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АНАЛИЗ КЛИНИКО-ПАТОГЕНЕТИЧЕСКИХ ВЗАИМООТНОШЕНИЙ ДИНАМИКИ ИЗМЕНЕНИЯ МАССЫ ТЕЛА И ФИБРИЛЛЯЦИИ ПРЕДСЕРДИЙ У ПАЦИЕНТОВ С ПЕРВИЧНЫМ ОЖИРЕНИЕМ

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Clinical and Pathogenetic Assessment of Relationships Between the Dynamics of Body Weight Changes and Atrial Fibrillation in Patients with Primary Obesity

Резюме

Цель исследования. Оценить влияние динамики массы тела на клиническое течение фибрилляции предсердий у пациентов, страдающих ожирением. **Материал и методы.** В исследование был включен 101 пациент с пароксизмальной либо персистирующей фибрилляцией предсердий, страдающий первичным ожирением. Дизайн исследования: ретроспективное, одноцентровое, сравнительное исследование. Ретроспективно в зависимости от динамики массы тела пациенты были разделены на 3 группы: увеличившие на ≥3% массу тела (группа 1, n=40), сохранившие исходную массу тела ±2,9% (группа 2, n=29), снизившие на ≥3% исходную массу тела (группа 3, n=32). Контрольные осмотры врачом проводились не реже 1 раза в 6 месяцев на протяжении не менее 36 месяцев. Изменение формы фибрилляции предсердий регистрировалось на основании клинической картины заболевания и данных холтеровского мониторирования электрокардиограммы в течение 7 дней. Группы были сопоставимы по полу (p=0,9267), возрасту (p=0,3841), росту (p=0,8900), форме заболевания (пароксизмальная фибрилляция предсердий/ персистирующая фибрилляция предсердий) (p=0,8826), выраженности симптомов фибрилляции предсердий по классификации Европейской ассоциации сердечного ритма (p=0,8687) и цифрам систолического артериального давления на начало исследования (p=0,4500). **Результаты.** При заключительном контрольном осмотре масса тела пациентов 1 группы увеличилась в среднем на 11,4 [9,3; 13,1] кг (p <0,001*), тогда как пациенты 3 группы продемонстрировали снижение массы тела в среднем на -6,2 [-8,4; -5,3] кг (p <0,001*). Снижение массы тела пациентов 2 группы было незначительным (p=0,5377) и составило -0,1 [-2,0; 1,3] кг. Прогрессирование заболевания от пароксизмальной формы к персистирующей наблюдалось у 15 (37%) пациентов 1 группы, у 9 (31%) пациентов 2 группы и у 2 (6%) пациентов 3 группы (p=0,0079*). Регресс аритмии от персистирующей формы к пароксизмальной в 1 группе не зарегистрирован (0%), во 2 группе обратное развитие заболевания отмечено у 1 пациента (3%) и в 3 группе — у 6 пациентов (19%) (p=0,0053*). Самопроизвольного восстановления синусо-

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вого ритма у пациентов 1 группы не наблюдалось, во 2 группе оно было отмечено у двух (7%), а в 3 группе — у 7 (22%) пациентов (p=0,0047*). Клиническая эффективность катетерной абляции оценивалась после окончания 3-месячного слепого периода. Потребность в проведении интервенционных процедур с целью восстановления синусового ритма и их кратность при сравнении групп существенно не отличалась. Однако при попарном сравнении, статистически значимой была разница между 1 и 3 группами участников (p=0,0079* и p=0,0374* соответственно). **Заключение.** Проведенное исследование демонстрирует взаимосвязь между динамикой массы тела и клиническим течением фибрилляции предсердий. Установлено, что прогрессирование ожирения непосредственно ассоциируется с прогрессированием данного типа аритмии. Напротив, снижение массы тела позволяет уменьшить риск усугубления тяжести заболевания, улучшить прогноз и течение фибрилляции предсердий вне зависимости от других значимых факторов риска, повысить эффективность терапии антиаритмическими препаратам и результативность интервенционного лечения.

Ключевые слова: *фибрилляция предсердий, восстановление синусового ритма, ожирение, контроль массы тела, предсердная кардиомиопатия*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

Aims. To evaluate the impact of body weight dynamics on the clinical course of atrial fibrillation in obese patients. **Materials and methods.** The study included 101 primary obese patients with paroxysmal or persistent atrial fibrillation. Study design: a retrospective, single-center, comparative study. Retrospectively according to the he body weight dynamics, patients were divided into 3 groups: those who increased their body weight by ≥3% (Group 1, n=40), maintained their initial body weight by ±2.9% (Group 2, n=29), and reduced their initial body weight by ≥3% (Group 3, n=32). Follow-up examinations by a doctor were carried out at least once every 6 months for minimum 36 months. Change in AF type was determined by disease patterns and 7-day Holter monitoring results. The groups were comparable in gender (p=0,9267), age (p=0,3841), height (p=0,8900), and disease form (Paroxysmal atrial fibrillation /Persistent atrial fibrillation) (p=0,8826), the severity of symptoms on the European Heart Rhythm Association score of atrial fibrillations (p=0,8687) and systolic blood pressure at the beginning of the study (p=0,4500). **Results.** At the final control examination, the body weight of patients in Group 1 increased by an average of 11,4 [9,3; 13,1] kg (p <0,001*), while weight loss in Group 3 averaged -6,2 [-8,4; -5,3] kg (p <0,001*). The decrease in body weight of Group 2 patients was insignificant (p=0,5377) and amounted to -0,1 [-2,0; 1,3] kg. The progression of the disease from paroxysmal to persistent form was observed among 15 (37%) patients in Group 1, 9 (31%) patients — in Group 2, 2 (6%) patients — in Group 3 (p=0,0079*). The regression of arrhythmia from persistent to paroxysmal form was not registered in group 1 (0%), in group 2, the reverse development of the disease was noted in 1 patient (3%) and in group 3 — in 6 patients (19%) (p=0,0053*). There were no free from AF patients in Group 1 at the final follow-up, while 2 (7%) patients were free from AF in Group 2 and 7 (22%) — in Group 3 (p=0,0047*). In patients undergoing ablation, procedural success was determined after a 3-month blind period. The need for interventional procedures to restore the sinus rhythm and their multiplicity when comparing the groups did not differ significantly. However, in a pairwise comparison, the difference between groups 1 and 3 of participants was statistically significant (p=0,0079* and p=0,0374*, respectively). **Conclusion.** This study demonstrates the relationships between the dynamics of body weight and the clinical course of atrial fibrillation. The progression of obesity leads to the progression of the disease. Weight-loss management reverses the type and natural progression of AF, improves the prognosis and the course of disease, regardless of other significant risk factors, increases the anti-arrhythmic therapy effect and the effect of interventional treatment.

Key words: *atrial fibrillation, sinus rhythm recovery, obesity, weight control, atrial cardiomyopathy*

Conflict of interests

The authors declare that this study, its theme, subject and content do not affect competing interests

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BMI — body mass index, SBP — systolic blood pressure, AF — atrial fibrillation, HR — heart rate, ECG — electrocardiogram, AF — atrial fibrillation, BMI — body mass index, EHRA-score — The European Heart Rhythm Association score of atrial fibrillations

Introduction

Atrial fibrillation (AF) is the most common supraventricular arrhythmia in modern clinical practice. Despite the consistent improvement of its diagnosis and management methods, AF significantly contributes to a deterioration of the quality of life, higher rates of disability and mortality of the population. AF is a progressive disease. Most patients develop persistent types of arrhythmia over time, and paroxysmal AF persists for a long time only in 2–3% of patients [1]. Several studies show that the clinical type of AF and the likelihood of disease progression are primarily determined by the presence of concomitant risk factors [2, 3].

Most modern studies on AF are aimed at exploring innovative approaches to the management of this disease and its complications. Along with this, a thorough analysis of risk factors contributing to the progression of AF continues.

Overweight and obesity are observed in 25% of patients with AF [2]. There is a direct correlation between the thickness and volume of epicardial adipose tissue and the risk of developing AF [4, 5]. A number of studies have shown that weight loss in the short term reduces the severity of symptoms in patients with AF [6, 7].

This study seeks to examine the long-term effect of body weight changes on the clinical course of AF in obese patients.

Material and Methods

This study randomly included patients with a body mass index > 30 kg/m^2 who were undergoing treatment for symptomatic paroxysmal or persistent AF at the State Budgetary Healthcare Institution "Diagnostic Center No. 5 of the Moscow City Health Department" from October 2016 to November 2019. Study design: retrospective, single-center, comparative study.

The protocol was approved by the local ethics committee. Written informed consent was obtained from all patients prior to enrollment in the study.

All patients were examined by a cardiologist in an outpatient setting at least once every six months for at least three years (36 months). Every six months during the follow-up visit, all patients were assessed for the severity of AF symptoms; electrocardiogram (ECG) in rest was performed, and 24-hour ECG monitoring was performed for seven days. The severity of AF symptoms was assessed according to the EHRA classification (European Heart Rhythm Association) [8]. The treatment strategy (heart rhythm or heart rate control) was determined by the attending cardiologist. Agents used to control the rhythm included class III antiarrhythmic agents according to the Vaughan — Williams classification in D-modification. Harrison: amiodarone and sotalol. The decision to refer for interventional treatment (transcatheter cryoballon ablation or radiofrequency ablation) was made by the attending physician if the symptoms of the disease persisted while taking medications. The "blind" period after ablation was three months. In the case of radiofrequency or cryoballon ablation, 24-hour ECG monitoring was additionally performed three months after the procedure and every six months thereafter.

The exclusion criteria were: persistent AF, a history of acute myocardial infarction or cardiac surgery over the past 12 months, hemodynamically significant congenital and acquired heart valve defects, impaired left ventricular function with a decrease in ejection fraction < 40%, malignant neoplasms in active phase, autoimmune and systemic inflammatory diseases, severe renal or hepatic failure, patients with diabetes mellitus on insulin therapy.

All patients were interviewed on the importance of body weight control; personalized recommendations for healthy eating and instructions on the need for graduated exercise were given. The group of obese patients who lost weight received non-drug therapy, changed lifestyle through dietary adjustments and increased the volume of physical activity. Individual risk factors were also monitored regularly (hypertension, diabetes mellitus, impaired glucose tolerance, obstructive sleep apnea, smoking and alcohol consumption), and, if necessary, treatment adjustment was carried out to modify risk factors. During the study, such indicators as blood pressure, glycemia, and dyslipidemia were corrected for all participants, and target values were achieved. Metformin was used to manage type 2 diabetes mellitus and impaired glucose tolerance, and if necessary, other oral antihyperglycemic agents were prescribed.

During the initial visit, the physician measured anthropometric parameters using medical scales and a stadiometer. Weighing was carried out without shoes and outerwear, then body mass index was calculated. The body weight of patients was subsequently measured at each follow-up appointment and independently at home using household scales.

According to the American Heart Association (AHA) and the American College of Cardiology (ACC) recommendations, a change in body weight of at least 3% from the baseline was considered significant [9]. Patients were retrospectively included in one of three groups depending on the changes in body weight: those who gained ≥ 3% of their baseline body weight (group 1), those who retained their baseline body weight ±2.9% (group 2), those who lost ≥ 3% of their baseline body weight (group 3).

The primary outcome of the study was a change in the type of AF at the time of the final examination (36 months). The type of AF was assessed based on the patient's complaints and 24-hour ECG monitoring data for seven days. Secondary outcomes included the severity of AF symptoms as measured by the EHRA scale and the need for interventional treatment.

Statistical Analysis

Statistical processing of the results was carried out using Python 3.8. Built-in functions from the Scipy module were used for calculations.

Quantitative parameters were assessed for compliance with normal distribution. To this end, the Shapiro — Wilk test was used.

Normal distribution test showed that data in the study were not normally distributed. Therefore, the calculations were subsequently carried out using nonparametric statistical methods.

Summaries of quantitative parameters were described using the median (Me) and lower and upper quartiles (Q1 — Q3): Me [Q1; Q3]. When comparing several samples of quantitative data with a distribution other than normal, the Kruskal-Wallis test was used. When statistically significant differences between the groups were detected, pairwise comparison of the populations was additionally carried out using the Mann — Whitney U-test.

The Wilcoxon W-test was used to test the differences between the two compared paired (linked "before" and "after") samples.

Results of qualitative characteristics are expressed in absolute numbers with the indication of proportions (%). The comparison of nominal data in independent groups was carried out using the Pearson χ^2 test. When the number of expected observations in any of the cells of the four-field table was less than 5, Fisher's exact test was used to assess the level of significance of the differences.

Differences were considered as statistically significant at $p \leq 0.05$.

Sample size was not pre-calculated.

Results

Demographic Parameters and Baseline Characteristics of Patients Included in the Study

Of 246 patients with paroxysmal or persistent AF who were treated at the State Budgetary Healthcare Institution "Diagnostic Center No. 5 of the Moscow Department of Health" from October 2016 to November 2019, 137 patients had a body mass index of more than 30 kg/m^2. After evaluating the exclusion criteria, 101 patients were included in the study.

When determining changes in body weight, all patients were retrospectively divided into three groups: increased body weight by ≥ 3% (group 1, n = 40), retained the baseline body weight ±2.9% (group 2, n = 29), decreased the baseline body weight by ≥ 3% (group 3, n = 32) (Fig. 1).

Groups were similar by gender (p = 0.9267), age (p = 0.3841), height (p = 0.8900), weight (p = 0.7052), BMI (p = 0.3880), type of disease (paroxysmal AF / persistent AF) (p = 0.8826), severity of symptoms on the EHRA scale (p = 0.8687) and the level of systolic blood pressure (SBP) at the beginning of the study (p = 0.4500), as well as the number of smokers (p = 0.6171), the level of alcohol consumption (p = 0.9682), the presence of arterial hypertension (p = 0.7700), diabetes mellitus (p = 0.9289), impaired glucose tolerance (p = 0.8351) and coronary heart disease (p = 0.8833). A statistically significant difference was recorded only in terms of hyperlipidemia (p = 0.0448 *). There were more patients with this risk factor in group 1 — 23 (58%) than in group 3 — 9 (28%) (p = 0.0127 *). The average number of antihypertensive and antiarrhythmic agents used was comparable at the start of the study (p > 0.05).

Clinical characteristics of patients at the time of enrollment in the study are presented in Table 1.

Body Weight Change

At the beginning of the study, the body weight of patients in groups 1, 2 and 3 was comparable (p = 0.7052); at the final examination, it was statistically significantly different (p < 0.001*), including during pairwise comparison of groups (p < 0.05).

The body weight of the patients of group 1 increased during the study from 98.4 [88.6; 106.8] to 110.5 [97.5; 118.2] kg (p < 0.001 *), in group 3, it decreased from 99.3 [89.3; 105.7] to 90.7 [82.4; 98.2] kg (p < 0.001 *), while patients of group 2 showed an insignificant decrease in body weight from 102.2 [88.3; 108.6] to 99.3 [87.9; 109.6] kg (p = 0.5377).

The parameter of change in body weight was different between all groups (group 1 — an increase of 11.4 [9.3; 13.1] kg, group 2 — a decrease of −0.1 [−2.0; 1.3] kg, group 3 — decrease by −6.2 [−8.4; −5.3] kg) (p < 0.001 *).

Effect of Body Weight Changes on the Progression of AF

Table 2 presents the effect of body weight changes on the progression of AF and the frequency of interventional treatment.

At the time of enrollment in the study, groups 1, 2 and 3 were comparable in terms of the disease form (p = 0.8826). Pairwise comparison of groups also revealed no statistical significance of differences between groups (p > 0.05). At baseline, there were 19 (47%) patients with paroxysmal AF and 21 (53%) patients with persistent AF in group 1, in group 2 (n = 29) — 14 (48%) patients with paroxysmal AF and 15 (52%) patients with persistent AF, in group 3 (n = 32) — 17 (53%) patients with paroxysmal AF and 15 (47%) patients with persistent AF (Fig. 1).

According to the results of the final check-up examination, a difference in the form of the disease was revealed between groups 1, 2 and 3 (p < 0.001 *). Pairwise comparison revealed a difference between groups 1 and 3 (p < 0.001 *) and between groups 2 and 3 (p = 0.0132 *). The difference between groups 1 and 2 was not significant (p = 0.2018).

AF progression from the paroxysmal to the persistent form differed between group 1 (15 (37%) patients), group 2 — 9 (31%) and group 3 — 2 (6%) (p = 0.0079 *). There was a significant difference between groups 1 and 3 (p = 0.0019 *) and groups 2 and 3 (p = 0.0119 *); the difference between groups 1 and 2 was insignificant (p = 0.5778) (Fig. 2 and 3).

The regression of arrhythmia from the persistent to the paroxysmal form also showed a difference between the groups (p = 0.0053 *). In group 1, no disease regression was recorded — 0 (0%), in group 2, there was a regression of AF in 1 patient (3%), in group 3 — in 6 patients (19%). However, the pairwise comparison of groups showed a significant difference only when comparing groups 1 and 3 (p = 0.0058 *).

Parameters such as "No changes in AF form" and "Complete recovery from AF" showed no statistically significant differences between the groups (p = 0.1615 and p = 0.7655, respectively). "Spontaneous restoration of sinus rhythm" (without ablation) differed in the groups (p = 0.0047 *): in group 1, no cases of spontaneous restoration of sinus rhythm were recorded — 0 patients (0%), in group 2 there were 2 cases (7%) and in group 3 — 7 (22%). However, a pairwise comparison of the groups showed a difference only between groups 1 and 3 (p = 0.0023 *).

Therefore, the study showed that obese patients whose body weight increased during the follow-up period (group 1 — 37%) and retained their baseline body weight (group 2 — 31%) have a higher rate of disease progression with the transformation of paroxysmal AF into persistent AF, in comparison with patients whose body weight decreased (group 3) — 6%), despite the adjustment of other significant risk factors (Fig. 2 and 3).

Weight loss was a significant mono- and multifactorial predictor of regression of the disease from the persistent to the paroxysmal form (group 3 — 19%, while group 1 — 0%, group 2 — 3%). A comprehensive analysis of obese patients whose body weight decreased (group 3), with concomitant modification of other risk factors showed a high probability of spontaneous restoration of sinus rhythm (group 3 — 22%, group 1 — 0%, group 2 — 7%) (Fig. 2 and 3).

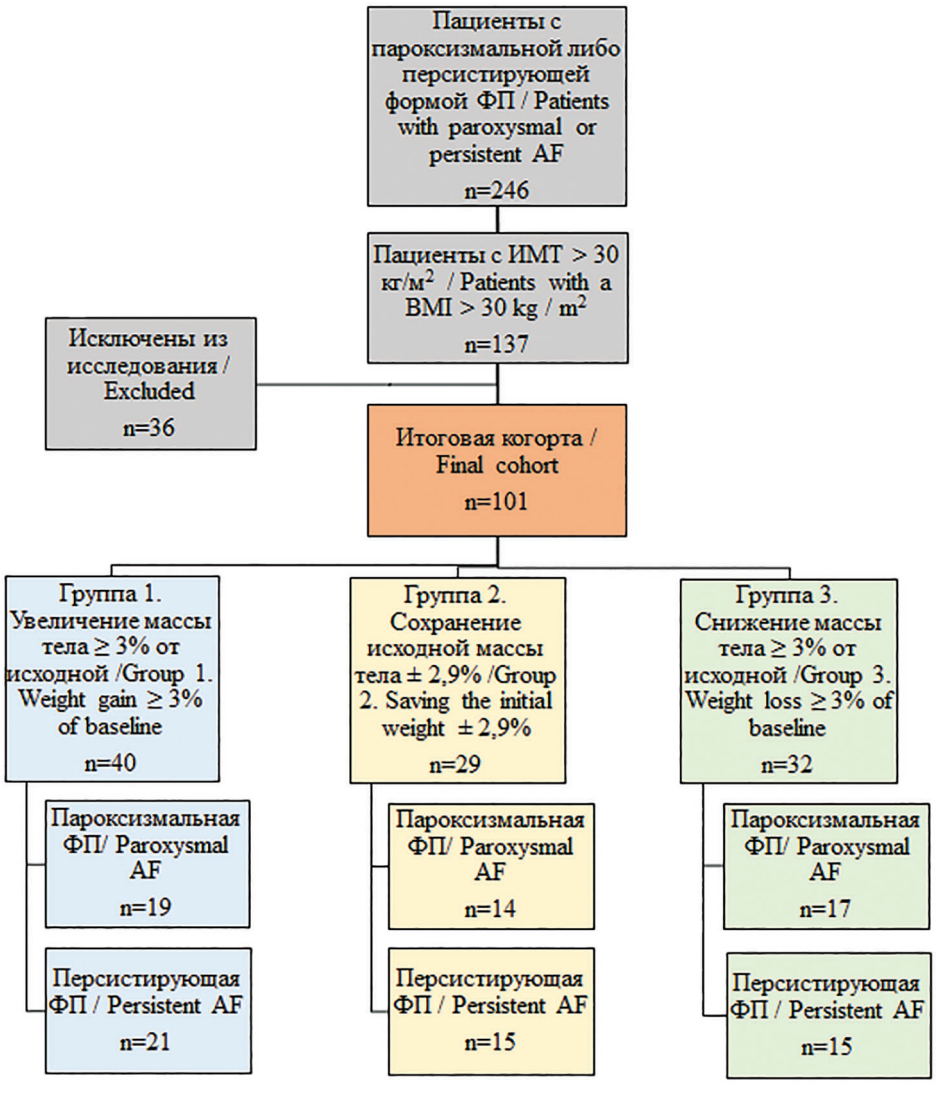

Figure 1. *The process of selecting patients for the study. Groups of patients depending on the dynamics of body weight. BMI — body mass index. AF — atrial fibrillation*

Table 1. Characteristics of patients at the time of inclusion in the study

Options	Group 1 (n=40)	Group 2 (n=29)	Group 3 (n=32)	Multiple comparison, p	Pairwise criterion, p
Age	52,0 [45,0; 65,0]	57,0 [47,0; 66,0]	58,5 [51,0; 70,2]	0,3841	1 2 : p=0,2363 1 3 : p=0,0806 2 3 : p=0,3167
Male, n (%)	31 (78%)	23 (79%)	26 (81%)	0,9267	1 2 : p=0,8572 1 3 : p=0,6970 2 3 : p=0,8491
Height, cm	172,0 [159,8; 177,2]	170,0 [162,0; 178,0]	172,0 [163,0; 178,2]	0,8900	1 2 : p=0,3463 1 3 : p=0,3436 2 3 : p=0,4654
Weight, kg	98,4 [88,6; 106,8]	102,2 [88,3; 108,6]	99,3 [89,3; 105,7]	0,7052	1 2 : p=0,2042 1 3 : p=0,4977 2 3 : p=0,2721
BMI (kg/m^2)	33,8 [32,1; 35,8]	34,4 [31,7; 37,2]	32,7 [31,7; 36,1]	0,3880	1 2 : p=0,1761 1 3 : p=0,2572 2 3 : p=0,1017
SAD (mm Hg st)	142,5 [135,0; 161,2]	139,0 [129,0; 154,0]	144,0 [126,8; 153,0]	0,4500	1 2 : p=0,2075 1 3 : p=0,1082 2 3 : p=0,4086
AF form					
Paroxysmal AF, n (%)	19 (47%)	14 (48%)	17 (53%)	0,8826	1 2 : p=0,9492 1 3 : p=0,6353 2 3 : p=0,7052
Persistent AF, n (%)	21 (53%)	15 (52%)	15 (47%)		
Risk factors					
Arterial hypertension, n (%)	31 (78%)	23 (79%)	23 (72%)	0,7700	1 2 : p=0,8572 1 3 : p=0,5839 2 3 : p=0,5007
Diabetes mellitus, n (%)	11 (28%)	8 (28%)	10 (31%)	0,9289	1 2 : p=0,9937 1 3 : p=0,7279 2 3 : p=0,7540
Impaired glucose tolerance, n (%)	4 (10%)	4 (14%)	3 (9%)	0,8351	1 2 : p=0,7124 1 3 : p=1,0000 2 3 : p=0,6988
Hyperlipidemia, n (%)	23 (58%)	13 (45%)	9 (28%)	0,0448*	1 2 : p=0,2983 1 3 : p=0,0127* 2 3 : p=0,1749
Coronary heart disease, n (%)	4 (10%)	4 (14%)	4 (13%)	0,8833	1 2 : p=0,7124 1 3 : p=1,0000 2 3 : p=1,0000
Excessive alcohol consumption (>140 ml of pure alcohol per week), n (%)	9 (23%)	7 (24%)	8 (25%)	0,9682	1 2 : p=0,8736 1 3 : p=0,8040 2 3 : p=0,9378
Smoking, n (%)	16 (40%)	15 (52%)	15 (47%)	0,6171	1 2 : p=0,3338 1 3 : p=0,5583 2 3 : p=0,7052
Taking medication					
Average number of antihypertensive drugs used	1,0 [1,0; 2,0]	1,0 [0,0; 1,0]	1,0 [0,0; 2,0]	0,7479	1 2 : p=0,2256 1 3 : p=0,3504 2 3 : p=0,3638
Average number of antiarrhythmic drugs used	1,0 [1,0; 1,0]	1,0 [0,0; 2,0]	1,0 [0,0; 1,0]	0,7960	1 2 : p=0,2812 1 3 : p=0,2923 2 3 : p=0,4662
EHRA score	2,5 [2,0; 3,0]	2,5 [2,5; 3,0]	2,5 [2,4; 3,0]	0,8687	1 2 : p=0,4665 1 3 : p=0,3219 2 3 : p=0,3299

Note: The data is presented as: "Me [Q1; Q3]" and "quantity (percentage share)". BMI — body mass index, SAD-systolic blood pressure, AF-atrial fibrillation, EHRA score-severity of AF symptoms according to the classification of the European Heart Rhythm Association [8]

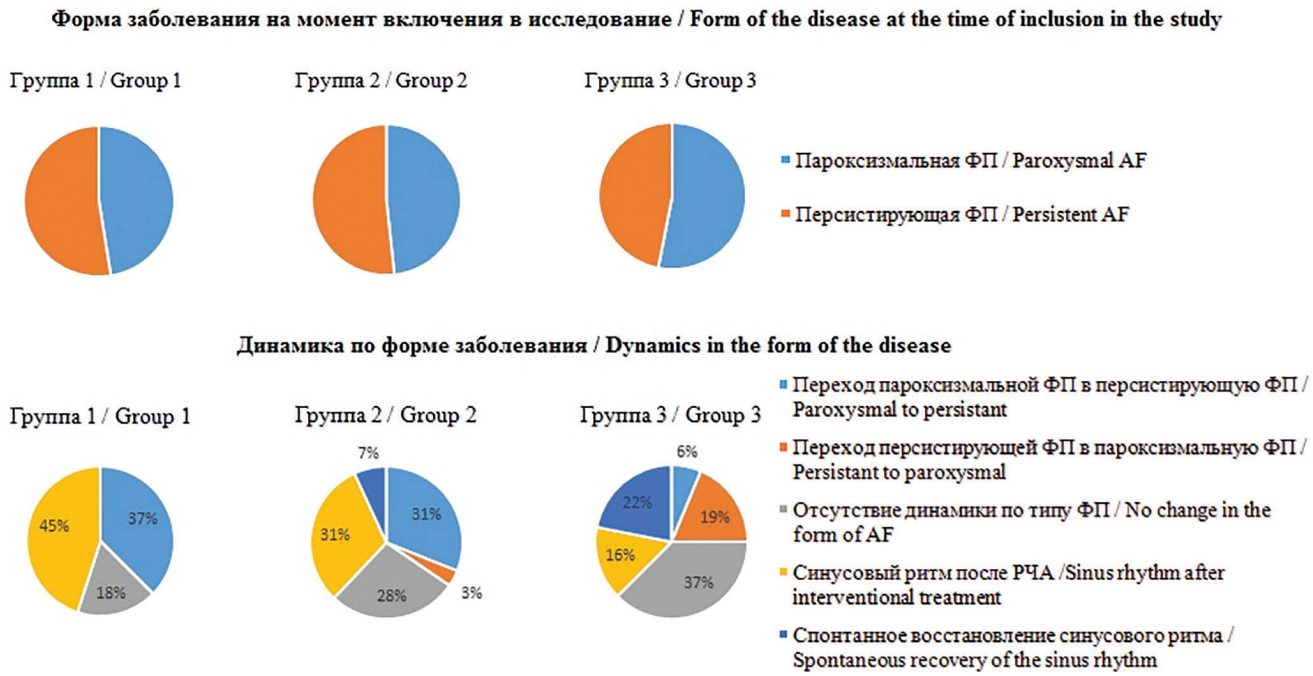

Figure 2. *Changing the form of the disease in dynamics*

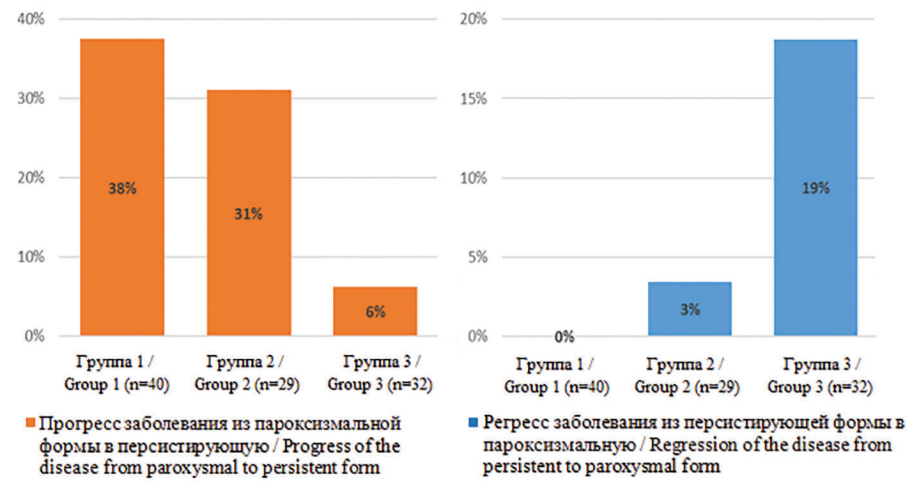

Figure 3. *Dependence of disease progression on changes in body weight*

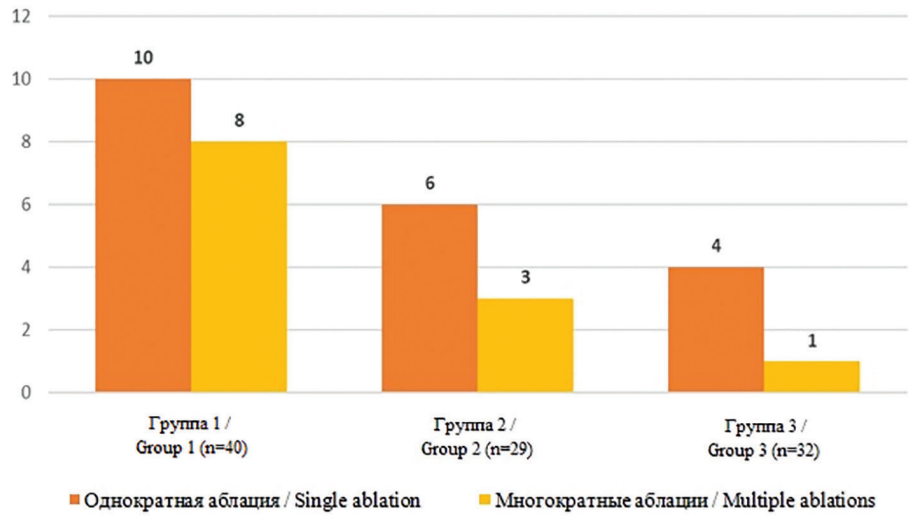

Figure 4. *Interventional treatment with the achievement of sinus rhythm, the need for repeated interventions (single ablation: p=0.4128, multiple ablation: p=0.0851)*

Table 2. *The effect of body weight dynamics on the change in the form of the disease and the frequency of interventional treatment*

Options	Group 1 (n=40)			Group 2 (n=29)			Group 3 (n=32)			value p	
	Initial value	Final value	Value p	Initial value	Final value	Value p	Initial value	Final value	Value p	Initial value	Final value
BMI (kg/m²)	33,8 [32,1; 35,8]	38,1 [35,5; 39,9]	<0,001*	34,4 [31,7; 37,2]	35,1 [32,2; 36,9]	0,4260	32,7 [31,7; 36,1]	30,3 [28,8; 34,2]	0,0011*	1 2 3: p=0,3880 1 2 : p=0,1761 1 3 : p=0,2572 2 3 : p=0,1017	1 2 3:p<0,001* 1 2 : p<0,001* 1 3 : p<0,001* 2 3 : p<0,001*
SAD (mm Hg)	142,5 [135,0; 161,2]	129,0 [120,2; 134,5]	<0,001*	139,0 [129,0; 154,0]	132,0 [120,0; 140,0]	0,0046*	144,0 [126,8; 153,0]	126,0 [115,8; 132,8]	0,0001*	1 2 3: p=0,4500 1 2 : p=0,2075 1 3 : p=0,1082 2 3 : p=0,4086	1 2 3:p=0,2327 1 2 : p=0,1548 1 3 : p=0,1912 2 3 : p=0,0505
Normal pressure (below 140 mm Hg), n (%)	19 (48%)	35 (88%)	0,0001*	15 (52%)	20 (69%)	0,1722	14 (44%)	30 (94%)	<0,001*	1 2 3: p=0,8236 1 2 : p=0,7290 1 3 : p=0,7510 2 3 : p=0,5334	123:p=0,0228* 1 2 : p=0,0588 1 3 : p=0,2215 2 3 :p=0,0119*
Weight, kg	98,4 [88,6; 106,8]	110,5 [97,5; 118,2]	<0,001*	102,2 [88,3; 108,6]	99,3 [87,9; 109,6]	0,5377	99,3 [89,3; 105,7]	90,7 [82,4; 98,2]	<0,001*	1 2 3: p=0,8236 1 2 : p=0,3463 1 3 : p=0,3436 2 3 : p=0,4654	123: p<0.001* 1 2 :p=0,0241* 1 3 : p<0,001* 2 3 :p=0,0106*
Average number of antihypertensive drugs used	1,0 [1,0; 2,0]	2,0 [1,8; 3,0]	0,0002*	1,0 [0,0; 1,0]	2,0 [2,0; 2,0]	0,0010*	1,0 [0,0; 2,0]	0,5 [0,0; 1,0]	0,0035*	1 2 3: p=0,7479 1 2 : p=0,2256 1 3 : p=0,3504 2 3 : p=0,3638	1 2 3:p=0,4500 1 2 :p=0,0060* 1 3 : p<0,001* 2 3 : p<0,001*
Average number of antiarrhythmic drugs used	1,0 [1,0; 1,0]	1,0 [0,0; 1,0]	0,0113*	1,0 [0,0; 2,0]	1,0 [0,0; 1,0]	0,0579	1,0 [0,0; 1,0]	0,0 [0,0; 1,0]	0,0014*	1 2 3: p=0,7960 1 2 : p=0,2812 1 3 : p=0,2923 2 3 : p=0,4662	1 2 3:p=0,0672 1 2 : p=0,2083 1 3 :p=0,0107* 2 3 : p=0,864
EHRA score	2,5 [2,0; 3,0]	2,5 [2,4; 3,0]	0,4917	2,5 [2,5; 3,0]	2,5 [2,0; 3,0]	0,4541	2,5 [2,4; 3,0]	2,0 [1,0; 2,0]	<0,001*	1 2 3: p=0,8687 1 2 : p=0,4665 1 3 : p=0,3219 2 3 : p=0,3299	1 2 3 p<0,001* 1 2:p=0,1680 1 3:p<0,001* 2 3:p<0,001*
AF form											
Paroxysmal AF, n (%)	19 (47%)	-		14 (48%)	-		17 (53%)	-		1 2 3: p=0,8826 1 2 : p=0,9492 1 3 : p=0,6353 2 3 : p=0,7052	
Persistent AF, n (%)	21 (53%)	-		15 (52%)	-		15 (47%)	-			
Transition of paroxysmal AF to persistent AF, n (%)	-	15 (38%)		-	9 (31%)		-	2 (6%)			123:p=0,0079* 1 2 : p=0,5778 1 3 :p=0,0019* 2 3 :p=0,0119*

Options	Group 1 (n=40)			Group 2 (n=29)			Group 3 (n=32)			value p	
	Initial value	Final value	Value p	Initial value	Final value	Value p	Initial value	Final value	Value p	Initial value	Final value
Transition of persistent AF to paroxysmal AF, n (%)	-	0 (0%)		-	1 (3%)		-	6 (19%)			123:p=0,0053* 1 2 : p=0,4203 1 3 :p=0,058* 2 3 : p=0,1064
Lack of dynamics in the form of AF, n (%)	-	7 (18%)		-	8 (28%)		-	12 (37%)			1 2 3:p=0,1615 1 2 : p=0,3160 1 3 : p=0,0557 2 3 : p=0,4101
Restoration of sinus rhythm: spontaneous or as a result of interventional treatment											
Complete freedom from AF, n (%)	-	18 (45%)		-	11 (38%)		-	12 (37%)			1 2 3:p=0,7655 1 2 : p=0,5571 1 3 : p=0,5212 2 3 : p=0,9723
Catheter ablation, n (%)		18 (45%)			9 (31%)			5 (16%)			123:p=0,0287* 1 2 : p=0,2407 1 3 :p=0,0079* 2 3 : p=0,1529
Without ablation, n (%)	-	0 (0%)		-	2 (7%)		-	7 (22%)			123:p=0,0047* 1 2 : p=0,1731 1 3 p=0,0023* 2 3 : p=0,1511
Single ablation, n (%)	-	10 (25%)		-	6 (21%)		-	4 (13%)			1 2 3:p=0,4128 1 2 : p=0,6754 1 3 : p=0,1830 2 3 : p=0,4961
Multiple ablations, n (%)	-	8 (20%)		-	3 (10%)		-	1 (3%)			1 2 3:p=0,0851 1 2 : p=0,3359 1 3 :p=0,0374* 2 3 : p=0,3385

Note: BMI — body mass index, SAD-systolic blood pressure, AF-atrial fibrillation, EHRA score-severity of AF symptoms according to the classification of the European Heart Rhythm Association [8]

Effect of Body Weight Changes on the Need to Take Antiarrhythmic Agents

At the time of enrollment in the study, there were no differences in the number of antiarrhythmic agents taken between the groups (p = 0.7960). To control heart rate (HR), patients of all groups took β-blockers or non-dihydropyridine calcium antagonists, and some patients took class III antiarrhythmic agents according to the Vaughan — Williams classification modified by D. Harrison to control sinus rhythm. In particular, amiodarone and sotalol were taken by 9 (23%) patients in group 1, 6 (21%) — in group 2 and 7 (22%) — in group 3.

During the study period, a decrease in the need for antiarrhythmic agents was revealed in groups 1 (p = 0.0113 *) and 3 (p = 0.0014 *), which was probably associated with a high frequency of restoration of sinus rhythm using interventional procedures in group 1 and spontaneous restoration of sinus rhythm in group 3. In group 2, no significant decrease in the amount of antiarrhythmic agents taken was demonstrated (p = 0.0579).

At the end of the study, there was no significant difference in the use of antiarrhythmic agents by patients (p = 0.0672). However, a pairwise comparison of groups showed a statistically significant difference between groups 1 and 3 (p = 0.0107 *) (Table 2).

Effect of Body Weight Change on Blood Pressure Control

At the end of the study, good blood pressure control was achieved in all groups. The number of patients who achieved the target systolic and diastolic blood pressure levels below 140 and 90 mm Hg was 34 (85%) in group 1, 25 (86.2%) in group 2 and 27 (84.4%) in group 3. However, patients from groups 1 and 2 required an increase in the number of antihypertensive agents to achieve the target blood pressure from 1 to 2 (p = 0.0002 * and p = 0.0010 *, respectively), while in the group of patients whose body weight decreased by more than 3% (group 3), the number of antihypertensive agents was reduced compared to the baseline values (p = 0.0035 *) (Table 2).

Effect of Body Weight Change on the Severity of Disease Symptoms

At the time of enrollment in the study, all participants were assigned a class of AF symptoms according to the modified EHRA scale. The median value of this parameter was comparable in all groups and amounted to 2.5 [2.0; 3.0] in group 1, 2.5 [2.5; 3.0] in group 2, and 2.5 [2.4; 3.0] in group 3 (p = 0.8687). At the final follow-up examination (36 months), the EHRA class was redefined in all patients. A significant decrease in the average severity of the symptoms of the disease was recorded only in group 3 patients whose body weight decreased by ≥ 3% of the baseline (p < 0.001 *) (Table 2).

Effect of Body Weight Change on the Need for Interventional Treatment

The frequency of restoration of sinus rhythm using interventional treatment was different in different groups (p = 0.0287 *). In group 1, sinus rhythm after catheter ablation was recorded in 18 (45%) patients; repeated interventions were performed in 8 (20%) of them. In group 2, sinus rhythm after catheter ablation was achieved in 9 (31%) patients; 3 (10%) of them required repeated interventions. Group 3 patients needed interventional treatment the least: sinus rhythm with catheter ablation was restored in 5 (16%) patients, while the need for multiple ablation was registered in 1 (3%) patient. However, a pairwise comparison of groups showed a significant difference in the use of interventional treatment only between groups 1 and 3 (p = 0.0079 *).

Increased body weight leads to a higher need for interventional treatment. However, no significant differences in the frequency of intervention in the groups were revealed (single ablation: p = 0.4128, multiple ablations: p = 0.0851). The pairwise comparison of groups for the need for multiple ablation revealed statistically significant difference between groups 1 and 3 (p = 0.0374 *) (Fig. 4).

Discussion

This study examines the relationship between body weight change and the progression of AF in obese patients. Results of this study suggest that weight loss not only reduces the severity of AF symptoms but can also lead to the reversal of the disease: transformation of persistent AF into paroxysmal AF, or restoration of sinus rhythm indefinitely.

AF is a disease that tends to progress in most patients. The paroxysmal form becomes persistent and then permanent [10–12]. This is due to the existing dynamic adaptive changes in the atrial myocardium, the so-called structural (electrical) remodeling that not only reduces the likelihood of sinus rhythm restoration and maintains the existing AF but also leads to the emergence of more and more paroxysms, "AF maintains AF" [12, 13]. Structural remodeling causes electrical dissociation (local heterogeneity of conductivity), depression of repolarization processes, and triggers several small foci of excitation circulation (micro re-entry) that stabilize arrhythmia and also ensure the maintenance of long-wavelength loops. The severity of atrial remodeling processes, in turn, determines the resistance of arrhythmia to medication and interventional treatment [14–16]. Even in patients with a single rhythm disturbance, structural and functional changes in the atria were revealed [17].

Successful interventional treatment does not prevent myocardial remodeling in itself [18]. This indicates

the primary role of the arrhythmogenic substrate in the development of AF, which is supported by inadequate treatment and the lack of correction of modifiable risk factors [19]. The most significant risk factors for AF include cardiac factors such as arterial hypertension and heart failure, as well as noncardiac factors, including diabetes mellitus, obesity, obstructive sleep apnea syndrome [20, 21].

Obesity is the main modifiable risk factor for a number of chronic diseases, including type 2 diabetes mellitus and cardiovascular diseases (CVD) [22]. In addition to the effect of obesity on the formation of arrhythmia substrate, associated conditions and, in some cases, pathogenetic diseases caused by obesity (arterial hypertension, obstructive sleep apnea syndrome, type 2 diabetes mellitus, dyslipidemia, and others), the independent role of obesity in arrhythmogenesis was revealed [23, 24]. Unsurprisingly, the exponential increase in AF incidence coincides with the rise in obesity prevalence. The established connection between obesity and AF in the context of a sharp increase in the prevalence of this disease determined the relevance of identifying the underlying pathogenetic mechanisms. Along with increased fatty infiltration of the atria, obesity leads to the diastolic dysfunction of the left ventricle, increased sympathetic activity and higher intensity of inflammation [8]. Today, the role of obesity as an arrhythmogenic substrate remains underestimated.

This study suggests that obesity adversely affects the effectiveness of antiarrhythmic drug therapy and the success of interventional treatment. Significant weight loss (≥ 3% from the baseline), along with the modification of other risk factors, has a beneficial effect on the course of the disease. It can lead to its reversal and restoration of sinus rhythm in some patients indefinitely. In patients taking antiarrhythmic agents, AF is much less likely to progress to more persistent forms in comparison with patients who have chosen a heart rate control strategy [25].

This study demonstrated that a decrease in body weight was associated with a decrease in the need for catheter ablation and its frequency, as well as in the use of antiarrhythmic agents .

Recognition of AF as a progressive disease based on the dynamic remodeling of the myocardium under the influence of risk factors requires early and aggressive intervention in relation to body weight and other modifiable risk factors. Timely correction of risk factors is becoming critical for present-day medicine in the context of the growing epidemic of obesity and AF. Managing risk factors reduces the rate of disease progression and improves long-term prospects for maintaining sinus rhythm.

This study contributes to the evidence base for the need for effective modification of risk factors, which is of strategic importance for both primary and secondary prevention of AF.

The relatively small sample size should be recognized as a limitation of this study.

Conclusion

AF is a progressive disease. Persistent obesity and concomitant weight gain are associated with an accelerated progression of the disease from the paroxysmal to the persistent form. However, this study showed that weight loss plays an inhibitory role on the processes of electrophysiological remodeling of the myocardium and even contributes to the reversal of persistent AF to paroxysmal AF, with the potential for restoration of sinus rhythm indefinitely.

In this regard, weight loss is a promising therapeutic strategy in the comprehensive treatment of patients with AF. Another important aspect is, in our opinion, the need to consider weight loss as a probable predictor of the success of interventional treatment at the planning stage of the latter.

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All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

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