythmia recurrence. M. Caputo et al. analyzed the echocardiographic parameters of the left atrium in patients with AF, and the ratio E/E' was an independent predictor of the occurrence of recurrent AF paroxysms during the year [22].

Other authors also proved the significance of this criterion in patients with AF after RPVI [23]. Li et al. analyzed the E/E' ratio in 103 patients with AF before radiofrequency LV isolation, and it turned out that the value of 11.2 was an independent predictor of arrhythmia recurrence within 3 months after surgery [24].

According to our data, the value of E/E' also proved to be prognostically significant in relation to arrhythmia recurrence in the groups of medical cardioversion and RFA of the LV when observed up to 6 months. Moreover, the greatest prognostic value was not the initial values of E/E', but their dynamics after 14 days. Thus, a significant decrease in this parameter by 2 weeks after the restoration of SR in the groups was a significant predictor of the preservation of SR for 6 months.

While in the group of patients with electro-pulse therapy (EPT), there were no significant differences in the dynamics of LA sizes and the E/E' ratio for 6 months, regardless of the presence or absence of recurrent arrhythmias.

CONCLUSIONS

Our data allow us to conclude that peak A, measured by transmitral blood flow, exceeding 0.5 m/s on the 1st day after rhythm restoration can be considered a significant criterion for maintaining SR for up to 6 months with any choice of cardioversion ($p < 0.05$). In addition, one of the predictors of maintaining sinus rhythm by month 6, according to our data, may be the absence of AF paroxysms during the first 2 weeks after SR restoration ($p < 0.001$).

Also, a decrease in dynamics after 2 weeks of such parameters of LA remodeling as the volume index and filling pressure (E/E') can serve as predictors of maintaining sinus rhythm for 6 months in patients with atrial fibrillation after successful medical cardioversion and radiofrequency ablation of the pulmonary veins. Whereas the absence of dynamics in these indicators or an increase, on the contrary, is associated with a high risk of recurrence of atrial fibrillation.

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Research Article

Antitachycardic Therapy of ICD in Patients with Multiple Morphologies of Monomorphous Ventricular Tachycardia Refractory to Therapy

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The article presents a description of a clinical case of a patient with structural myocardial pathology (postinfarction cardiosclerosis) with recurrent paroxysmal sustained monomorphic ventricular tachycardia (VT) refractory to the nominal recommended ICD (implantable cardioverter defibrillator) settings; as well as discusses the shortcomings of existing standard algorithms for antitachycardia pacing (ATP) of implantable cardioverter defibrillators and potential ways to increase its efficiency. The refractoriness of recurrent paroxysms of ventricular tachycardia to ATP therapy increases the risk of repeated ICD shocks.

Despite the existence of universal recommendations for ICD programming and ATP therapy, there is a need in clinical practice for individualized ATP programming in patients refractory to nominal settings. Increasing the number of ATP series and changing algorithms enables to increase the efficiency of ATP up to 80–89%. Refractoriness to standard ATP settings may be also overcome by using alternative ATP pacing algorithms (Ramp, Burst-plus, or Ramp-plus instead of Burst), changing the pacing interval, ATP sequence duration, pacing type, and even adding 1–2 extra stimuli, as well as using data from the previous intracardiac electrophysiological heart test.

The presented clinical case of a patient with postinfarction cardiosclerosis and paroxysmal stable monomorphic VT (SM-VT) of several morphologies demonstrates that the arrhythmogenic substrate after myocardial infarction changes for a long time without new stenoses in large coronary arteries and without new episodes of acute coronary syndrome, as well as generates several different morphologies of VT from one scar (with different heart rates) and the effect on hemodynamics. The efficiency of early ATP pacing may differ for VT of various morphologies, which makes it reasonable to use alternative pacing algorithms (in addition to the standard Burst sequences recommended by the 2019 Consensus on ICD programming) and testing possible ATP algorithms during ablation of monomorphic VT, including during preventive VT ablation before ICD implantation.

Keywords: antitachycardia pacing; implantable cardioverter-defibrillator; monomorphic ventricular tachycardia; clinical case of VT refractoriness.

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Научная статья

Антитахикардитическая терапия ИКД у пациентов с несколькими морфологиями мономорфной желудочковой тахикардии, рефрактерной к терапии

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В статье приводится описание клинического случая пациента со структурной патологией миокарда (постинфарктный кардиосклероз) с рецидивирующей пароксизмальной устойчивой мономорфной желудочковой тахикардией (ЖТ), рефрактерной к номинальным рекомендуемым настройкам имплантируемых кардиовертеров-дефибрилляторов (ИКД); обсуждаются недоставки существующих стандартных алгоритмов антитахикардитической стимуляции (АТС) ИКД и потенциальные пути увеличения ее эффективности. Рефрактерность рецидивирующих пароксизмов желудочковой тахикардии (ЖТ) к АТС-терапии увеличивает риск повторных разрядов ИКД.

Несмотря на наличие «универсальных» рекомендаций по программированию ИКД и АТС-терапии, в клинической практике существует потребность в индивидуализированной программации АТС у пациентов, рефрактерных к номинальным настройкам. Увеличение числа серий АТС и смена алгоритмов позволяет увеличить эффективность АТС до 80–89 %. Рефрактерность к стандартным настройкам АТС может быть также преодолена путем использования альтернативных алгоритмов АТС-стимуляции (Ramp, Burst-plus или Ramp-plus вместо Burst), изменения интервала стимуляции, длительности АТС-последовательности, типа стимуляции и даже добавления 1–2 экстрастимулов, а также с использованием данных предшествующего внутрисердечного ЭФИ.

Представленный клинический случай пациента с постинфарктным кардиосклерозом и пароксизмальной устойчивой мономорфной ЖТ (УМ–ЖТ) нескольких морфологий демонстрирует, что аритмогенный субстрат после перенесенного инфаркта миокарда изменяется на протяжении длительного времени без новых стенозов в крупных коронарных артериях и без новых эпизодов ОКС, а также генерировать несколько различных морфологий ЖТ из одного рубца (с разной ЧСС) и влиянием на гемодинамику. Эффективность ранней АТС-стимуляции может отличаться для ЖТ различной морфологии, что делает целесообразным использование альтернативных алгоритмов стимуляции (помимо стандартных Burst последовательностей, рекомендованных Консенсусом 2019 г. по программированию ИКД) и тестирование возможных АТС-алгоритмов в процессе выполнения аблации мономорфной ЖТ, в том числе при проведении превентивной аблации ЖТ перед имплантацией ИКД.

Ключевые слова: антитахикардитическая стимуляция; имплантируемый кардиовертер-дефибриллятор; мономорфная желудочковая тахикардия; клинический случай рефрактерности ЖТ.

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INTRODUCTION

Antitachycardia pacing (ATP) provides painless and most often safe relief of paroxysmal ventricular tachycardia (VT) in patients with implantable cardioverter-defibrillators (ICDs). The introduction of ATP therapy technology in ICDs in 1987 [2] was a significant step in the treatment of patients with VT. Currently, ATP is included in all international recommendations for ICD programming. However, with the accumulation of experience, shortcomings of ATP therapy have been revealed, and the efficiency of ATP algorithms in arresting rapid VT with a cycle length (CL) < 300 ms, proposed by the 2019 Consensus [3], is only 50%, and acceleration of VT can occur in 10% of cases receiving ATP therapy [4, 5]. The efficiency of ATP may decrease to an even greater extent in patients with multiple VT morphologies, which is more often observed in patients with structural pathology (after myocardial infarction) with a complex arrhythmogenic substrate. When ATP therapy is ineffective, the ICD uses maximum power discharge to arrest the persistent paroxysm of VT. Frequent discharges of ICD result in reduced quality of life [6] and increased mortality [7] in patients with ICDs. To eliminate the refractoriness of VT, in addition to the ICD algorithms recommended in the 2019 Consensus, antiarrhythmic therapy can increase (increase in drug doses and combination of antiarrhythmic drugs), the use of VT source ablation and individualized ATP programming, including that based on data obtained in performing intracardiac electrophysiological study (EPS) during endocardial catheter ablation (CA) of VT.

An ideal ATP algorithm should include automatic and customizable ATP for each VT in real time, taking into account the heart rate (HR), VT QRS complex morphology, and response to the previous series of ineffective ATP pacing. Such an algorithm can be created using artificial intelligence and implemented in the ATP ICD therapy program, which can be a further step in the improvement of ICD technology.

Case description

- Anamnesis: Patient (62 years old), diagnosed with postinfarction coronary heart disease (2015, non-Q-MI), cardiosclerosis. Condition after stenting of the circumflex branch of left coronary artery (2015). AV blockade 3 degree (since 2017). Implantation of pacemaker (2017) H1. (NYHA1). Arterial hypertension 2 degree, risk 4. Dyslipidemia.
- At the time of non-Q-AMI in 2015, the patient underwent stenting of the circumflex branch of the left coronary artery in 2015, with the achievement of complete revascularization. During 2015–2017, the patient did not have complaints during the intake of the recommended adequate therapy.
- In 2017, the patient developed a transient grade 3 AV block; as a result, a two-chamber electric cardiac pacemaker (ECP) was implanted, and the necessary pharmacotherapy was continued for 2 years with high adherence.
- Therapy (2017–June 2021): aspirin 75 mg/day, metoprolol 50 mg/day, ramipril 10 mg/day, and rosuvastatin 20 mg/day. During the unscheduled programming of the ECP (June 2021), sustained monomorphic VT was detected (HR, 188 beats per minute [bpm]; duration 8 min, stopped spontaneously). The patient requested unscheduled programming for this episode of palpitations, which was accompanied by a presyncope state. Coronary angiography (June 2021) revealed that the stent was passable. Hemodynamically insignificant stenoses of the coronary arteries were noted (up to 20%). ECHO-CG (2021) showed an end-diastolic dimension of 51 mm, end-systolic dimension of 34 mm, and left ventricular ejection fraction (V) of 59%. There was regurgitation on the mitral and tricuspid valves of 1 degree. Because of a device-detected (ECP) paroxysm of sustained VT, the patient underwent ECP replacement with an ICD (07.2021; Evera DR). When programming the ICD, the standard ICD settings recommended by the 2019 Consensus were used.

Therapy after icd implantation

Treatment. After ICD implantation, the dose of metoprolol was increased to 100 mg/day (amiodarone was not prescribed because this paroxysm was the only detected paroxysm of VT). The rest of the therapy was unchanged (aspirin 75 mg/day, ramipril 10 mg/day, and rosuvastatin 20 mg/day).

During the period from July 2021 to June 2022, the patient did not notice any cardiac arrhythmias, and no paroxysms of sustained VT were registered during the control programming in the course of pharmacotherapy (every 3 months). However, from June 2022, the patient began to notice sustained episodes of palpitations (up to several tens of minutes) without presyncopal and syncopal conditions, which were not detected on repeated ECG and 24-h ECG monitoring at the primary healthcare facility, until the patient was admitted to the district hospital with a stable paroxysm of monomorphic VT with HR of 155 bpm (total duration > 30 h). Intravenous administration of amiodarone did not lead to the relief of VT. As a result, procainamide was administered intravenously, which caused VT relief.

ATP therapy for this episode of VT was not initiated by the ICD because the established lower VT detection interval (in accordance with the 2019 Consensus guidelines) was set to 20 bpm less than the previously verified (2021) episode of sustained monomorphic VT (SM-VT), i.e. 167 bpm (which turned out to be higher than HR during sustained VT paroxysm, i.e., up to 155 bpm). According to the patient, until admission to the district hospital, he experienced weekly episodes of palpitations with an HR of 145–160 bpm. Coronary angiography performed at the primary healthcare facility (August 2022) did not differ from that previously performed in 2021 (the stent was passable, and hemodynamically insignificant stenoses of the coronary arteries were noted up to 20%).

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For further treatment, the patient was transferred to a level 4 center of medical care (State Republican Research and Practical Center "Cardiology").

Control programming of ICD Control (September 2022): from July to August 2022, ICDs were detected:

- One episode of sustained monomorphic VT (SM-VT) = 166 bpm (duration, 1 h 3 min; VT monitor mode without ATP therapy/no ICD discharge).
- One episode of SM-VT = 166 bpm (31 h 5.5 min; VT monitor mode without ATP therapy/no ICD discharge).
- One episode of sustained SM-VT with HR of 182–188 bpm; ATP therapy SM-VT with three attempts of ATP therapy without effect. After that, VT paroxysm was stopped by an ICD discharge (in accordance with the programmed algorithm).

The number of episodes of VT with an HR < 150 bpm in the last 3 months was not known because the lower detection threshold for VT in the monitor mode was set to > 150 bpm. Such recurrent episodes of slow VT occurred because the patient (according to him) noted periodic episodes of palpitations with a frequency of 140–145 bpm with preserved hemodynamics. Moreover, the presence of reciprocal or supra-VT was ruled out because of the presence of degree 3 AV blockade (since 2017). Paroxysms of atrial fibrillation and atrial flutter were also absent in the device memory.

Analysis of atp fragments for treatment of the episode of sustainable vt with hr of 182–188 BPM

The results of the analysis of fragments of ATP therapy demonstrated effective imposition of ATP pacing from the distal pole of the defibrillating electrode, with post-pacing interval at the time of ATP termination > VT cycle (but < 2 VT intervals), which indicated the entry of the ATP pacing sequence into the VT cycle (VT entrainment), but the inability of ATP therapy to arrest the paroxysm because of the inability to cause a bidirectional block in both directions in the vulnerable isthmus of VT. Thus, the ATP pacing cycle used was too long to achieve a critically short and effective refractory period (ERP) in the VT reentry cycle.

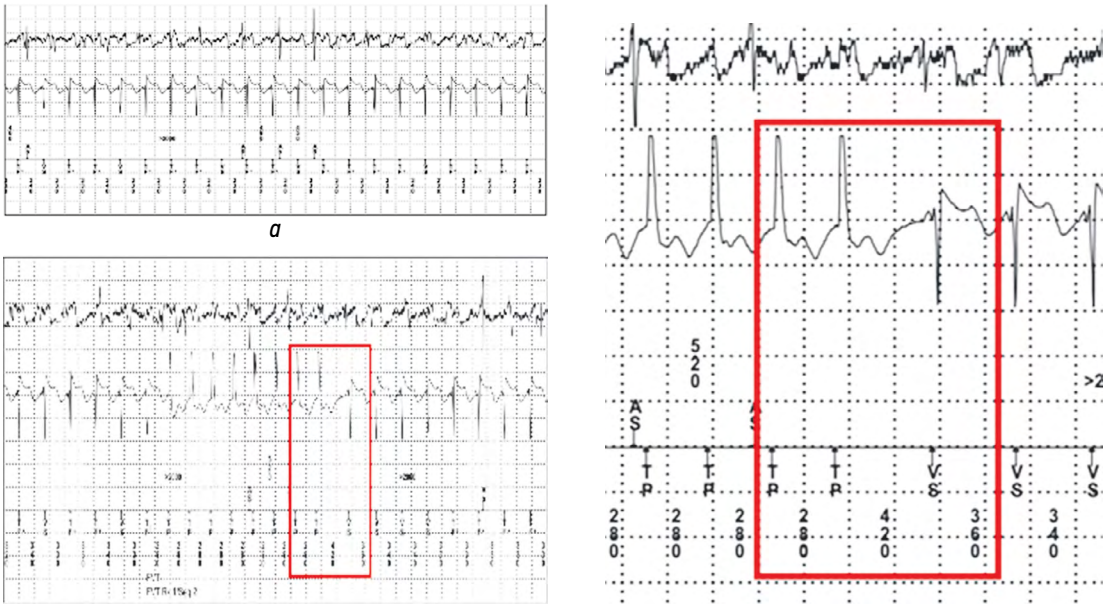


Fig. 1. ICD detects VT with a cycle of 330 ms (*a*), delivers a series of ATP pacing (*b*), whereas the analysis of the ICD endogram indicates effective pacing, with post-pacing interval of 420 ms. ATP has entered a VT cycle which is at a distance of (420–330)/2 = 45 ms from the ICD stimulation electrode. However, VT persists at the same rate

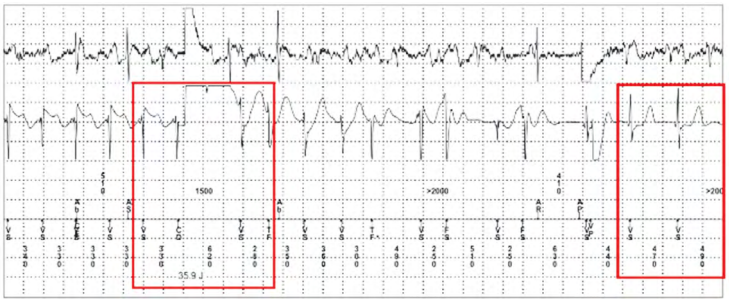


Fig. 2. Owing to the lack of effect of ATP pacing, the ICD delivers a discharge and stops VT

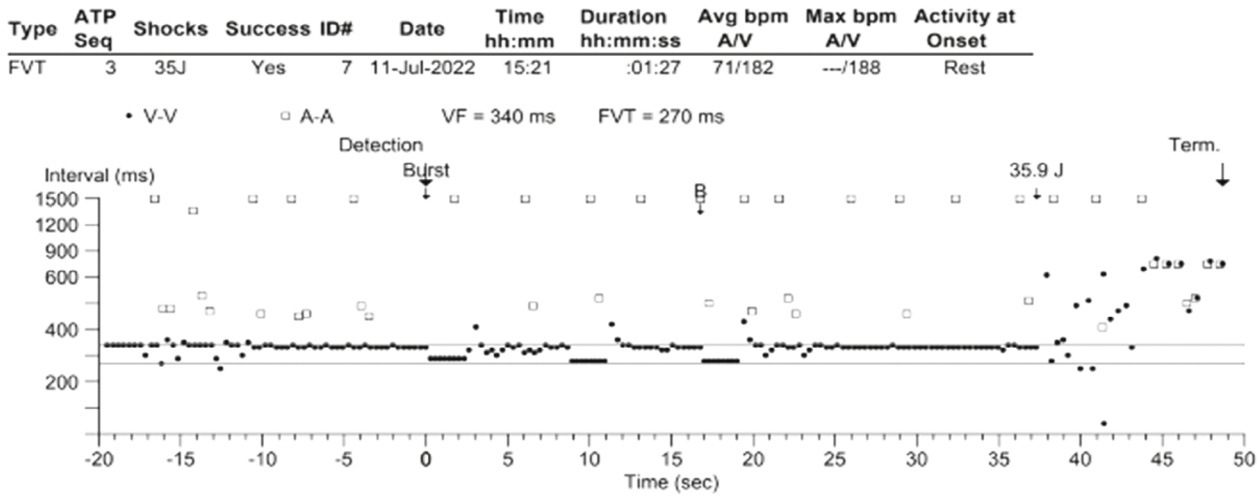


Fig. 3. Summary of the detected and arrested VT episodes. The total duration from the onset of the paroxysm to its arrest was 1 min 27 s. The episode of SM-VT with HR of 182–188 bpm was detected by ICD. To stop the ICD-detected VT, three attempts were made to arrest VT using ATP, starting from a cycle of 88% of the detected VT cycle. Thus, for the VT cycle of 330 ms, the first sequence of ATP Burst-1 is plotted with a cycle of 330 × 0.88 = 290 ms. The imposition was effective, and there were no signs of loss of capture. ATP "entered a VT cycle" but did not stop VT and was not effective. As VT persists, the ICD delivers the next series of cycles 10 ms shorter, i.e. 280 ms and then 270 ms. The duration of the post-stimulation interval (return cycle 1 of VT) ranged from 410 to 420 ms, which indicated the effective imposition of ATP pacing and the absence of loss of capture. However, this cycle of ATP pacing was too long to induce VT arrest (by creating a blockade in both directions of the VT reentry chain). Owing to the lack of VT arrest, the ICD delivered a discharge and stopped VT

Revealing the cause: analysis of ATP therapy fragments in device memory

A fragment of the programming protocol with VT detection, ATP therapy, and subsequent cardioversion is presented.

Owing to the inefficiency of ATP therapy and antiarrhythmic therapy (metoprolol + amiodarone), the patient underwent EEPS, arrhythmia substrate mapping, and ablation of the sources of detected VT.

EEPS results

- The patient underwent EEPS, using the EPS of the AXIOM Sensis XP system. From two different points of the right ventricle, using a quadripolar electrode installed in the right ventricle (RV), and a multi-programable Micropace stimulator, frequent and programable (with two extra pacings) stimulation was performed (including against the adrenaline infusion). However, inducing VT by pacing from the RV was not possible.
- Given the repeated episodes of sustained monomorphic VT with a suspected source in the left ventricle (LV), left ventricular substrate mapping was performed. In the region of the high sections of the anterior–lateral and lateral walls of the LV, a zone of low amplitude and fractionated signals (a zone of non-transmural scar) was revealed, along the edge of which early- and mid-diastolic potentials were also detected in sinus rhythm (at a distance of 1.0–1.5 cm from the annulus of the mitral valve (MV). When pacing mapping from this zone of the LV, the stimulated QRS complex matched 90%–95% with the morphology of the previously detected VT (during paroxysm at the outpatient stage). With programmed pacing from this zone against the intravenous infusion of adrenaline, paroxysmal stable VT of two different morphologies was reproducibly induced in the patient with a high percentage coincidence of induced VT with QRS of clinical VT (coincidence percentage of VT No.1 close to 100%). The HR of the two induced sustained monomorphic VT (SM-VT) was 155–165 bpm, which was accompanied by intact hemodynamics (blood pressure = 110/60 mm Hg).

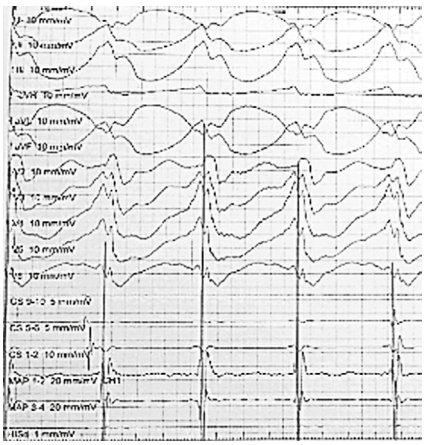
In addition, with programmed stimulation from the LV against adrenaline infusion, two slower non-sustained VTs (145 and 155 bpm; lasting 8–15 s) were induced, which differed in morphology from VT No. 1 and VT No. 2 and stopped spontaneously.

Given the preserved hemodynamics, in addition to substrate mapping in sinus rhythm, activation mapping of both SM-VT was performed using the Carto 3 system. The sources of "exit" of the two indicated VTs (zones of the earliest activation) were at a distance of 1.5 cm from each other and coincided with the extended zone of low amplitude and fractionated potentials in sinus rhythm. In this area, extended ablation was performed (scar homogenization with a power of 30 W and ablation time of 25 min) until the elimination of diastolic potentials. The affected area was connected to the MV ring by an additional ablation line. According to the ablation results, non-inducibility of both SM-VT was achieved (with frequent and programmed [up to two extra pacings] stimulation from the RV and LV, including

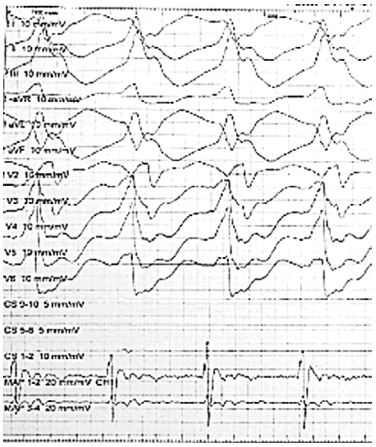
against adrenaline infusion. Thus, a positive clinical effect was achieved.

The presence of SM-VT of multiple morphologies increases the potential risk of recurrent VT after successful ablation compared with VT of a single morphology. Therefore, immediately before performing ablation during intracardiac EEPS, the efficiency of future antitachycardiac ATP protocols was tested in the X-ray operating room with stimulation from a quadripolar catheter placed in the area of the defibrillating ICD electrode. This aimed to establish the cause of the inefficiency of the previously used ATP therapy of ICD (before ablation) and test alternative ATP protocols (for customized ICD programming after ablation).

As a result of ATP simulation of ICD protocols in an X-ray operating room, typical ATP therapy using a series of burst

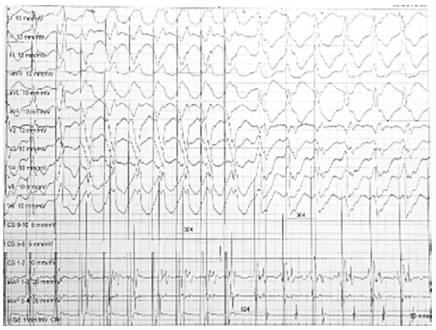


VT No. 1 (basic, clinical); heart rate = 164 bpm; CL = 360–365 ms.

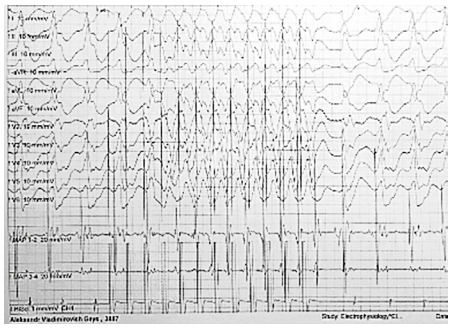


VT No. 2 (sustained monomorphic, induced on EEPS); heart rate = 160 bpm; CL = 370–375 ms

Fig. 4. SM-VT induced during EEPS of two main morphologies



a



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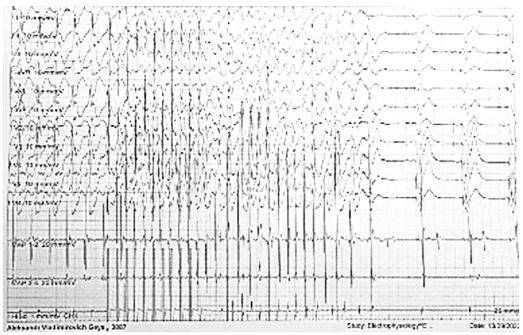
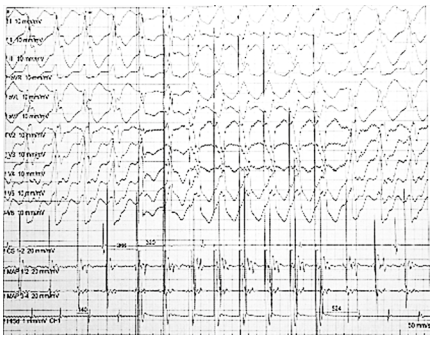


c



d

Fig. 5. *a* — Typical burst pacing from the right ventricular (RV) lead (88% of the SM-VT cycle). After ATP termination, VT continues with the same cycle of 365 ms. *b* — Typical burst pacing from the RV lead (83% of the SM-VT cycle). VT changed slightly the morphology and continues with the same cycle of 365 ms. *c* — "Aggressive" antitachycardic burst pacing from the RV lead (approximately 55% of the SM-VT cycle of 200 ms) with no effect. VT was maintained with the same cycle. *d* — "Aggressive" antitachycardiac burst pacing from the RV lead with a very short interval on the verge of an effective ventricular refractory period (approximately 52% of the SM-VT cycle of 190 ms). At the end of ATP stimulation, VT accelerates to 280–290 bpm and transforms into polymorphic VT (short fragment), with spontaneous arrest

stimulations, according to the recommendations of the 2019 Consensus, was deemed ineffective (Fig. 5).

The analysis of the results of intraoperative ATP with ultra-frequent stimulation demonstrated the following:

1. The ERP of the ventricles in sinus rhythm was 210 ms.
2. The ERP of the ventricles against long-term VT was < 190 ms.
3. The ERP of the ventricles with long-term VT was much shorter than the cycle of previously established antitachycardic ICD pacing in episodes of ineffective ATP at the outpatient stage (shortest pacing interval of 270 ms).

This fact was probably the reason for the inefficiency of ATP in this patient at the outpatient stage, which required changing the ATP settings for ICD therapy, which differ from those recommended by the 2019 Consensus.

Efficiency of ATP therapy during 3 months after ablation

During the follow-up period of 3 months, the patient had 2 episodes of VT with a heart rate of 168 bpm, which required the use of ATP stimulation. In both cases, Burst-pacing with a cycle length of 88% of the VT cycle (recommended by the 2019 Consensus) was ineffective. Both paroxysms of VT were effectively stopped by ATP pacing with a shorter coupling interval, namely paroxysm 1 from the series 1 with a coupling interval of 81% of the VT cycle, and the paroxysm 2 from the sequence 2 (30 ms shorter than 81% of the VT cycle), which confirmed the greater efficacy of a short pacing interval for slow VT in this patient, revealed during endocardial electrophysiological study. There were no ICD shocks during the follow-up period.

DISCUSSION

The setting protocols for ATP therapy for ICD have not changed significantly over the past 20 years, except for one important addition, that is, the lengthening of the VT detection time. Studies have shown that lengthening the time of VT detection from 18 to 30 of 40 VT intervals before applying ATP pacing or an ICD discharge can reduce reliably and significantly the number of ICD discharges [9]. This effect is achieved mainly by preventing unreasonable therapy of non-sustained VT. After obtaining similar results in several studies, a long VT detection interval has now become the standard for programming ATP therapy for ICD [10], although this prolongs the overall duration of VT paroxysm from its onset to arrest.

The experience of the arrhythmology department in the treatment of patients with paroxysmal VT with structural pathologies of the heart indicates that the main etiological cause of SM-VT directed for ablation in the Republican Scientific and Practical Center "Cardiology" was coronary heart disease (77.1%; 54 of 70 patients), and 62.9% of them had a history of myocardial infarction. In 60.0% of the cases, the posterobasal and posterolateral left ventricular wall was the VT substrate; and in 9 (12.9%) cases, multiple localizations of VT substrates were noted. Such an uneven distribution of localizations can be due to both the "survivor error" (high probability of being stopped for SM-VT from the posterolateral wall of the LV) and the anatomical or electrophysiological aspects of the myocardium of this zone, predisposing to maintaining SM-VT with preserved hemodynamics.

According to the ICD programming data, 104 VT episodes not stopped by ATP were detected in the monitored patients, which was accompanied by a total of 144 ICD discharges. Multiple localizations of VT substrates were registered in 30% of these cases. Patients were programmed according to the standard recommendations in the 2019 Consensus. Changes in programming parameters were made during the follow-up based on previous ineffective ATP therapy and the endocardial EPS (EEPS) protocol during the CA VT procedure.

The 2019 Consensus guidelines for optimal programming of ICDs recommend the use of ATP for the treatment of VT up to a high HR. The number of pulses in series and the number of series were not clearly defined. Ramp ATP and low-power cardioversion are not recommended. The nominal recommendation of the 2019 Consensus for all ICD manufacturers is "conservative" initial burst ATP therapy for monomorphic VT paroxysm after a long interval of VT detection (typically 30 of 40 ICD-detected VT complexes). The conservative start of ATP therapy implies a stimulation cycle length of 85–88% in the first series of burst stimulation (of the 8 stimulating complexes). If the first ATP sequence is ineffective for rapid VT (range, > 200–220 bpm), automatic cardioversion (up to five high-power discharges) is usually recommended.

For slow and medium HR VTs (up to 188 bpm), several sequences of burst ATP therapy can be performed (usually with 10-ms increments, i.e. each subsequent series of pacing shortens the pacing cycle by 10 ms). The number of pacing series is not specified in the 2019 Consensus guidelines; however, in practice, the number of sequences rarely exceeds 3–4 pacing series, after which the ICD is usually programmed to deliver cardioversion (usually with a maximum power discharge). An analysis of the CareLink ICD database (> 100,000 patients) demonstrated that only approximately 50% of patients with ICD had ≥3 ATP sequences programmed [11].

Frequent discharges of ICDs result in reduced quality of life [6] and increased mortality [7] in patients with ICDs. In routine clinical practice, many physicians use 1–2 series of ATP stimulation, after which cardioversion is programmed, despite convincing data confirming that increasing the number of stimulation series with a gradual shortening of the ATP stimulation cycle increases the efficiency of ATP therapy and reduces the number ICD discharges.

For example, the hypothesis that an increase in the number of series of ATP pacing leads to an increase in

the efficiency of ATP was, in particular, tested in the Shock-Less study (4112 patients). This study compared the total number of ICD discharges between two groups of patients, (1) nominal ICD programming parameters such as programming on ⩽ 3 ATP series (VT zone) and ⩽1 ATP sequence (in rapid VT zone) (nominal group), and (2) patients programmed to receive additional ATP sequences in VT (> 3) or rapid VT (> 1) zones [12]. In this study, 4359 VT episodes occurred in 591 patients over a mean follow-up of 19.6 ± 10.7 months.

Compared with the nominal group in the Shock-Less study, patients with additional ATP programming had a 39% reduction in the number of ICD discharges caused by detected VT episodes (0.46 episodes per patient-year vs. 0.28 episodes per patient-year; occurrence rate ratio [RR] 0.61, $p < 0.001$). Moreover, the number of ICD discharges for fast VT reduced by 44% (0.83 episodes per patient-year vs. 0.47 episodes per patient-year; RR 0.56; $p < 0.001$). A decrease in the number of ICD discharges was noted both in the groups with primary prevention of sudden cardiac death (SCD) (IRR 0.68; 95% confidence interval (CI) 0.51–0.90; $p = 0.007$) and secondary prevention of SCD (IRR 0.51; 95 % CI 0.35–0.72, $p < 0.001$). Thus, programming more than the nominal number of ATP sequences in VT zones (and even rapid VT) is associated with a lower rate of ICD discharges.

The key efficacy parameter is pacing with an ATP cycle duration short enough to achieve block in both directions of the VT reentry wave (or delivering a single extra pacing during the vulnerable period of VT reentry), but not the number of ATP series per se.

Thus, if ATP stimulation with a sufficiently short cycle is immediately chosen, it will stop the VT paroxysm from the first exposure. An increase in the number of ineffective ATP series leads to the prolongation of the VT paroxysm, and this, paradoxically, reduces ATP efficiency.

Several clinical studies have shown that even prolonging the detection time from 18 to 30/40 VT complexes leads to a decrease in the efficiency of ATP therapy, especially for rapid VT. Specifically, in the ADVANCE 3 study, a reduction in the efficiency of ATP therapy by up to 50% for rapid VT was noted [4].

Probably, prolonged paroxysm leads to the development of electrical myocardial remodeling, which is expressed in a shortening of the ERP of the myocardium and vulnerable VT isthmus, which in turn reduces the efficiency of slow, conservative series of ATP stimulation. The longer the time to effective therapy (a short ATP cycle is sufficient), the lower the efficiency of ATP and the higher the frequency of ICD discharges.

Thus, it is necessary to maintain a balance with a sufficiently long initial detection of VT (to prevent unreasonable treatment of non-sustained VT that can stop independently) and the application of effective ATP with a sufficiently short pacing cycle (stopping VT by achieving blockade in vulnerable VT isthmus). However, the ATP pacing cycle should not be excessively short to avoid warming up of VT, its acceleration, and/or transformation into polymorphic VT or ventricular fibrillation.

The presented clinical case reflects the shortcomings of the standardized approach to ICD programming recommended by the 2019 ICD programming consensus. A long detection interval in combination with a "conservative" start of ATP stimulation (88% of the length of the VT cycle), a slow sequential shortening of the ATP stimulation cycle (minus 10 ms) with a limited number of ATP stimulation sequences (4 stimulation series) does not allow stopping slow VTs that have a short ERP in the vulnerable isthmus of the reentry of VT, which does not allow for bidirectional blockade in both directions of the VT cycle (Fig. 6).

In the demonstrated clinical case, the cycle of clinical and EPS-induced VT was 365 ms. When applying the 2019 Consensus recommendations after a long VT detection interval (30 of 40 complexes, which corresponds to a detection duration of ≈ 11 sec), after the inefficiency of series 1 of ATP (88% of the SM-VT cycle, i.e. 321 ms), the device will gradually shorten the stimulation cycle (by 10 ms).

Thus, if additional three bursts of burst pacing are programmed, then the ICD will sequentially reach the length of the ATP pacing cycle of 321–311–301–291 ms, after which, with continued VT, it will deliver an ICD discharge. The total time to the restoration of sinus rhythm is approximately 46.7 s (≈ 11 s for detection, 27.7 s for delivering a series of four ineffective burst ATP pacing, and 8 s for charging the ICD before delivering a discharge). In this case, as follows from the above case, the length of the cycle of the ineffective ATP pacing 4 of ICD of 290 ms was much longer than the pacing cycle during EEPS that arrested VT during EEPS (190 ms). The paroxysm duration before an effective impact (ICD discharge after 46.7 s) was sufficient to cause electrical remodeling and reduce the efficiency of ATP pacing in a patient.

Possible methods to overcome refractoriness to ATP stimulation:

1. Use antiarrhythmic therapy that increases the length of the action potential and ERP of the myocardium in vulnerable VT isthmus (antiarrhythmic drugs of classes 1A, 1C, and III).

2. Use a more "aggressive" starting percentage of burst pacing (e.g., with 81% of the VT cycle length).

3. Use a larger number of sequences with a slow decrement (step of 10 ms), which may lead to a several-fold increase in the risk of VT acceleration and its transformation into ventricular fibrillation with an increase in the number of ATP series of > 6 [13].

4. Use a faster decrement between successive series of burst pacing (decrement step of 30 ms instead of that nominal of minus 10 ms recommended by the Consensus), at least for patients with slow and medium-fast VT with a history of episodes of ineffective ATP pacing, accompanied by potentially preventable ICD discharges.

5. Use ATP sequences such as burst plus or ramp plus, where, in addition to a series of 6–8 pacing of the same

a *b*

Pic. 6. *a* — ATP pacing with an insufficiently short pacing cycle produces blockade in one direction but does not achieve blockade in the antegrade propagating reentry wave. S1 stimulation "enters the VT cycle" (VT entrainment), but does not stop VT. *b* — S1 pacing "enters the VT cycle" and given the short interval, achieves blockade of impulse propagation in both directions (stops VT)

length, 1–2 extra pacings with a shorter coupling interval is added. Unfortunately, these algorithms are not available from all manufacturers.

6. Use "intelligent" ATP stimulation algorithms that automatically adjust to the parameters of the previous ineffective series of ATP stimulation (shortening the stimulation cycle, adding or decreasing the number of pacing in the series, adding 1 or 2 extra pacings with automatic adjustment of the changing auto number and length of the extra pacing cycle, etc.).

To prevent repeated ICD discharges in the patient described above after effective VT ablation of two morphologies, we made the following corrections to the standard settings of ATP ICD therapy (in case of VT recurrence):

1. As the initial therapy for VT, a "conservative" start of ATP therapy was retained (88% of the length of the VT cycle to reduce the risk of accelerated VT/transformation into ventricular fibrillation):

- Initial series of ATP pacing with a starting cycle of 88% (only two sequences with 10-ms steps were retained), which may be sufficient in the case of recurrent VT after the modification of the arrhythmogenic substrate because of ablation.

The number of pulses in the series was reduced to six pacings because the post-pacing interval of 410–420 ms indicates that four ATP cycles of a given length are sufficient to reach the pacing wave to the VT reentry circle; and + 2 pacings are left for other VT morphologies.

2. If the step 1 of the ATP pacing algorithm is ineffective, the step 2 of the ATP therapy algorithm includes the following:

- A series of stimulations with a starting cycle of 81% of the length of the VT cycle (6 pacing in each sequence).
- Decrement step–minus 30 ms, retained + 3 sequences in 30-ms steps (which for VT with an initial frequency of 164 bpm enables achieving quickly the length of the stimulation cycle of 206 ms (56% of the length of the VT cycle) after step 3 of the decrement and to shorten to the maximum the time to achieve the ERP (i.e., moment of potential efficiency of ATP pacing, approaching the ERP of the ventricles of 200–210 ms even against adrenaline infusion).
- The total duration from the onset of VT paroxysm to its relief by series 4 of ATP with a decrement of 30 ms will be 30.7 s (instead of 46.7 s), which is 34.3% shorter than the initial duration of the ineffective series of ATP, which ended with an ICD discharge.
- A faster shortening of the pacing cycle to an effective one will prevent rapid electrical remodeling ("warming up") of VT.

3. If step 2 is ineffective, the algorithm proceeds to step 3, that is, the programmed "conservative" Ramp plus:

- A series of stimulations with a starting cycle of 88% (instead of the nominal 75%) of the length of the VT cycle (six pacing in each sequence), plus
- Two nominal extra pacings with a length of 69% and 66% of the length of the VT cycle.

4. If steps 1–3 are ineffective, cardioversion with maximum energy of discharge is performed (steps 4–6).

The general opinion of the authors of the recommendations on ICD programming and analysis of the literature suggests that the risk of VT transformation is higher with the use of

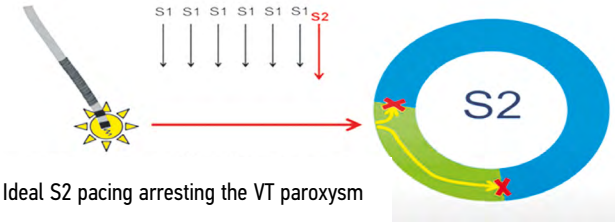


Fig. 7. After entering the reentry cycle, the application of the S2 pacing with a sufficiently short coupling interval "closes" the impulse propagation in both directions (due to the entry of vulnerable VT isthmus into the tissue refractoriness period)

more aggressive ramp and ramp plus sequences of ATP therapy (with a short initial coupling interval of 75%)[14] and [15]. Therefore, in the 2019 Consensus, ATP therapy should be started with a "conservative" burst (88%).

The concept of extra pacing (S2 and S3 [if necessary] assumes that the initial series of impulses with a fixed duration of the stimulation cycle [S1 pacing of 4–8 impulses] enter the VT cycle [VT entrainment; therefore, there is no need for an excessively short coupling interval for S1 (which, if excessively shortened, will more possibly accelerate VT).

VT relief was achieved by a single (or double) extra pacing S2, applied with a short enough coupling interval to "close" the electrically excitable vulnerable VT isthmus on the verge of ERP "gateway" or VT isthmus. Preliminary analysis performed on a simulator based on the database of remote ICD monitoring indicates an increase in the efficiency of this approach by 15%–20% compared with the standard burst ATP stimulation [16].

CONCLUSIONS

1. The clinical case presented clearly demonstrates that the arrhythmogenic substrate after myocardial infarction changes over a long period of time, and it may take several years for its "maturation". The arrhythmogenic substrate can continue to evolve after the identified episode 1 of VT without new stenoses of large coronary arteries and without new episodes of acute coronary syndrome, as well as generate several different VT morphologies from the same scar (with different heart rates) and influence on hemodynamics.

2. In case of insufficient efficiency of ATP pacing and/or repeated ICD shocks caused by the inefficiency of ATP aimed against monomorphic VT, it is advisable to use alternative pacing algorithms (in addition to the standard Burst sequences recommended by the 2019 Consensus on ICD programming).

3. It is reasonable to test possible ATP algorithms during ablation of monomorphic VT (when performing endocardial electrophysiological study), for example, when performing preventive ablation of VT before implantation of ICD as first line therapy for recurrent sustained monomorphic VT.

4. Newly developed ICDs and ATP therapy algorithms are in dire need of the introduction of artificial intelligence elements, especially for patients with multiple VT morphologies.

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