ISSN 2782-4284 (Print)
ISSN 2782-4233 (Online)

VOLUME 4 ISSUE 1 2024

Cardiac Arrhythmias

INTERNATIONAL PEER-REVIEW MEDICAL JOURNAL

https://journals.eco-vector.com/cardar

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Address:
3A Aptekarskiy lane, office 1N,
Saint Petersburg, 191186, Russia
E-mail: info@eco-vector.com
WEB: https://eco-vector.com
Phone: +7(812)6488367

Federal Supervisory Service on Mass Media, Information Technologies and Mass Communication (Roskomnadzor)
ПИ № ФС77-79865

Published 4 times a year

EDITORIAL
Address:
41 Kirochnaya street,
Saint Petersburg, 191015, Russia
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ISSN 2782-4284 (Print)
ISSN 2782-4233 (Online)

CARDIAC ARRHYTHMIAS

Volume 4 | Issue 1 | 2024

INTERNATIONAL PEER-REVIEW MEDICAL JOURNAL

Published under the supervision of Eurasian Arrhythmology Association

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УЧРЕДИТЕЛИ

- ООО «Эко-Вектор»
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ИЗДАТЕЛЬ

ООО «Эко-Вектор»
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E-mail: info@eco-vector.com
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Журнал зарегистрирован Федеральной службой по надзору в сфере массовых коммуникаций, связи и охраны культурного наследия, свидетельство о регистрации СМИ ПИ № ФС77-79865 от 18.12.2020

Выходит 4 раза в год

РЕДАКЦИЯ

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Тел.: +7(812)303-50-00
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ПОДПИСКА

На печатную версию журнала: Объединенный каталог «Пресса России» https://www.pressa-rf.ru. Подписной индекс на полугодие — 85697, на год — 85698.
На электронную версию журнала: https://journals.eco-vector.com; eLibrary.ru

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Оригинал-макет изготовлен ООО «Эко-Вектор».
Редактор: *И.Л. Уразовская*
Редактор переводческих проектов: *А.А. Богачев*

Формат 60 × 90$^{1}/_{8}$. Печать офсетная.
Усл. печ. л. 5,13. Тираж 200 экз. Цена свободная
Отпечатано в ООО «Типография Экспресс B2B».
191180, Санкт-Петербург, наб. реки Фонтанки, д. 104, лит. А, пом. 3Н, оф. 1.
Тел.: +7(812)646-33-77.
Подписано в печать 15.05.2024.
Заказ 4-4680-lv.
Выход в свет 24.05.2024..

16+

ISSN 2782-4284 (Print)
ISSN 2782-4233 (Online)

CARDIAC ARRHYTHMIAS

Том 4 | Выпуск 1 | 2024

МЕЖДУНАРОДНЫЙ МЕДИЦИНСКИЙ РЕЦЕНЗИРУЕМЫЙ ЖУРНАЛ

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КЛИНИЧЕСКИЕ СЛУЧАИ

DOI: https://doi.org/10.17816/cardar629168

Opportunities of metabolic treatment in paroxysmal atrial fibrillation patients with obesity, arterial hypertension and/or ischemic heart disease

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ABSTRACT

This article provides the experience of examination and treatment of paroxysmal atrial fibrillation patients with concomitant obesity, arterial hypertension and/or ischemic heart disease, who were prescribed levocarnitine in addition to traditional therapy. The addition of levocarnitine in management of atrial fibrillation was found to be capable of reducing the atrial fibrillation burden after cardioversion and improve the functional state of the patients.

Keywords: atrial fibrillation; levocarnitine; recurrence; prevention.

To cite this article

Balabanovich TI, Golyshko VS, Sinkevich IA, Shkuta ES, Veniadziktava EA, Baliuk PV, Knysh AV. Opportunities of metabolic treatment in paroxysmal atrial fibrillation patients with obesity, arterial hypertension and/or ischemic heart disease. *Cardiac Arrhythmias.* 2024;4(1):5–14. DOI: https://doi.org/10.17816/cardar629168

Received: 06.11.2023 **Accepted:** 26.12.2023 **Published online:** 06.05.2024

DOI: https://doi.org/10.17816/cardar629168

Возможности метаболической терапии у пациентов с пароксизмальной формой фибрилляции предсердий в сочетании с ожирением, артериальной гипертензией и/или ишемической болезнью сердца

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Аннотация

Приводится опыт обследования и лечения пациентов с пароксизмальной формой фибрилляции предсердий, страдающих ожирением, артериальной гипертензией и/или ишемической болезнью сердца, которым в дополнение к традиционной терапии был назначен левокарнитин (препарат «Карнимет», ИПТУП «Реб-Фарма», Республика Беларусь), что позволило эффективно и безопасно поддержать синусовый ритм после кардиоверсии и улучшить функциональный статус пациентов.

Ключевые слова: фибрилляция предсердий; левокарнитин; рецидив; профилактика.

Как цитировать

Балабанович Т.И., Голышко В.С., Синкевич И.А., Шкута Э.С., Венедиктова Е.А., Балюк П.В., Кныш А.В. Возможности метаболической терапии у пациентов с пароксизмальной формой фибрилляции предсердий в сочетании с ожирением, артериальной гипертензией и/или ишемической болезнью сердца // Cardiac Arrhythmias. 2024. Т. 4, № 1. С. 5–14. DOI: https://doi.org/10.17816/cardar629168

Рукопись получена: 06.11.2023 **Рукопись одобрена:** 26.12.2023 **Опубликована online:** 06.05.2024

INTRODUCTION

In recent decades, compelling evidence shows that atrial fibrillation (AF) is one of the most prevalent forms of cardiac rhythm disorders [1, 2]. To illustrate this point, R.G. Trohman et al. cited the following data: according to forecasts, by 2050, 6–12 million individuals in the United States will suffer from AF. In Asia, the number of patients with AF will reach 70 million. In Europe, the number of individuals affected by AF is projected to exceed 17.9 million by 2060 [1, 2]. The presence of AF increases the mortality risk by 1.5–3.5 times, initiates up to 20%–30% of stroke cases, exacerbates heart failure, vascular dementia, and depression, and reduces the quality of life [1]. This results in the pressing need for effective treatment and prevention of AF, which remains an unresolved problem. Despite medical, interventional, and surgical therapies for AF, a recurrent arrhythmia occurs in 40%–50% of cases [3]. This situation prompts the use of both general treatment concepts based on the most essential aspects and regularities of arrhythmia pathogenesis and specific but very important distinguishing features of different clinical and pathogenetic AF phenotypes.

Recently, reports on the efficacy of levocarnitine in the treatment of patients with cardiac problems have been published. In a meta-analysis of 13 studies involving 3.629 patients, J.J. DiNicolantonio et al. demonstrated that levocarnitine therapy for patients with myocardial infarction reduced the risk of total mortality by 27% and the risk of ventricular arrhythmias by 65% [4]. Several publications have noted that the inclusion of levocarnitine in traditional therapy enhances the antianginal effect, improves the clinical course of chronic heart failure (CHF), and has an anti-inflammatory effect [5–7]. However, in clinical practice, the use of levocarnitine for the AF treatment is less investigated. Existing literature data indicate that levocarnitine reduces the risk of postoperative AF after aortic valve reconstruction threefold [8]. A randomized trial involving patients who had undergone coronary artery bypass grafting demonstrated the efficacy of levocarnitine in relation to AF prevention [7].

The imbalance in fatty acid uptake and oxidation in cardiac cells in obesity-associated AF induces the development of lipotoxic atrial cardiopathy, which subsequently initiates lipid peroxidation processes and damage to membrane structures [9]. In these conditions, the activity of enzymes such as 5' adenosine monophosphate-activated protein kinase (AMPK) and carnitine palmitoyltransferase IB and other enzymes necessary for adequate β-oxidation of fatty acids, decrease [10]. In a series of experiments on rats with paroxysmal AF and obesity, Y. Zhang et al. observed that levocarnitine treatment resulted in increased AMPK activity, normalization of the β-oxidation process, and elimination of the proarrhythmic effects on the myocardium. This ultimately prevented AF progression and reversed cardiac remodeling [10]. Thus, the efficacy of levocarnitine in AF is convincing and pathogenetically justified and opens new perspectives in the treatment of this type of arrhythmia.

This study aimed to assess the efficacy of a complex treatment regimen that included levocarnitine in patients with paroxysmal AF and comorbidities such as obesity, arterial hypertension (AH), and/or coronary heart disease (CHD).

MATERIALS AND METHODS

This study analyzed the medical records of 60 inpatients hospitalized in the Cardiology Department of the City Clinical Hospital No. 3 of Grodno (Belarus) for paroxysmal AF with concomitant obesity, AH, and/or CHD. The patients were 48–83 years old (mean age, 65.0 ± 8.4 years). Of the total number of patients, 37 (61.7%) were male, and 23 (38.3%) were female.

The duration of AF history was determined for each patient. Of the 50 patients, 29 (58%) had a history of AF for up to 1 year, and 31 (62%) had a history of AF for > 1 year. Furthermore, all patients exhibited obesity, with an average body mass index (BMI) of 34.5 ± 3.2 kg/m^2. Grade I obesity was observed in 31 (51.7%) patients, grade II in 25 (41.7%), and grade III in 4 (6.6%). AH was diagnosed in 5 (90%) patients, with 11 exhibiting grade I and 44 exhibiting grade II. CHD was diagnosed in 49 (82%) patients, with 18 exhibiting postinfarction cardiosclerosis and 31 exhibiting functional class II stable angina. Moreover, 8 (13.3%) patients had a history of cerebral infarction, and 20 (33.33%) and 40 (66.67%) patients exhibited signs of CHF with New York Heart Association classes I and II, respectively. Furthermore, all patients exhibited a preserved left ventricular ejection fraction (LVEF) and were compensated.

The mean duration of the current AF episode was 48 h (the minimum and maximum AF durations were 14 h and 4 days, respectively). All patients underwent effective pharmacologic cardioversion using amiodarone, a class III antiarrhythmic drug. According to clinical protocols, all patients received conventional comprehensive treatment with individualized efficacy (amiodarone 400 [400–600] mg), β-adrenoblockers (metoprolol 50 [50–100] mg; bisoprolol 5 [2.5–5] mg), nitrates on demand (molsidomine 2 mg), hypolipidemic (atorvastatin 20 [20–40] mg), rosuvastatin 10 [10–20] mg), hypotensive agents (lisinopril 10 [10–20] mg, perindopril 4 [2–8] mg, ramipril 5 [5–10] mg), valsartan

160 [80–160] mg), amlodipine 10 [5–10] mg), diuretics (spironolactone 25 [25–50] mg, torasemide 2.5 [2.5–5] mg, indapamide 2.5 mg), and anticoagulants (rivaroxaban 20 mg). A medical committee decided on the use of the metabolic cytoprotector levocarnitine (Carnimet, REB-PHARMA, Republic of Belarus) in a combined therapeutic regimen because of the lack of optimal efficacy of the previous therapeutic approach and the patient provided written consent. The study was approved by the local ethics committee of the clinic (December 30, 2022, No. 1484/01-M).

A total of 30 patients (main group) aged 48–83 years (18 (60%) men and 12 (40%) women; average age, 65.5 ± 8.92 years) received Carnimet (REB-PHARMA) for 10 days in hospital. In addition to the standard therapeutic regimen, the patients were administered the drug at a dose of 1.0 g/5 mL once daily via slow intravenous infusion. At the time of hospital discharge, the optimal combined therapy for the underlying disease was recommended, including levocarnitine at a dose of 2.0 g orally for up to 3 months. Lifestyle modification recommendations were also provided, including adherence to a Mediterranean diet and optimal physical activity. The control group consisted of 30 patients aged 54–83 years (19 (63.3%) men, 11 (36.7%) women; mean age, 64.5 ± 8.01 years) who received only standard individualized medication with the above groups of drugs without levocarnitine. Patients were excluded from the study if they had a history of cardiac surgery or non-coronary myocardial disease, epilepsy, diabetes mellitus, malignant neoplasms, or thyroid dysfunction. In addition, patients who had a chronic decompensated disease of an internal organ, an active inflammatory process of any localization, and anemia or were taking antioxidants or other drugs used for cardiotropic metabolic therapy were also excluded.

Before prescribing Carnimet, patients undergo an inpatient clinical and instrumental examination, which includes 12-lead electrocardiography, BMI calculation according to the Quetelet formula (BMI = body weight (kg) / height (m^2)), conventional laboratory tests, a 6-minute walk test (6MWT), and echocardiography (Echo-CG) on Mindray DC-60 device (Shenzhen Mindray Bio-Medical Electronics Co, Ltd, China) using the P4-2 transducer with a frequency band of 2–4 MHz to determine standard protocol parameters.

A complex treatment regimen incorporating levocarnitine was evaluated 12 (10; 12) weeks after its initiation. The frequency of AF recurrence, 6MWT changes, and dynamics of Echo-CG parameters were considered. The statistical analysis was conducted using Statistica 10.0 and RStudio 1.1.183. Data were tested for conformity to a normal distribution using the Shapiro – Wilk *W*-criterion. As the majority of the quantitative characteristics were not normally distributed, nonparametric statistical analysis methods were employed in the comparison. Nonnormally distributed continuous parameters are provided as median (*Me*) and interquartile range (25^{th}; 75^{th} percentile). Conversely, normally distributed quantitative signs are presented as the arithmetic mean *M* and standard deviation σ ($M \pm \sigma$). The Mann – Whitney *U*-test was employed to assess the disparities between two independent groups in terms of quantitative characteristics. The Kruskal – Wallis test was used to test the hypothesis of equality of the medians of the studied indicators across multiple groups. Fisher's exact test and Pearson's χ^2 were employed to compare independent groups in terms of qualitative characteristics. Spearman nonparametric correlation analysis was performed. The frequency of AF recurrence was analyzed using the Kaplan – Meier method. A multivariate logistic regression analysis was employed to assess the relationship between the studied parameters and the achievement of the endpoint. A logistic regression equation with a binary response and a logit function of the relationship was constructed. Cox regression analysis was also conducted. An odds ratio (OR) was calculated for parameters with the highest diagnostic efficacy of reaching the endpoint. The reliability of differences in groups was accepted at the level of statistical significance $p < 0.05$.

RESULTS AND DISCUSSION

Groups L_1 and L_0 were comparable by sex and age. No significant intergroup differences in the occurrence of comorbidities were noted. All patients reported good tolerability of Carnimet and had not experienced adverse reactions during its administration. Table 1 presents the initial characteristics of the patients.

During hospitalization, no significant differences in drug therapy (except for levocarnitine prescription) were found in the studied groups (Table 2).

In the dynamic study, the L_1 group showed a statistically significant increase in exercise tolerance from 421.5 (390–430) m at baseline to 440 (430; 480) m at 12 (10–12) weeks ($p = 0.0002$). In the L_0 group, 6MWT results did not change significantly during the follow-up period ($p = 0.75$). At week 12 of levocarnitine therapy, exercise tolerance significantly increased in the L_1 group compared with that in the L_0 group (Table 3).

BMI decreased significantly over 12 (10; 12) weeks in the L_1 group, i.e., from 35.3 ± 3.6 kg/m^2 to 32.84 ± 3.5 kg/m^2 ($p = 0.02$). In contrast, the L_0 group did not demonstrate a similar reduction in BMI, with 33.6 ± 2.5 kg/m^2 initially

and 34.5 ± 3.1 kg/m^2 after 12 (10; 12) weeks (p = 0.16). No significant change in weight (even a trend toward weight gain was noted) was found, and the initial and final weights at 12 (10; 12) weeks of 33.6 ± 2.5 and 34.5 ± 3.1 kg/m^2 (p = 0.16). When comparing changes in BMI, the L_1 group showed a significant decrease in BMI compared with the L_0 group (p = 0.04).

During hospitalization, with Echo-CG at sinus rhythm performed on day 1 after cardioversion, the L_1 and L_0 groups did not show significant differences in the studied parameters (Table 1). At the subsequent control examination, conducted 12 (10–12) weeks later, the anteroposterior dimension of the LA slightly decreased in both groups. In the L_1 group, the LA dimension decreased from 42 (40–46) mm to 41 (37–46) mm, whereas in the L_0 group, it decreased from 41 (40–43) mm to 40 (37–45) mm. However, these changes were not statistically significant. In addition, no significant changes were found in the pulmonary artery systolic pressure (PASP) and left ventricular myocardial mass index (LVMMI) (Table 3). The initial Echo-CG data and subsequent dynamic assessments revealed a notable improvement in the LVEF from 57% (55%–62%) to 59% (54%–66%) in

Table 1. Clinical characteristics of the patients
Таблица 1. Исходная характеристика пациентов

Indices	Group L_1 (n = 30)	Group L_0 (n = 30)	p
Sex: male/female, n (%)	18 (60) / 12 (40)	19 (63.3) / 11 (36.7)	0.79
Age, years	65.5 ± 8.92	64.5 ± 8.01	0.53
BMI, kg/m^2	35.3 ± 3.6	33.7 ± 2.5	0.16
Smoking status, n (%)	14 (46.7)	12 (40)	0.39
CHA2DS2-VASc, %	3 (2; 4)	3 (2; 4)	0.94
Obesity:			
– Grade I, n (%)	13 (43.3)	18 (60)	0.34
– Grade II, n (%)	14 (46.7)	11 (36.7)	
– Grade III, n (%)	3 (10)	1 (3.3)	
Arterial hypertension:			
– Grade I, n (%)	3 (10)	7 (23.3)	
– Grade II, n (%)	23 (76.7)	21 (70)	0.31
– No arterial hypertension, n (%)	4 (13.3)	2 (6.7)	
Coronary heart disease:			
– Postinfarction cardiosclerosis, n (%)	10 (33.3)	8 (26.7)	0.58
– stable angina, class II, n (%)	16 (53.4)	15 (50)	
– No coronary heart disease, n (%)	4 (13.3)	7 (23.3)	
Chronic heart failure:			
– Class I, n (%)	10 (33.3)	10 (33.3)	1.0
– Class II, n (%)	20 (66.7)	20 (66.7)	
Stroke history, n (%)	4 (13.3)	4 (13.3)	1.0
Glucose (vein), mmol/L	5.6 (4.8; 6.1)	5 (4.71; 5.5)	0.09
eGFR, mL/min/1.73 m^2	74.5 (67; 86)	79 (70; 89)	0.15
Anteroposterior dimension of the LA, mm	42 (40; 46)	41 (40; 43)	0.27
LVEF (B-mode), %	57 (55; 62)	56.5 (52; 60)	0.53
PASP, mmHg	27 (25; 32)	25 (24; 29)	0.19
LVMMI, g/m^2	128.5 (115; 150)	127 (116; 139)	0.97
E/A ratio	0.76 (0.67; 0.83)	0.73 (0.65; 0.8)	0.39

Note: ИМТ — body mass index; рСКФ — estimated glomerular filtration rate; ЛП — left atrium; ФВ ЛЖ — left ventricular ejection fraction; ИММЛЖ — left ventricular myocardial mass index; сДЛА — pulmonary artery systolic pressure

Примечание: ИМТ — индекс массы тела; ИММЛЖ — индекс массы миокарда левого желудочка; ЛП — левое предсердие; рСКФ — расчетная скорость клубочковой фильтрации; сДЛА — систолическое давление в легочной артерии; ФВ ЛЖ — фракция выброса левого желудочка.

the L_1 group (p = 0.01). Dynamic assessment of *LV* diastolic dysfunction demonstrated a significant enhancement in the initially impaired *E/A* ratio in both groups (Table 3). Moreover, after 12 (10–12) weeks, the *E/A* ratio significantly increased in the L1 group compared with that in the L_0 group (0.88 [0.8–0.9] and 0.81 [0.73–0.84], respectively; p = 0.003).

The median period of freedom from AF after cardioversion in the sample patients was 12 (9; 12) weeks. AF recurred in 4 (13%) patients of the L_1 group and 13 (43%) of the L_0 group (p = 0.01). All cases were controlled by amiodarone drug cardioversion. A greater frequency of paroxysms with disrupted rhythm was observed in the L_0 group in comparison with the L_1 group (p = 0.03). In the L_1 group, 13% of patients had recurrent AF up to once in 3 months. In the L_0 group, 27% of the patients had AF recurrence up to once in 2 months, whereas the L_1 group maintained sinus rhythm. Monthly AF recurrence was observed only in 7% of patients in the L_0 group. The Kaplan – Meier analysis of freedom from recurrence in the L_1 and L_0 groups is presented in Figure 1. Cox regression analysis identified levocarnitine intake as the only statistically significant protective factor against AF recurrence (p = 0.008). In addition to the aforementioned predictors and protectors of freedom from AF, other variables were also included in

Table 2. Comparative assessment of inpatient treatment
Таблица 2. Сравнительная оценка стационарного лечения пациентов

Drugs	Group L_1 (n = 30)	Group L_0 (n = 30)	p
Amiodarone, *n* (%)	30 (100)	30 (100)	1.0
Beta-adrenoblockers, *n* (%)	25 (83.3)	27 (90)	0.45
Rivaroxaban, *n* (%)	30 (100)	30 (100)	1.0
ACEI or ARB, *n* (%)	30 (100)	30 (100)	1.0
Amlodipine, *n* (%)	26 (86.7)	27 (90)	0.69
Statins, *n* (%)	30 (100)	30 (100)	1.0
Diuretics, *n* (%)	24 (80)	23 (76.7)	0.75
Molsidomine (on demand), *n* (%)	26 (86.7)	23 (76.7)	0.32

Table 3. Dynamics of the indicators in patients receiving levocarinitine therapy
Таблица 3. Динамика основных показателей пациентов на фоне терапии левокарнитином

Indices	Group	Time		p	$P_{L_1-L_0}$ after 3 months
		Baseline	After 3 months		
BMI, kg/m^2	L_1	35.3 ± 3.6	32.84 ± 3.5	0.02	0.04
	L_0	33.6 ± 2.5	34.5 ± 3.1	0.16	
6MWT, m	L_1	421.5 (390; 430)	440 (430; 480)	0.00002	0.01
	L_0	422 (410; 460)	425.5 (400; 430)	0.75	
Anteroposterior dimension of the LA, mm	L_1	42 (40; 46)	41 (37; 46)	0.17	0.56
	L_0	41 (40; 43)	40 (37; 45)	0.16	
LVEF (B-mode), %	L_1	57 (55; 62)	59 (54; 66)	0.01	0.00001
	L_0	56.5 (52; 60)	56 (53; 58)	0.68	
PASP, mmHg	L_1	27 (25; 32)	26 (22; 30)	0.09	0.34
	L_0	25 (24; 29)	25.5 (24; 32)	0.59	
LVMMI, g/m^2	L_1	128.5 (115; 150)	127 (114; 149)	0.88	0.53
	L_0	127 (116; 139)	126 (113; 142)	0.49	
E/A ratio	L_1	0.76 (0.67; 0.83)	0.88 (0.8; 0.9)	0.00003	0.003
	L_0	0.73 (0.65; 0.8)	0.81 (0.73; 0.84)	0.02	

Note: 6-MX — 6-minute walk test; ИМТ — body mass index; рСКФ — estimated glomerular filtration rate; ЛП — left atrium; ФВ ЛЖ — left ventricular ejection fraction; ИМТЛЖ — left ventricular myocardial mass index; сДЛА — pulmonary artery systolic pressure.

Примечание: 6-МХ — 6-минутная ходьба; ИМТ — индекс массы тела; ИММЛЖ — индекс массы миокарда левого желудочка; ЛП — левое предсердие; рСКФ — расчетная скорость клубочковой фильтрации; сДЛА — систолическое давление в легочной артерии; ФВ ЛЖ — фракция выброса левого желудочка.

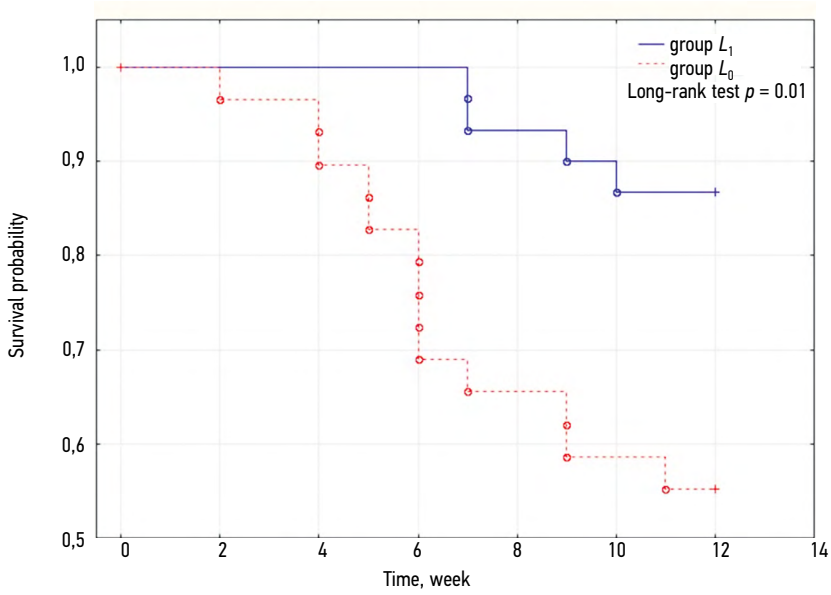

Fig. 1. Kaplan – Meier curves of end-point "atrial fibrillation recurrence"
Рис. 1. Кривые Каплана – Майера для конечной точки «рецидив фибрилляции предсердий»

the range of analyzed predictors. However, these variables were found to be statistically insignificant. These included the sex (p = 0.05) and age (p = 0.54) of the patients, presence of AH (p = 0.66), CHD (p = 0.21), CHF (p = 0.16), diabetes mellitus (p = 0.45), history of stroke (p = 0.98), BMI (p = 0.35), LVEF (p = 0.85), and LA size (p = 0.31).

The effect of the studied clinical variables on the risk of AF recurrence was evaluated. Multivariate regression analysis demonstrated that levocarnitine therapy exhibited an independent, positive effect on the maintenance of sinus rhythm (OR 0.13; p < 0.01). Conversely, male sex (OR 7.42; p = 0.001) and E/A ratio (OR 4.2; p = 0.02) were identified as independent factors negatively affecting sinus rhythm maintenance.

AH, CHD, and CHF are quite common comorbidities in patients with AF. The underlying mechanisms of AF are complex and involve ischemia, changes in the electrophysiological state of cardiomyocytes, and myocardial structural remodeling. These processes play a significant role in the AF initiation and maintenance of these pathologies. A potential cause of electrical remodeling is mitochondrial dysfunction [11, 12]. The mitochondria synthesize adenosine-5-triphosphate (ATP) to ensure active transmembrane ion transport in myocardiocytes, support energy homeostasis, and maintain adequate ionotropic, chronotropic, and dromotropic states of the myocardium. In the paroxysmal AF, the energy requirements of cardiomyocytes increase. Initially, this causes a compensatory increase in ATP synthesis. However, mitochondrial dysfunction ensues, accompanied by decreased ATP release. This contributes to the activation of anaerobic glycolysis, lactate accumulation, decline in intracellular pH, and impaired cardiomyocyte function. Mitochondrial damage also results in the release of free radicals (particularly superoxide anion radicals) into the cytosol, which blocks the cardiac ryanodine receptor (RyR2) located in the sarcoplasmic reticulum membrane, leading to calcium ion overload. Proinflammatory cytokines (tumor necrosis factor-α, interleukin (IL)-1β, IL-6, etc.) and reactive oxygen species can activate myocardial fibrosis, which serves as a substrate for the re-entry mechanism in AF. Dastan F. et al. reported their noteworthy experience of using levocarnitine in patients with AF who underwent coronary bypass surgery. Levocarnitine exerted an anti-inflammatory effect due to low levels of C-reactive protein [7]. In experiments using animal models with simulated CHF, levocarnitine increased the level of fatty-acid-binding proteins (FABPs), which is decreased in patients with AF and CHF. This contributes to adequate β-oxidation. Secondary levocarnitine deficiency occurred in 50% of CHF cases [13]. In some studies of patients with CHF, levocarnitine positively affected the reduction of brain natriuretic peptide levels, inflammatory markers, and improvement of intracardiac hemodynamics [6, 14].

Individuals with obesity have a high risk for AF, and these conditions share common pathogenetic mechanisms. In both AF and obesity, secondary levocarnitine deficiency, decreased activities of CPT IB, AMRK, and PGC1α proteins, and activation of glycolysis enzymes in the atria are typically observed [10, 11]. Levocarnitine therapy can exert a favorable therapeutic effect on AF and obesity concurrence. In experimental conditions, levocarnitine therapy exerted a cardioprotective effect and reduced the risk of AF in experimental rats with obesity and arrhythmia. This effect

was attributed to the activation of the AMPK-dependent pathway and relief of mitochondrial dysfunction [10].

A 10% reduction in body weight (BMI < 27 kg/m²) is considered an effective method of preventing AF [2]. Furthermore, levocarnitine was found to be an effective drug for reducing body weight [15], correcting physical activity levels, achieving antianginal effects, and improving myocardial contractile function and tolerance to chronic oxygen deficiency. The combination of metabolic and standard therapy, as evidenced by our data, improves the functional status of patients, contributes to BMI correction, and demonstrates regression of diastolic dysfunction, which correlates with the aforementioned publications [5–8, 10–14]. Furthermore, our multivariate regression analysis demonstrated that levocarnitine therapy exerted an independent favorable prognostic effect on the prevention of AF recurrence. These data are consistent with the findings of Y. Shingu et al. [8].

The findings of this study confirm the positive role of levocarnitine as an adjunct to standard therapy in the prevention of paroxysmal AF in patients with obesity, AH, and/or CHD. The mechanisms of AF suppression in obesity, AH, and/or CHD and heart failure are related to the complex interactions between levocarnitine and carnitine transport system proteins and FABP proteins and the ability of levocarnitine to intensify β-oxidation processes, release cardiomyocytes from toxic products of oxidative processes, protect mitochondrial function, reduce myocardial inflammation and interstitial fibrosis, and maintain cellular energy homeostasis. The study's key features include the use of levocarnitine after pharmacologic cardioversion in patients with AF, obesity, AH, and/or CHD. In addition, a novel prescribing regimen for levocarnitine is proposed, which has not previously been used in clinical trials.

This study has some limitations. The results can only be considered to an identical group of patients with a follow-up period of 12 weeks or less. To confirm the results of the study, a larger sample of patients with a longer follow-up period is necessary to evaluate the long-term results. More studies of the effects of levocarnitine on patients with AF are warranted, taking into account the shortcomings and limitations of previous studies.

CONCLUSIONS

The incorporation of levocarnitine into the standard treatment regimen for patients with paroxysmal AF in the context of obesity, AH, and/or CHD represents a safe and efficacious approach to the secondary prevention of AF recurrences.

ADDITIONAL INFORMATION

Ethics approval. Written consent was obtained from the patients for publication of relevant medical information and all accompanying images within the manuscript.

Author contribution. Thereby, all authors confirm that their authorship complies with the international ICMJE criteria (all authors have made a significant contribution to the development of the concept, research, and preparation of the article, as well as read and approved the final version before its publication). Personal contribution of the authors: T.I. Balabanovich — research concept and design, literature review, data collection and processing, text writing and editing, integration of all article parts; V.S. Golyshko — literature review, data analysis, statistical data analysis, making final edits; I.A. Sinkevich, E.S. Shkuta — data collection and analysis, discussion of data obtained, text editing, making edits; L.A. Veniadziktava, P.V. Baliuk, A.V. Knysh — data collection and analysis, concept of research parameters, text and tables editing.

Competing interests. The authors declare that they have no competing interests.

Funding source. This study was not supported by any external sources of funding.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Заключение этического комитета. Исследование одобрено этическим комитетом Городской клинической больницы № 3 г. Гродно от 30.12.2022 № 1484/01-М. Авторы получили письменное согласие пациентов на публикацию медицинских данных.

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией. Вклад каждого автора: Т.И. Балабанович — концепция и дизайн исследования, обзор литературы, сбор и обработка материала, написание и редактирование текста, ответственность за целостность всех частей статьи; В.С. Голышко — обзор литературы, сбор и статистическая обработка материалов, редактирование текста; И.А. Синкевич, Э.С. Шкута — сбор и обработка материалов, обсуждение полученных данных, редактирование текста; Е.А. Венедиктова, П.В. Балюк, А.В. Кныш — сбор материала, концепция параметров исследования, обработка информации, редактирование таблиц и текста.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

REFERENCES

1. Hindricks G, Potpara T, Dagres N, et al. ESC Scientific Document Group. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J.* 2021;42(5):373–498. doi: 10.1093/eurheartj/ehaa945

2. Trohman RG, Huang HD, Sharma PS. Atrial fibrillation: primary prevention, secondary prevention, and prevention of thromboembolic complications: part 1. *Front Cardiovasc Med.* 2023;10:1060030. doi: 10.3389/fcvm.2023.1060030

3. Vizzardi E, Curnis A, Latini MG, et al. Risk factors for atrial fibrillation recurrence: a literature review. *J Cardiovasc Med (Hagerstown).* 2014;15(3):235–253. doi: 10.2459/jcm.0b013e328358554b

4. DiNicolantonio JJ, Lavie CJ, Fares H, et al. L-carnitine in the secondary prevention of cardiovascular disease: systematic review and meta-analysis. *Mayo Clin Proc.* 2013;88(6): 544–551. doi: 10.1016/j.mayocp.2013.02.007

5. Zhao G, Zhang H, Wang Y, et al. Effects of levocarnitine on cardiac function, urinary albumin, hs-CRP, BNP, and troponin in patients with coronary heart disease and heart failure. *Hellenic J Cardiol.* 2020;61(2):99–102 doi: 10.1016/j.hjc.2018.08.006

6. Kinugasa Y, Sota T, Ishiga N, et al. L-carnitine supplementation in heart failure patients with preserved ejection fraction; a pilot study. *Geriatr Gerontol Int.* 2020;20(12):1244–1245. doi: 10.1111/ggi.14060

7. Dastan F, Talasaz AH, Mojtahedzadeh M, et al. Randomized trial of carnitine for the prevention of perioperative atrial fibrillation. *Semin Thorac Cardiovasc Surg.* 2018;30:7–13. doi: 10.1053/j.semtcvs.2017.08.006

8. Shingu Y, Katoh N, Ooka T, et al. L-carnitine supplementation for the prevention of postoperative atrial fibrillation in aortic valve surgery. *Gen Thorac Cardiovasc Surg.* 2021;69(11):1460–1466. doi: 10.1007/s11748-021-01616-2

9. Astashkin EI, Glezer MG. Cardiac lipotoxic effects of obesity. *Arterial Hypertension.* 2009;15(3):335–341. (In Russ.) doi: 10.18705/1607-419X-2009-15-3-335-341

10. Zhang Y, Fu Y, Jiang T, et al. Enhancing fatty acids oxidation via L-carnitine attenuates obesity-related atrial fibrillation and structural remodeling by activating AMPK signaling and alleviating cardiac lipotoxicity. *Front Pharmacol.* 2021;12:771940. doi: 10.3389/fphar.2021.771940

11. Muszyński P, Bonda TA. Mitochondrial dysfunction in atrial fibrillation-mechanisms and pharmacological interventions. *J Clin Med.* 2021;10(11):2385. doi: 10.3390/jcm10112385

12. Gasparova I, Kubatka P, Opatrilova R, et al. Perspectives and challenges of antioxidant therapy for atrial fibrillation. *Naunyn Schmiedebergs Arch Pharmacol*. 2017;390(1):1–14. doi: 10.1007/s00210-016-1320-9

13. Sciatti E, Lombardi C, Ravera A, et al.. Nutritional deficiency in patients with heart failure. *Nutrients.* 2016;8(7):442. doi: 10.3390/nu8070442

14. Song X, Qu H, Yang Z, et al. Efficacy and safety of L-carnitine treatment for chronic heart failure: a meta-analysis of randomized controlled trials. *Biomed Res Int.* 2017;2017:6274854. doi: 10.1155/2017/6274854

15. Trukhan DI. Role and location of L-carnitine in cytoprotection and correction of metabolic processes in patients with metabolic syndrome. *Medical Council.* 2017;(12):182–187. EDN: ZQTJYB doi: 10.21518/2079-701X-2017-12-182-187

СПИСОК ЛИТЕРАТУРЫ

1. Hindricks G., Potpara T., Dagres N., et al. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the task force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC // Europ Heart J. 2021. Vol. 42, N. 5. P. 373–498. doi: 10.1093/eurheartj/ehaa945

2. Trohman R.G., Huang H.D., Sharma P.S. Atrial fibrillation: primary prevention, secondary prevention, and prevention of thromboembolic complications: part 1 // Front Cardiovasc Med. 2023. Vol. 10. P. 1060030. doi: 10.3389/fcvm.2023.1060030

3. Vizzardi E., Curnis A., Latini M.G., et al. Risk factors for atrial fibrillation recurrence: a literature review // J Cardiovasc Med (Hagerstown). 2014. Vol. 15, N. 3. P. 235–253. doi: 10.2459/jcm.0b013e328358554b

4. DiNicolantonio J.J., Lavie C.J., Fares H., et al. L-carnitine in the secondary prevention of cardiovascular disease: systematic review and meta-analysis // Mayo Clin Proc. 2013. Vol. 88, N. 6. P. 544–551. doi: 10.1016/j.mayocp.2013.02.007

5. Zhao G., Zhang H., Wang Y., et al. Effects of levocarnitine on cardiac function, urinary albumin, hs-CRP, BNP, and troponin in patients with coronary heart disease and heart failure // Hellenic J Cardiol. 2020. Vol. 61, N. 2. P. 99–102 doi: 10.1016/j.hjc.2018.08.006

6. Kinugasa Y., Sota T., Ishiga N., et al. L-carnitine supplementation in heart failure patients with preserved ejection fraction; a pilot study // Geriatr Gerontol Int. 2020. Vol. 20, N. 12. P. 1244–1245. doi: 10.1111/ggi.14060

7. Dastan F., Talasaz A.H., Mojtahedzadeh M., et al. Randomized trial of carnitine for the prevention of perioperative atrial fibrillation // Semin Thorac Cardiovasc Surg. 2018. Vol. 30. P. 7–13. doi: 10.1053/j.semtcvs.2017.08.006

8. Shingu Y., Katoh N., Ooka T., et al. L-carnitine supplementation for the prevention of postoperative atrial fibrillation in aortic valve surgery // Gen Thorac Cardiovasc Surg. 2021. Vol. 69, N. 11. P. 1460–1466. doi: 10.1007/s11748-021-01616-2

9. Асташкин Е.И., Глезер М.Г. Липотоксические эффекты в сердце, наблюдаемые при ожирении // Артериальная гипертензия. 2009. Т. 15, № 3. С. 335–341. doi: 10.18705/1607-419X-2009-15-3-335-341

10. Zhang Y., Fu Y., Jiang T., et al. Enhancing fatty acids oxidation via L-carnitine attenuates obesity-related atrial fibrillation and structural remodeling by activating AMPK signaling and alleviating cardiac lipotoxicity // Front Pharmacol. 2021. Vol. 12. P. 771940. doi: 10.3389/fphar.2021.771940

11. Muszyński P., Bonda T.A. Mitochondrial dysfunction in atrial fibrillation-mechanisms and pharmacological interventions // J Clin Med. 2021. Vol. 10, N. 11. P. 2385. doi: 10.3390/jcm10112385

12. Gasparova I., Kubatka P., Opatrilova R., et al. Perspectives and challenges of antioxidant therapy for atrial fibrillation // Naunyn Schmiedebergs Arch Pharmacol. 2017. Vol. 390, N. 1. P. 1–14. doi: 10.1007/s00210-016-1320-9

13. Sciatti E., Lombardi C., Ravera A., et al. Nutritional deficiency in patients with heart failure // Nutrients. 2016. Vol. 8, N. 7. H. 442. doi: 10.3390/nu8070442

14. Song X., Qu H., Yang Z., et al. Efficacy and safety of L-carnitine treatment for chronic heart failure: a meta-analysis of randomized controlled trials // Biomed Res Int. 2017. Vol. 2017. P. 6274854. doi: 10.1155/2017/6274854

15. Трухан Д.И. Роль и место L-карнитина в цитопротекции и коррекции метаболических процессов у пациентов с метаболическим синдромом // Мед. совет. 2017. Т. 12. С. 182–7. EDN: ZQTJYB doi: 10.21518/2079-701X-2017-12-182-187

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DOI: https://doi.org/10.17816/cardar625555

First experience of treating patients with atrial fibrillation using thoracoscopic isolation with left atrial appendage excision in the North-Western State Medical University named after I.I. Mechnikov

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ABSTRACT

The given article describes the first experience of a thoracoscopic isolation of pulmonary veins and left atrial appendage excision in the North-Western State Medical University named after I.I. Mechnikov. The clinical case features a woman with a long history of paroxysmal atrial fibrillation, severe left atrium dilation, failure in a pace control drug therapy and no effect of radiofrequency catheter isolation of pulmonary veins.

Additionally, there outlined the advantages and the significance of employing the method of thoracoscopic ablation in patients with symptomatic paroxysmal and long-term persistent atrial fibrillation, — in case if antiarrythmic drugs and radiofrequency catheter ablation proved ineffective, as well as in patients with a long-term persistent atrial fibrillation along with a severe left atrium dilation.

Keywords: paroxysmal form of atrial fibrillation; thoracoscopic ablation; radiofrequency isolation of the pulmonary veins; excision of the left atrial appendage.

To cite this article

Yakovlev DA, Lenkin AI, Stepanova VV, Marinin VA, Petrov NV, Verendeev VK. First experience of treating patients with atrial fibrillation using thoracoscopic isolation with left atrial appendage excision in the North-Western State Medical University named after I.I. Mechnikov. *Cardiac Arrhythmias.* 2024;4(1):15–22. DOI: https://doi.org/10.17816/cardar625555

Received: 11.01.2024 **Accepted:** 06.03.2024 **Published online:** 06.05.2024

DOI: https://doi.org/10.17816/cardar625555

Первый опыт лечения пациентов с фибрилляцией предсердий методом торакоскопической деструкции аритмогенных зон сердца с резекцией ушка левого предсердия в ФГБОУ ВО СЗГМУ И.И. Мечникова

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АННОТАЦИЯ

Описан первый опыт применения в СЗГМУ им. И.И. Мечникова торакоскопической изоляции коллекторов легочных вен с резекцией ушка левого предсердия, на клиническом примере пациентки с длительным анамнезом пароксизмальной фибрилляции предсердий, выраженной дилатации левого предсердия, неэффекивностью медикаментозной терапии для контроля ритма и отсутствием эффекта от радиочастотной катетерной изоляции устьев легочных вен.

Обсуждается преимущества и важность использования методики торакоскопической абляции у пациентов с симптомной пароксизмальной фибрилляцией предсердий при неэффективности консервативной стратегии и радиочастотной катетерной абляции, а также у пациентов с длительноперсистирующей фибрилляцией предсердий, в том числе со значимой дилатацией левого предсердия.

Ключевые слова: пароксизмальная фибрилляция предсердий; торакоскопическая деструкция аритмогенных зон сердца; радиочастотная изоляция устьев легочных вен; резекция ушка левого предсердия.

Как цитировать

Яковлев Д.А., Ленькин А.И., Степанова В.В., Маринин В.А., Петров Н.В., Верендеев В.К. Первый опыт лечения пациентов с фибрилляцией предсердий методом торакоскопической деструкции аритмогенных зон сердца с резекцией ушка левого предсердия в ФГБОУ ВО СЗГМУ И.И. Мечникова // Cardiac Arrhythmias. 2024. Т. 4, № 1. С. 15–22. DOI: https://doi.org/10.17816/cardar625555

Рукопись получена: 11.01.2024 **Рукопись одобрена:** 06.03.2024 **Опубликована online:** 06.05.2024

BACKGROUND

Atrial fibrillation (AF) is currently one of the most frequently diagnosed forms of cardiac rhythm disorders, and the number of newly diagnosed AF cases is continuously increasing worldwide [1, 2]. The most significant complications of this arrhythmia include ischemic stroke, often incapacitating patients, and/or left ventricular dysfunction, which causes severe heart failure.

Basic approaches to AF treatment, aimed at attempting to restore sinus rhythm (SR), include drug therapy, which involves the control of heart rhythm or rate, or an endovascular strategy, which consists mainly of transvenous catheter isolation of the pulmonary vein ostia (IPVO), as the main AF triggers using exposure to high-frequency current, that is, radiofrequency isolation (RFA) of the IPVO. The latter method is a proven and very effective treatment of paroxysmal AF (PAF), making it the first-line treatment for PAF. The absence of PAF within 1 year after the procedure is reported in 80% of patients with PAF [3].

Unfortunately, catheter isolation of the PVs is not always able to eliminate arrhythmia, and if it returns, catheter procedures required repeatedly. In addition, the probability of SR restoration and the effectiveness of its maintenance are also reduced in patients with chronic PAF. One of the modern methods of treating these patients is minimally invasive surgical intervention, involving thoracoscopic epicardial destruction of the arrhythmogenic zones of the heart with resection (deactivation) of the left atrial appendage (LAA) or thoracoscopic radiofrequency ablation (TRFA) [4, 5]. This surgical method involves endoscopic bilateral antral isolation of the left and right PVs (RPVs) and drawing ablation lines along the roof and posterior wall of the left atrium to form a closed contour, a box lesion set. LAA amputation is performed to prevent potential cardioembolic complications, which is caused by the extremely high risk of blood clots (up to 90%) in this cardiac structure in AF and their subsequent migration into the vessels of the systemic circulation [6]. The LAA is resected using a special suturing device or removed from the bloodstream by clipping. According to the European Clinical Guidelines for the Diagnostics and Treatment of AF of 2020, thoracoscopic epicardial ablation has a class IIa indication in patients with failed previous catheter ablations and in symptomatic cases with chronic PAF refractory to drug therapy [7].

DESCRIPTION OF A CLINICAL CASE

Patient D (female, aged 63 years) presented for the surgical treatment of complex cardiac arrhythmias and electrical stimulation to the Department of Cardiac Surgery, Peter the Great Clinic of the Mechnikov North Western State Medical University, because of frequent episodes of "heart failure", shortness of breath, and associated general weakness, which significantly reduced her quality of life. The medical history revealed PAF for approximately 10 years, for which she received protective antiarrhythmic therapy with one or another antiarrhythmic drug for 7 years, including metoprolol, bisoprolol, and sotahexal. However, because of the ineffectiveness and an increase in the number of attacks up to 4–6 times a week, in 2018, she was referred to the Peter the Great Clinic for catheter RFA of the PVO. In 2018, RFA of the PVO was performed using the CARTO 3 non-fluoroscopic navigation system (Biosense Webster, Inc., USA). Anatomical mapping of the left atrium was performed, according to which the LA volume significantly exceeded the echocardiography values (250 vs 178 mL). Using a THERMOCOOL SMARTTOUCH SF ablation catheter (Biosense Webster) with contact force measurement, ablation effects were applied to isolate the right and left PV collectors. PV isolation was monitored using a LASSO catheter (Biosense Webster). An acute effect was obtained in the form of PV isolation. The patient was discharged with β-blocker therapy, angiotensin-converting-enzyme inhibitors, and new oral anticoagulants. However, a year after the surgery, AF began to recur initially no more than once every few months and by the time of re-application up to several attacks weekly. During the examination, according to 24-h Holter ECG monitoring (Fig. 1), PAFs were recorded with a total duration of approximately 5 h, with a heart rate of 48–169 beats per minute. After discussion with arrhythmologists, due to the presence of clinical symptoms, taking into account the disease duration (10 years of PAF), and significant dilatation of the LA, hospitalization was recommended for thoracoscopic destruction of the arrhythmogenic zones of the heart and LAA resection.

The principal diagnosis was made preoperatively (hypertension II, risk of cardiovascular complications 3, PAF, EHRA IIb, condition post-catheter RF IPVO (2018)). Complications were NYHA grade II heart failure with preserved ejection fraction, CHA2DS2-VASc of 3, and HAS-BLED of 2. Concomitant diseases were type II diabetes mellitus, which was managed by oral antihyperglycemic therapy and grade I obesity.

In addition to the routine preoperative examination, which included laboratory and clinical instrumental methods, to rule out anomalies in the entry of the PVs into the LA, assess the size and volume of the left atrium and LAA, and exclude the presence of a thrombus in the LAA, in the preoperative period (48 h before intervention), the patient underwent multislice contrast computed tomography (MSCT)

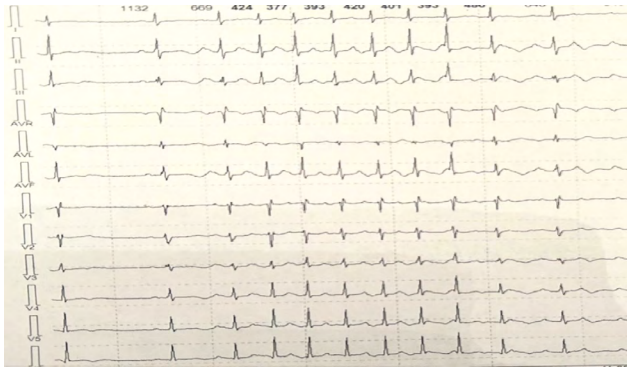

Fig. 1. 24-hour ECG monitor (50 mm/s) of patient D in the presence of paroxysmal atrial fibrillation
Рис. 1. Суточное электрокардиографическое мониторирование (50 мм/с) пациентки Д. на фоне пароксизма фибрилляции предсердий

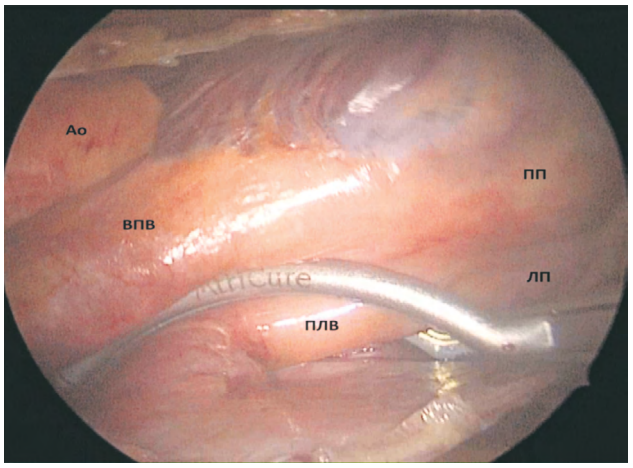

Fig. 2. Stage of the thoracoscopic isolation of the pulmonary veins with a bipolar clamp electrode. Ao — aorta; ЛП — left atrium; ПП — right atrium; ПЛВ — right pulmonary veins; ВПВ — superior vena cava
Рис. 2. Этап торакоскопической изоляции легочных вен биполярным зажимом — электродом. ПП — правое предсердие; Ao — аорта; ВПВ — верхняя полая вена; ЛП — левое предсердие; ПЛВ — правые легочные вены

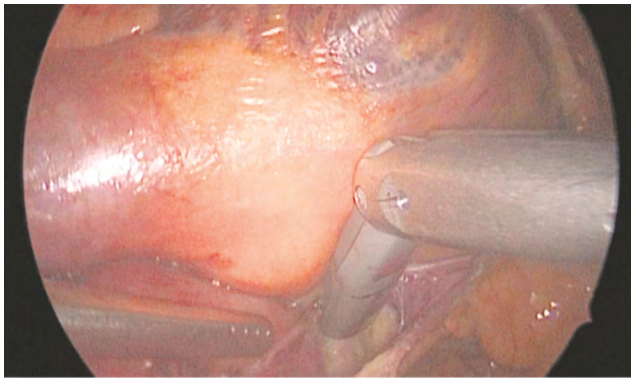

Fig. 3. Stage of ablation with a unidirectional bipolar electrode of the ganglion plexuses in the right pulmonary veins ostium
Рис. 3. Этап абляции однонаправленным биполярным электродом ганглионарных сплетений в области устьев правых легочных вен

of the heart. According to MSCT data, the LA volume was 189 mL, measuring 70 × 45 × 60 mm, the RPVs enter into the atrium as a single collector, whereas the left PVs have a common arrangement. The LAA measured 37 × 17 mm, and no blood clots were detected in the cavity. Transthoracic echocardiography and coronary angiography (performed to rule out significant stenoses of the coronary arteries) did not reveal any additional pathology. Two days before surgery, the patient discontinued taking indirect anticoagulants and started taking low-molecular-weight heparins in an adequate dosage.

The surgery was performed in May 2021. Under endotracheal anesthesia with selective one-lung ventilation, thoracoscopic approach to the right hemisphere was made through three separate punctures in the chest.

After opening the oblique and transverse sinuses of the pericardium, antral isolation of the RPVs was subsequently performed using a special bipolar Isolator Synerg Clamp (AtriCure Inc., USA) at 10 radiofrequency impacts, with transmural control (Fig. 2).

Moreover, using a bipolar unidirectional electrode, an Isolator RF pen (AtriCure Inc.) from the same access, continuous epicardial ablation lines were applied along the LA roof and base. The upper line was drawn to the LAA from the right superior PV, through the transverse sinus, and the lower line was drawn from the right inferior PV to the left inferior PV, along the LA inferior wall. The autonomic ganglion plexuses, as part of the cardiac autonomic nervous system, can be triggers of pathological excitation outside the PVs, triggering AF episodes [8]. They were also subjected to ablation effects, being located in the subepicardial fatty tissue, particularly in the area of the RPV confluence and Waterston's groove (Fig. 3).

Then, the surgery proceeded from the left-sided approach, with the same sequence of actions, namely, tenfold isolation of the antral segments of the left PVs with a bipolar clamp, with transmural control, and further revision, under visual control, of the lines of the epicardial ablation of the left atrium (posterior wall and roof), with the creation of a closed circuit along box lesion type (Fig. 4).

The ligament of Marshall, located in the epicardial fat fold between the left PVs and the LAA, is also easily accessible from this approach, which is also a potential arrhythmogenic substrate. In our case, it was also subjected to ablation.

The final stage of surgical treatment was LAA resection, which was performed using a special endoscopic cutting and suturing device, the ENDO GIA stapler (Tyco Healthcare Group, North Haven, USA). After installing drains in both pleural cavities and completing the surgery, the patient was

transported to the resuscitation and intensive care unit for further case follow-up.

The patient was discharged on day 7 after surgery in satisfactory condition. For the first 3 months, antiarrhythmic therapy for such patients involves the intake of amiodarone (100 mg/day), followed by 24-h monitoring and discontinuing the drug if SR persists.

For 2.5 years after the surgery, the patient subjectively feels well, no PAFs were noted either clinically or according to 24-h ECG monitoring while taking bisoprolol 5 mg/day, fosinopril 20 mg/day, and xarelto 20 mg/day.

DISCUSSION

TRFA, supplemented by LAA resection, has been known since 2005, after R.K. Wolf et al. [9] published their results of bilateral epicardial PV ablation for AF with LAA removal through a minimally invasive approach with video-assisted support. The undoubted advantage of thoracoscopic RFA in comparison with the maze surgery introduced into clinical practice by J.L. Cox is significantly associated with less surgical aggression and absence of the need to use cardiopulmonary bypass with cardiac arrest, which can have a decisive influence on the results of treatment in patients with severe comorbid pathology [10, 11]. Compared with open surgery, thoracoscopic ablation is less traumatic and has fewer perioperative complications and shorter hospitalization periods. Compared with endovascular PV isolation, according to recent studies, TRFA is more traumatic but demonstrates more optimistic results in maintaining SR in patients with PAF and those referred for repeated catheter intervention who are resistant to drug therapy [12, 13].

The presented clinical case of the treatment of a patient with chronic PAF and a previous history of catheter-based IPVO is one of the first cases of surgical treatment of such patients at the Mechnikov North Western State Medical University by thoracoscopic destruction of arrhythmogenic zones. To date, with surgical treatment of complex cardiac arrhythmias and electrical stimulation in the Department of Cardiac Surgery, a total of 23 such surgeries have been performed over 2.5 years. The main results are still subject to serious analysis; howeve, the first findings can already be shared.

All cases referred for TRFA were previously discussed by a team of doctors, including an arrhythmologist, an anesthesiologist, and a cardiac surgeon. The indications considered the absolute lack of prospects for drug antiarrhythmic therapy and catheter intervention. Only 3 out of 23 patients had not previously undergone endovascular ablation. These were symptomatic patients with chronic PAF

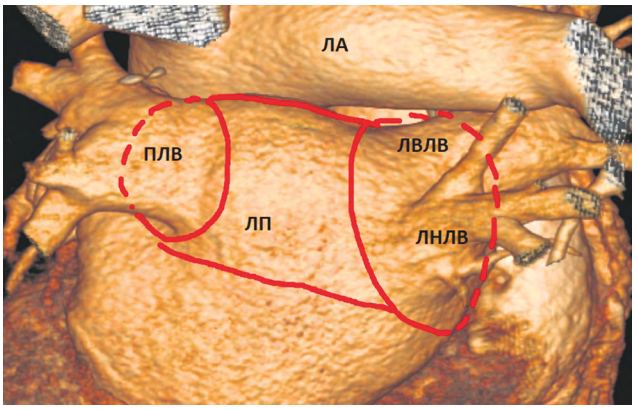

Fig. 4. Formation of ablation lines during thoracoscopic RFA: ПЛВ — right pulmonary veins (single collector); ЛВЛВ — left superior pulmonary vein; ЛНЛВ — left inferior pulmonary vein; ЛП — left atrium; ЛА — pulmonary artery Ablation lines are indicated in red

Рис. 4. Формирование линий абляции при выполнении торакоскопической радиочастотной абляции: ПЛВ — правые легочные вены (единым коллектором); ЛВЛВ — левая верхняя легочная вена; ЛНЛВ — левая нижняя легочная вена; ЛП — левое предсердие; ЛА — легочная артерия. Красным цветом обозначены линии абляции

and increased LA sizes, whose treatment with catheter RFA was considered inappropriate. The maximum duration of AF noted in patients who underwent surgery was 15 years, with a maximum of 4 catheter ablations in the history.

Basically, surgery is performed on patients who had undergone one or more transvenous catheter RFA, and the pericardium tissues damaged by inflammation were intraoperatively revealed, which somewhat complicates the main stage and lengthens the surgery, particularly in the initial stages. This may have occurred because two patients required conversion to sternotomy (in one case with the use of cardiopulmonary bypass) due to bleeding. In case 1, it could be caused by damage to the right superior PV, and in case 2 (in an older man) it could be caused by LA damage. In both cases, bleeding was stopped, and the rhythm was restored intraoperatively.

In two patients, TRFA was abandoned during the surgical intervention because at the initial stage dense adhesions were noted in the pericardial cavity. Their presence is a contraindication for thoracoscopic surgery because of the critical risk of fatal bleeding. Unfortunately, neither MSCT of the heart with contrast nor preoperative transthoracic echocardiography could predict the presence of adhesive process in the pericardium. Among other contraindications to TRFA, the following should be noted: (a) a history of open heart surgery (for the same reason, the formation of adhesions in the pericardium), (b) a thrombus in the LAA (due to the high risk of its dislocation during the intervention), and (c) the patient's inability to tolerate one-lung ventilation

(concomitant pulmonary pathology causing severe respiratory failure).

According to the primary analysis, the majority of the patients who underwent surgery maintained SR during the first 6 months after TRFA, which corresponds to the main data published in the literature [14]. Despite the first optimistic results, patient follow-up will allow for a more objective study. Recently, an increasing number of studies have indicated the need for a combined hybrid approach (catheter and thoracoscopic) in the treatment of complex groups of patients with chronic PAF resistant to drug and endovascular treatment [15, 16]. Some of the patients from our group who underwent surgery will also require this method.

CONCLUSIONS

This study presents a clinical case of the successful thoracoscopic destruction of the arrhythmogenic zones of the heart with LAA resection and ablation of the ligament of Marshall in a patient with chronic AF (paroxysmal AF for 10 years) and severe LA dilatation that was unresponsive to drug therapy and catheter IPVO first performed at the Mechnikov North Western State Medical University. This case demonstrates the consistency of the method and good prospects for its practical application in the treatment of this category of patients.

ADDITIONAL INFORMATION

Ethics approval. Written consent was obtained from the patient's legal representatives for the publication of medical information and images.

Author contribution. All of the authors have made significant contributions to the concept development and the article preparation. All authors were directly involved in the clinical case presented and the treatment method discussed; the final article version was read and approved before publication.

Each author's contribution. D.A. Yakovlev — direct surgical interventions, data gathering and its analysis, article conception and text writing; A.I. Lenkyn — Anaesthetic support of surgical interventions, analysis of the received data, text writing; V.V. Stepanova — direct performance of catheter ablation for atrial fibrillation presented as a clinical example, development of the article concept, text writing, gathering of statistical material; V.A. Marinin — participation in the treatment process, development of the article concept, final editing; N.V. Petrov — practical participation in the treatment process, materials processing and design research; V.K. Verendeev — design research, literature review, gathering and processing of the material.

Competing interests. The authors declare that they have no competing interests.

Funding source. This study was not supported by any external sources of funding.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Заключение этического комитета. Получено письменное согласие законных представителей пациента на публикацию медицинских данных и фотографий.

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, и подготовку статьи, принимали непосредственное участие в представленном в качестве клинического случая и обсуждаемом методе лечения, прочли и одобрили финальную версию перед публикацией.

Вклад каждого автора. Д.А. Яковлев — непосредственное исполнение хирургических вмешательств, сбор и анализ полученных данных, разработка концепции статьи и написание текста; А.И. Ленькин — анестезиологическое обеспечение вмешательств, анализ полученных данных, написание текста; В.В. Степанова — непосредственное выполнение операции катетерной радиочастотной абляции, представленной в качестве клинического примера, разработка концепции статьи, написание текста, сбор статистического материала; В.А. Маринин — участие в лечебном процессе, разработка концепции, внесение окончательной правки; Н.В. Петров — практическое участие в лечебном процессе, обработка материалов и дизайн исследования; В.К. Верендеев — дизайн исследования, обзор литературы, сбор и обработка материалов.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

REFERENCES

1. Ariss R, Minhas A, Patel N, et al. Contemporary trends and in-hospital outcomes of catheter and stand-alone surgical ablation of atrial fibrillation. *Europace*. 2022;24(2):218–225. doi: 10.1093/europace/euab198

2. Belluschi I, Lapennaa E, Carino D, et al. Long-term results of thoracoscopic ablation of paroxysmal atrial fibrillation: is the glass half full or half empty? *Eur J Cardiothorac Surg*. 2021;60(4):850–856. doi: 10.1093/ejcts/ezab138

3. Haldar S, Khan H, Boyalla V, et al. Catheter ablation vs. thoracoscopic surgical ablation in long-standing persistent atrial fibrillation: CASA-AF randomized controlled trial. *Eur Heart J*. 2020;41(47):4471–4480. doi: 10.1093/eurheartj/ehaa658

4. Vos L, Bentala M, Geuzebroek G, et al. Long-term outcome after totally thoracoscopic ablation foratrial fibrillation. *J Cardiovasc Electrophysiol*. 2020;3(1):40–45. doi: 10.1111/jce.14267

5. Kubota H, Ohtsuka T, Ninomiya M, et al. Thoracoscopic infrared ablation to create a box lesion as a treatment for atrial fibrillation. *J Cardiothorac Surg*. 2022;17(1):1. doi: 10.1186/s13019-021-01750-1

6. Buqing Ni, Zidun W, Weidong G, et al. Thoracoscopic Left Atrial Appendage Excision Plus Ablation for Atrial Fibrillation to Prevent stroke. *Semin Thorac Cardiovasc Surg*. 2021;33(1):61–67. doi: 10.1053/j.semtcvs.2020.06.041

7. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J*. 2021;42(5): 373–498. doi: 10.1093/eurheartj/ehaa612

8. Krivosheev Y, Bashta D, Simonyan A, et al. Ablation of ganglionic plexuses combined with pulmonary vein isolation after drug testing of «hidden» atriovenous conduction with exclusion of extrapulmonary triggers in patients with paroxysmal atrial fibrillation. *Patologiya krovoobrashcheniya i kardiokhirurgiya*. 2018;22(3):25–38. (In Russ.) EDN: VLVAWO doi: 10.21688-1681-3472-2018-3-25-38

9. Wolf R, Schneeberger E, Osterday R, et al. Video-assisted bilateral pulmonary vein isolation and left atrial appendage exclusion for atrial fibrillation. *J Thorac Cardiovasc Surg*. 2005;130(3):797–802. doi: 10.1016/j.jtcvs.2005.03.041

10. Kwon HJ, Jeong D, Park SJ, et al. Long-term outcome of totally thoracoscopic surgical ablation in atrial fibrillation: A single-center experience. *Int J Cardiol Heart Vasc*. 2021;36:100861. doi: 10.1016/j.ijcha.2021.100861

11. On YK, Jeong DS. Updates in hybrid AF ablation: a hybrid approach to surgical epicardial ablation and cather endocardial ablation in persistent atrial fibrillation. *Int J Arrhythm*. 2022;23(5):1–9. doi: 10.1186/s42444-021-00056-6

12. Revishvili A, Taimasova I, Artyukhina E, et al. Mid-term outcomes of thoracoscopic and hybrid therapy of atrial fibrillation. *Journal of Arrhythmology*. 2021;28(3):5–12. (In Russ.) EDN: PVNCAU doi: 10.35336/VA-2021-3-5-12

13. Petersen J, Pecha S. What we need to do so that the glass is more than half full in stand-alone thoracoscopic ablation. *Eur J Cardiothorac Surg*. 2021;60(4):857–858. doi: 10.1093/ejcts/ezab351

14. Lyashenko V, Ivanchenko A, Postol A, et al. Recurrence of arrhythmias after thoracoscopic MAZE procedure. *Cardiac Arrhythmias*. 2023;3(2):5–16. doi: 10.17816/cardar492331

15. Pong T, Shah R, Carlton C, et al. Hybrid ablation for atrial fibrillation: safety & efficacy of unilateral epicardial access. *Semin Thorac Cardiovasc Surg*. 2023;35(2):277–286. doi: 10.1053/j.semtcvs.2022.03.003

16. Kim J, Jeong D, Kwon HJ, et al. Effectiveness of the early staged hybrid approach for treatment of symptomatic atrial fibrillation: the electrophysiology study could be deferred? *J Korean Med Sci*. 2021;36(43):e276. doi: 10.3346/jkms.2021.36.e276

СПИСОК ЛИТЕРАТУРЫ

1. Ariss R., Minhas A., Patel N., et al. Contemporary trends and in-hospital outcomes of catheter and stand-alone surgical ablation of atrial fibrillation // Europace. 2022. Vol. 24, No. 2. P. 218–225. doi: 10.1093/europace/euab198

2. Belluschi I., Lapennaa E., Carino D., et al. Long-term results of thoracoscopic ablation of paroxysmal atrial fibrillation: is the glass half full or half empty? // Eur J Cardiothorac Surg. 2021. Vol. 60, No. 4. P. 850–856. doi: 10.1093/ejcts/ezab138

3. Haldar S., Khan H., Boyalla V., et al. Catheter ablation vs. thoracoscopic surgical ablation in long-standing persistent atrial fibrillation: CASA-AF randomized controlled trial // Eur Heart J. 2020. Vol. 41, No. 47. P. 4471–4480. doi: 10.1093/eurheartj/ehaa658

4. Vos L., Bentala M., Geuzebroek G., et al. Long-term outcome after totally thoracoscopic ablation foratrial fibrillation // J Cardiovasc Electrophysiol. 2020. Vol. 3, No. 1. P. 40–45. doi: 10.1111/jce.14267

5. Kubota H., Ohtsuka T., Ninomiya M., et al. Thoracoscopic infrared ablation to create a box lesion as a treatment for atrial fibrillation // J Cardiothorac Surg. 2022. Vol. 17, No. 1. P. 1. doi: 10.1186/s13019-021-01750-1

6. Buqing Ni., Zidun W., Weidong G., et al. Thoracoscopic Left Atrial Appendage Excision Plus Ablation for Atrial Fibrillation to Prevent stroke // Semin Thorac Cardiovasc Surg. 2021. Vol. 33, No. 1. P. 61–67. doi: 10.1053/j.semtcvs.2020.06.041

7. Hindricks G., Potpara T., Dagres N., et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC // Eur Heart J. 2021. Vol. 42, No. 5. P. 373–498. doi: 10.1093/eurheartj/ehaa612

8. Кривошеев Ю., Башта Д., Симонян А., и др. Аблация ганглионарных сплетений в сочетании с изоляцией легочных вен после медикаментозного тестирования «скрытого» атриовенозного проведения с исключением внелегочных триггеров у пациентов с пароксизмальной формой фибрилляции предсердий // Патология кровообращения и кардиохирургия. 2018. Т. 22, № 3. С. 25–38. EDN: VLVAWO doi: 10.21688-1681-3472-2018-3-25-38

9. Wolf R., Schneeberger E., Osterday R., et al. Video-assisted bilateral pulmonary vein isolation and left atrial appendage exclusion for atrial fibrillation // J Thorac Cardiovasc Surg. 2005. Vol. 130, No. 3. P. 797–802. doi: 10.1016/j.jtcvs.2005.03.041

10. Kwon HJ., Jeong D., Park SJ., et al. Long-term outcome of totally thoracoscopic surgical ablation in atrial fibrillation: A single-center experience // Int J Cardiol Heart Vasc. 2021. Vol. 36. P. 100861. doi: 10.1016/j.ijcha.2021.100861

11. On Y.K., Jeong D.S. Updates in hybrid AF ablation: a hybrid approach to surgical epicardial ablation and cather endocardial ablation in persistent atrial fibrillation // Int J Arrhythm. 2022. Vol. 23, No. 5. P. 1–9. doi: 10.1186/s42444-021-00056-6

12. Ревишвили А., Таймасова И., Артюхина Е., и др. Среднесрочные результаты торакоскопического и гибридного лечения фибрилляции предсердий // Вестник аритмологии. 2021. Т. 28, № 3(105). С. 5–12. EDN: PVNCAU doi: 10.35336/VA-2021-3-5-12

13. Petersen J., Pecha S. What we need to do so that the glass is more than half full in stand-alone thoracoscopic ablation // Eur J Cardiothorac Surg. 2021. Vol. 60, No. 4. P. 857–858. doi: 10.1093/ejcts/ezab351

14. Lyashenko V., Ivanchenko A., Postol A., et al. Recurrence of arrhythmias after thoracoscopic MAZE procedure // Cardiac Arrhythmias. 2023. Vol. 3, No. 2. P. 5–16. doi: 10.17816/cardar492331

15. Pong T., Shah R., Carlton C., et al. Hybrid ablation for atrial fibrillation: safety & efficacy of unilateral epicardial access // Semin Thorac Cardiovasc Surg. 2023. Vol. 35, No. 2. P. 277–286. doi: 10.1053/j.semtcvs.2022.03.003

16. Kim J., Jeong D., Kwon HJ., et al. Effectiveness of the early staged hybrid approach for treatment of symptomatic atrial fibrillation: the electrophysiology study could be deferred? // J Korean Med Sci. 2021. Vol. 36, No. 43. P. e276. doi: 10.3346/jkms.2021.36.e276

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DOI: https://doi.org/10.17816/cardar626655

Obstructive sleep apnea as a potentially reversible cause of nighttime bradyarrhythmias. Clinical case

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ABSTRACT

Obstructive sleep apnea syndrome is a common condition, especially among obese patients. Patients with obstructive sleep apnea syndrome have an increased risk of developing arterial hypertension and cardiovascular events, as well as cardiac arrhythmias, which include reflexively occurring bradyarrhythmias and episodes of asystole at night. Treatment of obstructive sleep apnea syndrome leads to an improvement in the patient's quality of life and also reduces cardiovascular risk and eliminates associated bradyarrhythmias during night sleep.

Keywords: obstructive sleep apnea syndrome; respiratory therapy; non-invasive ventilation; bradyarrhythmias.

To cite this article

Kucherenko NG, Bebekh AN, Umarova IA, Abukova AR. Obstructive sleep apnea as a potentially reversible cause of nighttime bradyarrhythmias. Clinical case. *Cardiac Arrhythmias.* 2024;4(1):23–30. DOI: https://doi.org/10.17816/cardar626655

Received: 08.02.2024 **Accepted:** 10.03.2024 **Published online:** 06.05.2024

DOI: https://doi.org/10.17816/cardar626655

Синдром обструктивного апноэ сна как потенциально обратимая причина брадиаритмий в ночные часы. Клинический случай

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АННОТАЦИЯ

Синдром обструктивного апноэ сна является распространенным заболеванием, особенно среди больных ожирением. У пациентов с синдром обструктивного апноэ сна повышаются риски развития артериальной гипертензии и сердечно-сосудистых событий, чаще возникают нарушения ритма сердца, к которым относятся в том числе рефлекторно возникающие брадиаритмии и эпизоды асистолии в ночные часы. Лечение синдрома обструктивного апноэ сна не только приводит к улучшению качества жизни пациента, но и позволяет снизить сердечно-сосудистые риски, а также устранить ассоциированные с ним брадиаритмии во время ночного сна.

Ключевые слова: синдром обструктивного апноэ сна; респираторная терапия; неинвазивная вентиляция легких; брадиаритмии.

Как цитировать

Кучеренко Н.Г., Бебех А.Н., Умарова И.А., Абукова А.Р. Синдром обструктивного апноэ сна как потенциально обратимая причина брадиаритмий в ночные часы. Клинический случай // Cardiac Arrhythmias. 2024. Т. 4, № 1. С. 23–30. DOI: https://doi.org/10.17816/cardar626655

Рукопись получена: 08.02.2024 **Рукопись одобрена:** 10.03.2024 **Опубликована online:** 06.05.2024

INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is characterized by recurrent episodes of airway obstruction at the pharyngeal level, cessation of pulmonary ventilation with persistent respiratory effort, decreased blood oxygen saturation, gross sleep fragmentation, and excessive daytime sleepiness [1].

The estimated prevalence of OSAS in individuals aged >30 years is between 5% and 7%. This condition affects approximately one billion people worldwide, with OSAS risk being correlated with body mass index (BMI) [2, 3]. OSAS is more prevalent in middle-aged and older men and postmenopausal women, and central obesity is the most significant and potentially modifiable risk factor for its development. Many patients with BMI ⩾ 30 kg/m^2 suffer from OSAS [4]. The dynamic airway lumen obstruction in OSAS can be caused by anatomical and/or functional factors. The most prevalent cause is the narrowing of the upper airway lumen associated with adipose tissue accumulation, which establishes the conditions for their collapse and obstruction during sleep [5, 6, 7].

The severity of OSAS is typically quantified by the apnea–hypopnea index (AHI). Diagnostic procedures (nocturnal cardiorespiratory/respiratory monitoring and polysomnography) during sleep involve assessing the frequency of obstructive events. Apnea is defined as the cessation of airflow for at least 10 s. Hypopnea is defined as a decrease in airflow of at least 30% for at least 10 s, accompanied by a reduction in oxygen saturation of at least 4%. According to the American Academy of Sleep Medicine, OSAS can be classified according to the AHI, which defines 5–15/h mild OSAS, 15–30/h as moderate, and ⩾30/h as severe [8].

Pathological daytime sleepiness, which may not always be perceived by the patient and is often described as fatigue, lassitude, or decreased energy, is a significant and prevalent consequence of sleep disturbance. Sleepiness leads to decreased social engagement and cognitive abilities and mediates the risk of accidents and motor vehicle accidents. Up to 20% of traffic accidents are thought to be related to falling asleep at the wheel. In clinical settings, OSAS may present with various additional symptoms, although none are diagnostic [4].

An increase in cardiovascular risks is another unfavorable consequence of sleep apnea. Consequently, a pathogenic link between OSAS and several cardiovascular diseases, including arterial hypertension (AH), heart rhythm disorders, heart failure, ischemic heart disease, and acute cerebrovascular disorders, has been established. OSAS can be a cause of pulmonary hypertension and plays a role in the development of metabolic syndrome and insulin resistance [9].

AH is a common comorbidity of OSAS. In approximately half of patients with OSAS, AH is accompanied by peculiarities in the blood pressure profile, including non-reduction or an increase in blood pressure at night. In >80% of cases, AH that is resistant to therapy with ⩾3 drugs is accompanied by OSAS.

Hypoxemia, autonomic dysregulation, and changes in intrathoracic pressure can lead to structural and functional remodeling of the atria and fibrosis development. This process increases the risk of cardiac rhythm disturbances, which are more frequent in individuals with more severe OSAS and hypoxemia. The mechanisms underlying arrhythmogenesis are based on changes in myocardial automatism, trigger activity, and re-entry mechanisms [10]. Abnormal automaticity can be associated with multiple factors, such as changes in sympathetic and parasympathetic tone, acid–base balance, and electrolyte disturbances at the membrane and submembrane levels [11]. OSAS causes repetitive, cyclic changes in sympathetic tone. During apnea attacks, an increase in the tone of the vagus nerve results in bradycardia, which is then followed by a sympathetic discharge caused by hypoxemia and hypercapnia. This, in turn, contributes to the formation of arrhythmias due to beta-adrenergic stimulation [12, 13].

OSAS increases the risk of atrial fibrillation by four times [14]. Arrhythmogenic effects of OSAS are also realized in the increased risk of atrial fibrillation recurrence after cardioversion, a twofold increased risk of recurrence after radiofrequency ablation, and decreased effectiveness of antiarrhythmic therapy [15–17].

OSAS is detected in 68% of patients with sleep-related bradyarrhythmias [20]. The most frequently recorded features at night are sinoatrial block, grade II atrioventricular block, ventricular extrasystole, and unstable ventricular tachycardia. At night, the incidence of arrhythmias can reach 50% [18–20]. The cyclic nature of heart block in OSAS is attributed to the occurrence of apnea episodes [21–25]. Nevertheless, bradyarrhythmias related to OSAS frequently do not indicate heart diseases and are reflexive. This occurs during ineffective respiratory efforts when hypoxemia in the absence of pulmonary ventilation causes bradycardia. In such cases, bradyarrhythmias manifest solely during sleep and dissipate following OSAS therapy [26]. According to C. Zwillich et al., the duration and severity of bradycardia correlate with the degree of hypoxemia during apnea [26].

H.F. Becker et al. demonstrated a resolution or reduction in the frequency of grade II–III atrioventricular blockade

and/or sinus node arrest with the effective treatment of OSAS [27].

Non-invasive ventilation (NIV), an effective method of respiratory support, involves creating positive airway pressure using nasal, oronasal, or face masks [28, 29]. The choice of the NIV regimen depends on the nature of respiratory disorders. Continuous positive airway pressure (CPAP) therapy is an NIV with continuous positive airway pressure throughout the respiratory cycle (inhalation and exhalation). CPAP therapy primarily maintains upper airway patency during sleep and prevents airway collapse. This treatment is considered the "gold standard" for treating OSAS. CPAP therapy is extremely effective in eliminating apnea and hypopnea. Although various treatment options are available for this condition, positive airway pressure therapy remains the mainstay of OSAS treatment since its introduction into practice in 1981 [30, 31]. CPAP therapy is initiated only after instrumental confirmation of the disease (mainly in moderate and severe OSAS). An individualized interface should be selected for comfort, and different masks may be better suited for people with different facial structures. To be effective, CPAP therapy should be used for at least 4 h per day for at least five nights per week. Currently, both the CPAP mode (which employs individually selected constant pressure) and the automatic positive airway pressure (APAP, auto-CPAP, an automated mode that employs algorithms to increase the pressure when episodes of sleep apnea are registered and to decrease it when they are absent) [28, 32].

CPAP therapy for OSAS results in clinically significant improvements in daytime sleepiness, ability to maintain wakefulness, and sleep-related quality of life indicators. CPAP therapy improves the AH course, including a reduction in blood pressure in resistant AH. A reduction in the risk of cardiovascular events was also established [28]. Continuous positive pressure NIV eliminates nocturnal bradyarrhythmias, which points to OSAS as the cause of these disorders [26, 27, 33].

CLINICAL CASE

Patient N., a 54-year-old man, presented with complaints of dyspnea during moderate physical activity and an associated decrease in tolerance to physical activity, daytime sleepiness, difficulty in nasal breathing, and snoring, which was corroborated by others. The patient also reported episodes of pressing sensations in the chest lasting up to 2 min during exercise and subsiding at rest. He attributed the appearance and progression of these symptoms to an increase in body weight over several years.

The medical history included hypertension, atherosclerosis of the brachiocephalic arteries with hemodynamically insignificant (35%–40%) stenosis of the common carotid arteries on both sides, grade 3 obesity, liver steatosis, and dyslipidemia. The patient was consistently taking antihypertensive drugs (sartans, diuretics, and calcium blockers).

The outpatient daily electrocardiogram (ECG) Holter monitoring revealed 33 pauses of >2000 ms, with a maximum duration of 3646 s, in sinus rhythm, which occurred during nocturnal sleep. No atrioventricular conduction disorder was identified. In addition, episodes of accelerated supraventricular rhythm with a heart rate of 75 beats/min were observed following a pause of 2114 ms during sleep. The calculated circadian index was 1.4. A total of 584 single supraventricular extrasystoles were observed, in addition to 9 paired and 12 group extrasystoles. The examination also revealed single polymorphic polytopic ventricular extrasystoles (48 in total), including insertion and bigeminy type. One paired monomorphic ventricular extrasystole was observed. No clinically significant repolarization disorders were observed at rest or during exercise.

The patient was referred to the L.G. Sokolov North-West District Research and Clinical Center of the Federal Medical and Biological Agency for further examination, including the exclusion of nocturnal respiratory disorders.

Upon examination, the patient was found to be in a satisfactory condition. The patient was conscious and alert. The skin had a normal color and moderate moisture. The patient exhibited excessive subcutaneous adipose tissue development, with a height of 1.72 m, body weight of 134 kg, and body mass index of 45.3 kg/m^2. The abdominal region exhibited characteristics of obesity. His pulse was rhythmic and satisfactory in terms of filling and tension, with a rate of 72 beats per minute, and his blood pressure was 150/100 mm Hg. The heart tones were muffled. Both chest sides were involved in breathing. The percussion sound was clear pulmonary. Auscultation revealed vesicular breathing, with no rales. The frequency of respiratory movements was 18/min. The abdominal volume increased because of subcutaneous adipose tissue accumulation and was soft and painless. There was no edema.

In the therapeutic department, the patient underwent respiratory monitoring at night. The results indicated severe OSAS. The AHI, desaturations index, average blood oxygen saturation, and minimum were 64.6/h, 62.3/h, 89%, and 69%, respectively.

Based on the findings of the respiratory study conducted at night, a course of respiratory therapy for OSAS was initiated. The patient underwent CPAP therapy at night using a Prisma 20A device (Loewenstein Medical (Weinmann), Germany) in the APAP mode through the oronasal mask. The patient reported a notable improvement in sleep quality,

reduction in daytime sleepiness, and enhancement in general well-being. The AHI during CPAP therapy was 5/h.

Daily Holter ECG monitoring of the ECG confirmed the absence of signs of conduction disturbances and pauses in respiratory therapy for OSAS. Sinus rhythm with a normal circadian profile and normal total variability was recorded during the study. A single, paired, and group ventricular extrasystole were recorded, along with a few supraventricular extrasystoles, including 35 single and 1 paired. No ischemic repolarization changes were found at rest or on exertion.

In light of the clinical presentation and diagnostic testing results, a comprehensive search for coronary heart disease was initiated. Coronary angiography revealed significant stenosis of the anterior interventricular artery, prompting subsequent angioplasty with stenting.

In this patient on CPAP therapy, severe OSAS and the elimination of heart rhythm pauses permitted the consideration of these changes in Holter ECG monitoring as secondary (reflex) to apnea and hypopnea episodes and the exclusion of contraindications to beta-adrenoblockers such as sinus node dysfunction. This included prescribing optimal drug therapy for ischemic heart disease.

CONCLUSIONS

1. In clinical practice, OSAS must be urgently verified, given its high prevalence and the increased risk of cardiovascular disease.

2. The provision of respiratory therapy at night eliminates OSAS as a potentially reversible cause of heart rhythm abnormalities and a risk factor for cardiovascular disease.

ADDITIONAL INFORMATION

Ethics approval. The study was approved by North-Western state medical university named after I.I. Mechnikov of Sciences Ethics Committee, protocol No. 10, 11.10.2023.

Author contribution. Thereby, all authors confirm that their authorship complies with the international ICMJE criteria (all authors have made a significant contribution to the development of the concept, research, and preparation of the article, as well as read and approved the final version before its publication).

Personal contribution of the authors. N.G. Kucherenko, A.N. Bebekh — data analysis, writing the main part of the text; I.A. Umarova — data analysis; A.R. Abukova — data analysis, literature review.

Competing interests. The authors declare that they have no competing interests.

Funding source. This study was not supported by any external sources of funding.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Заключение этического комитета. Исследование было одобрено этическим комитетом Северо-Западного государственного университета им. И.И. Мечникова (протокол № 10 от 11.10.2023).

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Вклад каждого автора. Н.Г. Кучеренко, А Н. Бебех — анализ полученных данных, написание текста; И.А. Умарова — анализ полученных данных; А.Р. Абукова — анализ полученных данных, обзор литературы.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

REFERENCES

1. Guilleminault C, Tilkian A, Dement WC. The sleep apnea syndromes. *Annu Rev Med*. 1976;27:465–484. doi: 10.1146/annurev.me.27.020176.002341

2. Kapur V, Strohl KP, Redline S, et al. Underdiagnosis of sleep apnea syndrome in U.S. communities. *Sleep Breath*. 2002;6(2):49–54. doi: 10.1007/s11325-002-0049-5

3. Benjafield AV, Ayas NT, Eastwood PR, et al. Estimation of the global prevalence and burden of obstructive sleep apnea: a literature-based analysis. *The Lancet. Respir Med*. 2019;7(8):687–698. doi: 10.1016/S2213-2600(19)30198-5

4. Gottlieb DJ, Punjabi NM. Diagnosis and management of obstructive sleep apnea: a review. *JAMA*. 2020;323(14):389–1400. doi: 10.1001/jama.2020.3514

5. Manuel AR, Hart N, Stradling JR. Correlates of obesity-related chronic ventilatory failure. *BMJ*. 2016;3(1):e000110. doi: 10.1136/bmjresp-2015-000110

6. Patinkin ZW, Feinn R, Santos M. Metabolic consequences of obstructive sleep apnea in adolescents with obesity: a systematic literature review and meta-analysis. *Childhood Obesity*. 2017;13(2):102–110. doi: 10.1089/chi.2016.0248

7. Rapoport DM, Garay SM, Epstein H, Goldring RM. Hypercapnia in the obstructive sleep apnea syndrome. A reevaluation of the "Pickwickian syndrome". *Chest.* 1986;89(5):627–635. doi: 10.1378/chest.89.5.627

8. Kapur VK, Auckley DH, Chowdhuri S, et al. Clinical practice guideline for diagnostic testing for adult obstructive sleep apnea: an American Academy of Sleep Medicine clinical practice guideline. *J Clin Sleep Med.* 2017;13(3):479–504. doi: 10.5664/jcsm.6506

9. Yeghiazarians Y, Jneid H, Tietjens JR, et al. Obstructive sleep apnea and cardiovascular disease: a scientific statement from the American Heart Association. *Circulation*. 2021;144(3):56–67. doi: 10.1161/CIR.0000000000000988

10. Mann D, Zipes D, Libby P, Bonow R. *Braunwald's heart disease: a textbook of cardiovascular medicine*. *11*th *ed.* Philadelphia (PA): Elsevier/Saunders; 2015.

11. Vetulli HM, Elizari MV, Naccarelli GV, Gonzalez MD. Cardiac automaticity: basic concepts and clinical observations. *J Interv Card Electrophysiol*. 2018;52(3):263–270. doi: 10.1007/s10840-018-0423-2

12. Drager LF, Bortolotto LA, Figueiredo AC, et al. Obstructive sleep apnea, hypertension, and their interaction on arterial stiffness and heart remodeling. *Chest*. 2007;131(5):1379–1386. doi: 10.1378/chest.06-2703

13. Chadda KR, Fazmin IT, Ahmad S, et al. Arrhythmogenic mechanisms of obstructive sleep apnea in heart failure patients. *Sleep*. 2018;41(9):zsy136. doi: 10.1093/sleep/zsy136

14. Semelka M, Wilson J, Floyd R. Diagnosis and treatment of obstructive sleep apnea in adults. *Am Fam Physician.* 2016;94(5): 355–360.

15. Tung P, Levitzky YS, Wang R, et al. Obstructive and central sleep apnea and the risk of incident atrial fibrillation in a community cohort of men and women. *J Am Heart Assoc*. 2017;6(7):e004500. doi: 10.1161/JAHA.116.004500

16. Kharats VE. The problem of association between obstructive sleep apnea and atrial fibrillation in cardiology practice. *The Siberian Journal of Clinical and Experimental Medicine*. 2022;37(3):41–48. (In Russ.) EDN: SEKBFJ doi: 10.29001/2073-8552-2022-37-3-41-48

17. Linz D, McEvoy RD, Cowie MR, et al. Associations of obstructive sleep apnea with atrial fibrillation and continuous positive airway pressure treatment: a review. *JAMA Cardiology*. 2018;3(6):532–540. doi: 10.1001/jamacardio.2018.0095

18. Poluektov MG. Primary and secondary insomnias and sleep related breathing disturbances. *S.S.* Korsakov Journal of Neurology and Psychiatry. 2011;111(9(2)):10–18. (In Russ.) EDN: PYWSMD

19. Lipford MC, Flemming KD, Calvin AD, et al. Associations between cardioembolic stroke and obstructive sleep apnea. *Sleep*. 2015;38(11):1699–1705. doi: 10.5665/sleep.5146

20. Zorina AV, Kulagina AM, Kazarina AV, et al. Obstructive sleep apnea in patients with atrial fibrillation. *Neurological Journal*. 2017;22(4): 177-81. (In Russ.) doi: 10.18821/1560-9545-2017-22-4-177-181

21. Buzunov RV, Legeyda IV, Tsareva EV. *Snoring and obstructive sleep apnea in adults and children. Guidelines for doctors*. Moscow; 2013. 124 p. (In Russ.)

22. Sahlin C, Sandberg O, Gustafson Y, et al. Obstructive sleep apnea is a risk factor for death in patients with stroke: a 10-year follow-up. *Arch Intern Med*. 2008;168(3):297–301. doi: 10.1001/archinternmed.2007.70

23. Kuznetsov AN, Vinogradov O1. *Ischemic stroke. Diagnosis, treatment, prevention. Pocket guide. 3rd ed.* Moscow: RAEN; 2014. 90 p. (In Russ.)

24. Lavergne F, Morin L, Armitstead J, et al. Atrial fibrillation and sleep-disordered breathing. *J Thorac Dis*. 2015;7(12):575–584. doi: 10.3978/j.issn.2072-1439.2015.12.57

25. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur J Cardiothorac Surg*. 2016;50(5):1–88. doi: 10.1093/ejcts/ezw313

26. Zwillich C, Devlin T, White D, et al. Bradycardia during sleep apnea. Characteristics and mechanism. *J Clin Invest*. 1982;69(6):1286–1292. doi: 10.1172/jci110568

27. Becker H, Brandenburg U, Peter JH, Von Wichert P. Reversal of sinus arrest and atrioventricular conduction block in patients with sleep apnea during nasal continuous positive airway pressure. *Am J Respir Crit Care Med*. 1995;151(1):215–218. doi: 10.1164/ajrccm.151.1.7812557

28. Patil SP, Ayappa IA, Caples SM, et al. Treatment of adult obstructive sleep apnea with positive airway pressure: an American Academy of Sleep Medicine systematic review, meta-analysis, and grade assessment. *J Clin Sleep Med*. 2019;15(2):301–334. doi: 10.5664/jcsm.7638

29. Mokhlesi B, Masa JF, Brozek JL, et al. Evaluation and management of obesity hypoventilation syndrome. An official American Thoracic Society clinical practice guideline. *Am J Respir Crit Care Med*. 2019;200(3):6–24. doi: 10.1164/rccm.201905-1071ST

30. Sullivan CE, Issa FG, Berthon-Jones M, Eves L. Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares. *Lancet*. 1981;1(8225):862–865. doi: 10.1016/s0140-6736(81)92140-1

31. Patil SP, Ayappa IA, Caples SM, et al. Treatment of adult obstructive sleep apnea with positive airway pressure: an American Academy of Sleep Medicine clinical practice guideline. *J Clin Sleep Med*. 2019;15(2):335–343. doi: 10.5664/jcsm.7640

32. Buzunov RV, Palman AD, Melnikov AYu, et al. Diagnostics and treatment of obstructive sleep apnea syndrome in adults. Recommendations of the Russian society of sleep medicine. *Effective pharmacotherapy. Neurology and Psychiatry. Special issue «Sleep and Sleep Disorders»*. 2018;35:34–45. (In Russ.)

33. Grimm W, Hoffmann J, Menz V, et al. Electrophysiologic evaluation of sinus node function and atrioventricular conduction in patients with prolonged ventricular asystole during obstructive sleep apnea. *Am J Cardiol.* 1996;77(15):1310–1314. doi: 10.1016/s0002-9149(96)00197-x

СПИСОК ЛИТЕРАТУРЫ

1. Guilleminault C., Tilkian A., Dement W.C. The sleep apnea syndromes // Annu Rev Med. 1976. Vol. 27. P. 465–484. doi: 10.1146/annurev.me.27.020176.002341

2. Kapur V., Strohl K.P., Redline S., et al. Underdiagnosis of sleep apnea syndrome in U.S. communities // Sleep Breath. 2002. Vol. 6, N. 2. P. 49–54. doi: 10.1007/s11325-002-0049-5

3. Benjafield A.V., Ayas N.T., Eastwood P.R., et al. Estimation of the global prevalence and burden of obstructive sleep apnea: a literature-based analysis // The Lancet. Respir Med. 2019. Vol. 7, N. 8. P. 687–698. doi: 10.1016/S2213-2600(19)30198-5

4. Gottlieb D.J., Punjabi N.M. Diagnosis and management of obstructive sleep apnea: a review // JAMA. 2020. Vol. 323, N. 14. P. 389–1400. doi: 10.1001/jama.2020.3514

5. Manuel A.R., Hart N., Stradling J.R. Correlates of obesity-related chronic ventilatory failure // BMJ. 2016. Vol. 3, N. 1. P. e000110. doi: 10.1136/bmjresp-2015-000110

6. Patinkin Z.W., Feinn R., Santos M. Metabolic consequences of obstructive sleep apnea in adolescents with obesity: a systematic literature review and meta-analysis // Childhood Obesity. 2017. Vol. 13, N. 2. P. 102–110. doi: 10.1089/chi.2016.0248

7. Rapoport D.M., Garay S.M., Epstein H., Goldring R.M. Hypercapnia in the obstructive sleep apnea syndrome. A reevaluation of the "Pickwickian syndrome" // Chest. 1986. Vol. 89, N. 5. P. 627–635. doi: 10.1378/chest.89.5.627

8. Kapur V.K., Auckley D.H., Chowdhuri S., et al. Clinical practice guideline for diagnostic testing for adult obstructive sleep apnea: an American Academy of Sleep Medicine clinical practice guideline // J Clin Sleep Med. 2017. Vol. 13, N. 3. P. 479–504. doi: 10.5664/jcsm.6506

9. Yeghiazarians Y., Jneid H., Tietjens J.R., et al. Obstructive sleep apnea and cardiovascular disease: a scientific statement from the American Heart Association // Circulation. 2021. Vol. 144, N. 3. P. 56–67. doi: 10.1161/CIR.0000000000000988

10. Mann D., Zipes D., Libby P., Bonow R. *Braunwald's heart disease: a textbook of cardiovascular medicine*. 11th ed. Philadelphia (PA): Elsevier/Saunders, 2015.

11. Vetulli H.M., Elizari M.V., Naccarelli G.V., Gonzalez M.D. Cardiac automaticity: basic concepts and clinical observations // J Interv Card Electrophysiol. 2018. Vol. 52, N. 3. P. 263–270. doi: 10.1007/s10840-018-0423-2

12. Drager L.F., Bortolotto L.A., Figueiredo A.C., et al. Obstructive sleep apnea, hypertension, and their interaction on arterial stiffness and heart remodeling // Chest. 2007. Vol. 131, N. 5. P. 1379–1386. doi: 10.1378/chest.06-2703

13. Chadda K.R., Fazmin I.T., Ahmad S., et al. Arrhythmogenic mechanisms of obstructive sleep apnea in heart failure patients // Sleep. 2018. Vol. 41, N 9. P. zsy136. doi: 10.1093/sleep/zsy136

14. Semelka M., Wilson J., Floyd R. Diagnosis and treatment of obstructive sleep apnea in adults // Am Fam Physician. 2016. Vol. 94, N. 5. P. 355–360.

15. Tung P., Levitzky Y.S., Wang R., et al. Obstructive and central sleep apnea and the risk of incident atrial fibrillation in a community cohort of men and women // J Am Heart Assoc. 2017. Vol. 6, N. 7. P. e004500. doi: 10.1161/JAHA.116.004500

16. Харац В.Е. Проблема ассоциации обструктивного апноэ сна и фибрилляции предсердий в условиях кардиологической практики // Сибирский журнал клинической и экспериментальной медицины. 2022. Т. 37, № 3. С. 41–48. EDN: SEKBFJ doi: 10.29001/2073-8552-2022-37-3-41-48

17. Linz D., McEvoy R.D., Cowie M.R., et al. Associations of obstructive sleep apnea with atrial fibrillation and continuous positive airway pressure treatment: a review // JAMA Cardiology. 2018. Vol. 3, N. 6. P. 532–540. doi: 10.1001/jamacardio.2018.0095

18. Полуэктов М.Г. Первичные и вторичные инсомнии и расстройства дыхания во сне // Журнал неврологии и психиатрии им. С.С. Корсакова. 2011. Т. 111, № 9–2. С. 10–18. EDN: PYWSMD

19. Lipford M.C., Flemming K.D., Calvin A.D., et al. Associations between cardioembolic stroke and obstructive sleep apnea // Sleep. 2015. Vol. 38, N. 11. P. 1699–1705. doi: 10.5665/sleep.5146

20. Зорина А. В., Кулагина А. М., Казарина А. В. и др. Синдром обструктивного апноэ сна у пациентов с фибрилляцией предсердий // Неврологический журнал. 2017. Т. 22, № 4. С. 177–81. doi: 10.18821/1560-9545-2017-22-4-177-181

21. Бузунов Р.В., Легейда И.В., Царева Е.В. Храп и синдром обструктивного апноэ сна у взрослых и детей. Практическое руководство для врачей. Москва, 2013. 124 с.

22. Sahlin C., Sandberg O., Gustafson Y., et al. Obstructive sleep apnea is a risk factor for death in patients with stroke: a 10-year follow-up // Arch Intern Med. 2008. Vol. 168, N. 3. P. 297–301. doi: 10.1001/archinternmed.2007.70

23. Кузнецов А.Н., Виноградов О.И. Ишемический инсульт. Диагностика. Лечение. Профилактика. Карманный справочник. 3-е изд. Москва: РАЕН, 2014. 90 с.

24. Lavergne F., Morin L., Armitstead J., et al. Atrial fibrillation and sleep-disordered breathing // J Thorac Dis. 2015. Vol. 7, N. 12. P. 575–584. doi: 10.3978/j.issn.2072-1439.2015.12.57

25. Kirchhof P., Benussi S., Kotecha D., et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS // Eur J Cardiothorac Surg. 2016. Vol. 50, N. 5. P. 1–88. doi: 10.1093/ejcts/ezw313

26. Zwillich C., Devlin T., White D., et al. Bradycardia during sleep apnea. Characteristics and mechanism // J Clin Invest. 1982. Vol. 69, N. 6. P. 1286–1292. doi: 10.1172/jci110568

27. Becker H., Brandenburg U., Peter J.H., Von Wichert P. Reversal of sinus arrest and atrioventricular conduction block in patients with sleep apnea during nasal continuous positive airway pressure // Am J Respir Crit Care Med. 1995. Vol. 151, N. 1. P. 215–218. doi: 10.1164/ajrccm.151.1.7812557

28. Patil S.P., Ayappa I.A., Caples S.M., et al. Treatment of adult obstructive sleep apnea with positive airway pressure: an American Academy of Sleep Medicine systematic review, meta-analysis, and grade assessment // J Clin Sleep Med. 2019. Vol. 15, N. 2. P. 301–334. doi: 10.5664/jcsm.7638

29. Mokhlesi B., Masa J.F., Brozek J.L., et al. Evaluation and management of obesity hypoventilation syndrome. An

official American Thoracic Society clinical practice guideline // Am J Respir Crit Care Med. 2019. Vol. 200, N. 3. P. 6–24. doi: 10.1164/rccm.201905-1071ST

30. Sullivan C.E., Issa F.G., Berthon-Jones M., Eves L. Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares // Lancet. 1981. Vol. 1, N. 8225. P. 862–865. doi: 10.1016/s0140-6736(81)92140-1

31. Patil S.P., Ayappa I.A., Caples S.M., et al. Treatment of adult obstructive sleep apnea with positive airway pressure: an American Academy of Sleep Medicine clinical practice guideline // J Clin Sleep Med. 2019. Vol. 15, N. 2. P. 335–343. doi: 10.5664/jcsm.7640

32. Бузунов Р.В., Пальман А.Д., Мельников А.Ю., и др. Диагностика и лечение синдрома обструктивного апноэ сна у взрослых. Рекомендации Российского общества сомнологов // Эффективная фармакотерапия. Неврология. Спецвыпуск «Сон и его расстройства». 2018. № 35. С. 34–45.

33. Grimm W., Hoffmann J., Menz V., et al. Electrophysiologic evaluation of sinus node function and atrioventricular conduction in patients with prolonged ventricular asystole during obstructive sleep apnea // Am J Cardiol. 1996. Vol. 77, N. 15. P. 1310–1314. doi: 10.1016/s0002-9149(96)00197-x

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DOI: https://doi.org/10.17816/cardar630134

Multifaces of hypertrophic cardiomyopathy: a case of transformation of hypertrophic phenotype into dilated

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ABSTRACT

The article presents a clinical case of a rather rare course of hypertrophic cardiomyopathy with the transformation of a hypertrophic phenotype into a dilated phenotype against the background of the "burned-out phase" phenomenon, ventricular and supraventricular rhythm disturbances, and multiple genetic mutations. Timely started disease-modifying therapy (quadruple therapy) for chronic heart failure led to reverse positive remodeling of the left chambers of the heart.

Keywords: hypertrophic burnout cardiomyopathy; non-sustained ventricular tachycardia; atrial fibrillation; global longitudinal strain; left atrial strain; quadruple therapy.

To cite this article

Novikova TN, Andreeva AE, Bitakova FI, Novikov VI, Gladysheva KA, Petrova PV, Stalnova PA, Tokareva NA. Multifaces of hypertrophic cardiomyopathy: a case of transformation of hypertrophic phenotype into dilated. *Cardiac Arrhythmias.* 2024;4(1):31–41. DOI: https://doi.org/10.17816/cardar630134

Received: 11.04.2024 **Accepted:** 23.04.2024 **Published online:** 06.05.2024

DOI: https://doi.org/10.17816/cardar630134

Многоликая гипертрофическая кардиомиопатия: случай трансформации гипертрофического фенотипа в дилатационный

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АННОТАЦИЯ

Представлен клинический случай довольно редкого течения гипертрофической кардиомиопатии с трансформацией гипертрофического фенотипа в дилатационный фенотип на фоне феномена «выгорания» (burned-out phase), желудочковых и суправентрикулярных нарушений ритма, множественных генетических мутаций. Своевременно начатая болезнь-модифицирующая терапия (квадротерапия) хронической сердечной недостаточности привела к обратному позитивному ремоделированию левых камер сердца у пациента.

Ключевые слова: гипертрофическая кардиомиопатия выгорания; неустойчивая желудочковая тахикардия; фибрилляция предсердий; глобальная продольная деформация; продольная деформация левого предсердия; квадротерапия.

Как цитировать

Новикова Т.Н., Андреева А.Е., Битакова Ф.И., Новиков В.И., Гладышева К.А., Петрова П.В., Стальнова П.А., Токарева Н.А. Многоликая гипертрофическая кардиомиопатия: случай трансформации гипертрофического фенотипа в дилатационный // Cardiac Arrhythmias. 2024. Т. 4, № 1. С. 31–41. DOI: https://doi.org/10.17816/cardar630134

Рукопись получена: 11.04.2024 **Рукопись одобрена:** 23.04.2024 **Опубликована online:** 06.05.2024

INTRODUCTION

The 2023 ESC Guidelines for the Management of Cardiomyopathies have largely changed the approaches to the classification of cardiomyopathies (CMPs) [1]. Currently, the following types of CMPs are distinguished: hypertrophic, dilated, Non–dilated left ventricular cardiomyopathy (NDLVC), arrhythmogenic, and restrictive cardiomyopathy.

The recommendations are based on a phenotypic approach to CMP classification and diagnosis. Importantly, family members may have different phenotypic manifestations, and in the same patient, as the disease develops and progresses, a phenotypic variant of CMP may transform into another. The predominant cardiac phenotype at the time of initial diagnosis should guide the diagnosis and follow-up of the patient. The case of using this approach in real clinical practice is presented herein.

CLINICAL CASE

Patient R., aged 62 years, has been under the care of the clinic since 2002. Regarding his medical history, he actively participated in various sports in his youth, including alpine skiing and wrestling. The suspicion of heart pathology first arose in 1995 (at the age of 34), when, for the first time in his life, an electrocardiogram (ECG) was taken before a competition (the results were not provided). ECG changes detected led to the diagnosis of an acute myocardial infarction, despite the absence of any complaints at the time. The patient was hospitalized for 3 weeks, followed by rehabilitation. After 2 months, the polyclinic at the patient's place of residence again detected signs of acute myocardial infarction on the control ECG and suggested rehospitalization. However, the patient categorically refused this suggestion due to the absence of complaints and good health. Complaints of palpitations and chest discomfort during moderate physical activity were first documented in 2002, at the age of 41. The patient was subsequently referred to the city antiarrhythmic center for further evaluation. Upon examination, he was diagnosed with hypertrophic CMP (HCMP) without left ventricular (LV) outflow tract obstruction. Daily ECG monitoring revealed a high premature ventricular complexes(PVCs) count, with approximately 10.000 events per day. Coronarography was performed for the pain syndrome. The subepicardial coronary arteries were free of hemodynamically significant stenoses. In addition, coronary systolic reverse flow, previously described in the literature in patients with HCMP and identified as a potential cause of subendocardial myocardial ischemia, was observed [2, 3]. A slow-release metoprolol succinate (Betaloc 30K®) at a dose of 100 mg per day was prescribed. The number of PVCs decreased during the therapy, although they did not entirely disappear. An attempt to increase the dose of beta-blocker was accompanied by a decrease in systolic blood pressure to 85 mmHg. In 2007 (at the age of 46), sustained hemodynamically significant ventricular tachycardia (VT) accompanied by a drop in blood pressure was recorded for the first time; in addition, paroxysmal and persistent forms of atrial fibrillation (AF) occurred. For several months, in addition to slow-release metoprolol succinate, the patient received amiodarone, which demonstrated a positive clinical effect. However, amiodarone was discontinued because of the occurrence of cordarone-induced thyrotoxicosis. In the same year, the patient received a dual-chamber implantable cardioverter-defibrillator (ICD) that can control ventricular rhythm disturbances and had function of cardioversion of AF. Owing to the frequent painful triggering of the ICD in response to AF and the deterioration of the patient's quality of life, the patient and his attending physician decided to disable the function of cardioversion of AF. In 2008, pulmonary vein cryoisolation was performed because of the frequent symptomatic episodes of AF. During several years after of pulmonary vein cryoisolation AF did not recur. Considering the high risk of AF recurrence and structural changes in the left chambers of the heart, the patient took propafenone 150 mg 2 times a day and warfarin in addition to metoprolol succinate sustained release. A gradual increase in the dosage of metoprolol succinate (increases of 12.5 mg at intervals of no more than 2 weeks) allowed us to reach the maximum dose (200 mg per day). The therapy was effective in preventing AF recurrence, although recurrent sustained VT led to ICD activation several times a year. Because the ICD battery depleted, the ICD was replaced in 2012. The newly installed ICD did not has the function of cardiovercion of AF but had a function of antitachycardia pacing (ATP) as a way to terminate VT. Recurrent sustained VT persisted and led to ICD activation several times a year. Since 2018, rare AF recurrence have been documented. In 2018 the patient was diagnosed with type 2 diabetes mellitus and dyslipidemia. In addition to rhythm disturbances, the patient reported chest discomfort and dyspnea during moderate exercise, with progressive worsening of exercise tolerance. Since 2018 patient took slow-release metoprolol succinate (200 mg daily), apiksaban (5 mg twice daily), dapagliflozin (10 mg daily), and rosuvastatin (20 mg daily).

In 2020, the ICD was replaced once more due to battery exhaustion. Repeated coronary angiography was performed before ICD replacement. Coronary angiography did not register coronary systolic reversed flow phenomenon. A 60% stenosis of diagonal branch of the left coronary artery

was detected. Fractional flow reserve (FFR) was assessed (>0.8). So the stenosis did not require revascularization. No significant changes were observed in the other coronary arteries.

The patient's condition markedly decline in February 2021. He presented to the clinic with complaints of dyspnea and chest discomfort, not only by exercise, but also at night. Echocardiography revealed a markedly different picture than that observed during the initial treatment in 2002. LV exhibited slight dilatation, with an end-diastolic volume index (EDVI) of 75 mL/m^2. The left atrium (LA) demonstrated pronounced dilatation, with a left atrial volume index (LAVI) of 68 ml/m^2. Diffuse hypokinesia of all LV walls, a reduction in myocardial thickness of the interventricular septum (IVS) from 19 to 12 mm, and an decrease in LV ejection fraction (EF) up to 40% were observed. An elevation in pulmonary artery systolic pressure (PASP) up to 52 mm Hg was also noted. In addition to severe systolic dysfunction, the patient had severe diastolic dysfunction (grade 3):

$$VE / VA = 2{,}1;\ VE / Em \text{ (mean)} = 16.3,$$

where *VE* is the velocity of the transmittral blood flow in the rapid filling phase, *VA* is the velocity of the transmittral blood flow at LA systole, and *Em* is the mean value of the sum of the velocities of the septal and lateral segments of the mitral valve annulus.

Contrasted chest computed tomography (CT), which was performed to exclude pulmonary embolism as the cause of the rapid deterioration in the condition, confirmed dilatation of the left heart chambers, fluid in the posterior parts of the pleural cavities on both sides (not more than 150 mL on each side), and signs of interstitial pulmonary edema. No data supporting pulmonary embolism were obtained. Brain natriuretic peptide level were elevated up to 1,683 pkg/mL. The patient did not undergo cardiac magnetic resonance imaging (MRI) because he had an ICD. Torasemide (10 mg daily), eplerenone (25 mg daily with subsequent increase in dose to 50 mg daily after 1 month), and valsartan + sacubitril (Uperio®) dose titration from 50 mg twice daily were added to the current therapy with metoprolol succinate (200 mg daily), apixaban (5 mg twice daily), dapagliflozin (10 mg daily), rosuvastatin (20 mg daily). Propafenone was discontinued because the EF decreased. After stabilization of the condition, stress echocardiography (stress EchoCG test) was performed. The patient's condition was considered transformation of a hypertrophic phenotype into a dilated phenotype with a burned-out phase and ventricular and supraventricular rhythm disturbances [3, 4]. EF dynamics for 2008–2021 are shown in Table 1.

Genetic testing was performed owing to the atypical disease course. Massive parallel sequencing of a panel of 17 genes associated with HCMP revealed two mutations: Glu163del mutation in *TNNT2* (heterozygous carrier), which codes for the synthesis of the troponin T protein. This mutation is clearly associated with HCMP and has a high penetrance. In addition, the identified mutation was associated with a high risk of sudden cardiac death (SCD). The second mutation, a truncating variant located in the M-band, was found in *TTN* (heterozygous carrier), which codes for the synthesis of titin protein. It is likely to be pathogenic. *TTN* mutations are associated with several types of cardiac and skeletal myopathies (hypertrophic, dilated, and restrictive CMPs, LV hypertrabecularity, distal Myoshi muscular dystrophy, Salih myopathy, etc.).

The patient has two children: the older daughter has confirmed HCMP but has not been genotyped, and the younger son has no genetic or phenotypic manifestations of HCMP.

During therapy, the patient's condition improved significantly, and the dyspnea stopped. Rhythm disturbances persisted as rare non-sustained atrial tachycardia and VT. The maximum well-tolerated daily dose of valsartan and sacubitril did not exceed 200 mg when titrated, and persistent hypotension occurred when further increases were attempted. The patient was then seen in May 2022, and an ECG was performed (Fig. 1).

The control EchoCG demonstrated positive dynamics, with an increase in EF to 49%, decrease in EDVI to 45 mL/m^2, LAVI remained the same (68 ml/m^2), PASP decreased to 29 mmHg. Diastolic function parameters exhibited improvement, with *VE/VA* = 1.1 and *VE/Em* ratio (mean) = 10.3 (grade 1 diastolic dysfunction). Longitudinal deformation of the LV myocardium was determined (in the 2D-strain mode). It was significantly impaired, with a value of –15% (which is below the normal range of –18%). Maximum myocardial deformation disturbances were observed in the hypertrophied IVS (the zone is colored pale pink in Fig. 2).

Table 1. Dynamics of ejection fraction for 2008–2021
Таблица 1. Динамика фракции выброса за 2008–2021 годы

Year	2008	2009	2010	2014	2015	2018	2020	2021
EF, %	68	64	61	60	59	59	51	40

Note: ФВ — ejection fraction.
Примечание: ФВ — фракция выброса.

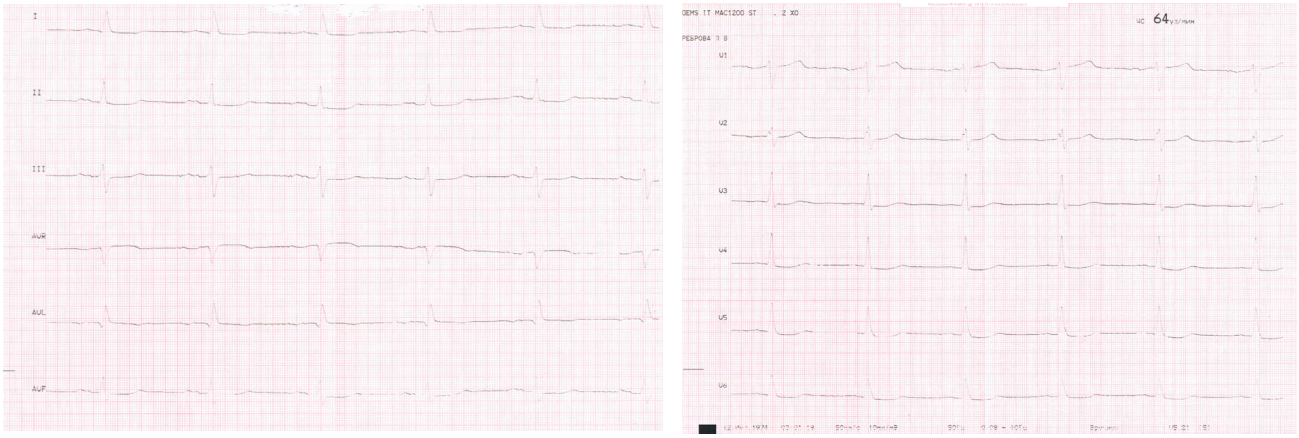

Fig. 1. Patient's ECG in May 2022 (recording speed is 50 mm/s)
Рис. 1. Электрокардиограмма пациента в мае 2022 года (скорость записи 50 мм/с)

In consideration of the notable LA dilatation, LA function was evaluated in the longitudinal strain mode (2D strain) (Fig. 3). As in the case of longitudinal LV myocardial strain, LA myocardial strain parameters were abnormal. The deformation index during the reservoir phase was equal to 13% (with a mean normal value of 39%, 95% confidence interval [CI] 38%–41%). During the conduit phase, it was 5% (with a mean normal value of 23%, 95% CI 21%–25%), whereas during the contractile phase, it was 8% (with a mean normal value of 17%, 95% CI 16%–19%) [6]. Notably, the strain indices during the conduit and contractile phases were negative, as the LA myocardium shortens during these phases. For the convenient comparison of indices, it is customary to discard the minus sign. In our patient, the LA function during all three phases was significantly impaired.

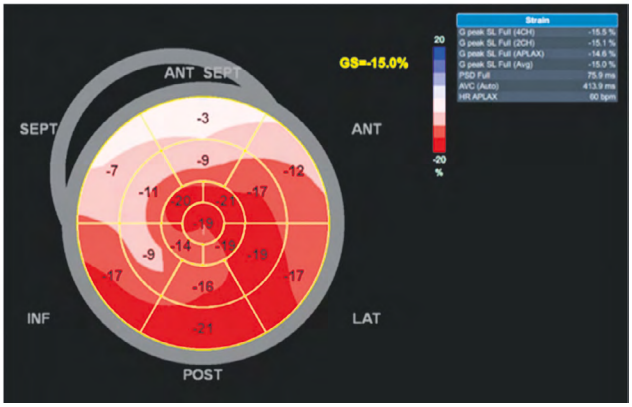

Fig. 2. Bull's eye format of peak global longitudinal strain of the left ventricular myocardium. Explanation in the text
Рис. 2. Пиковая глобальная деформация миокарда ЛЖ в формате «бычий глаз». Объяснение в тексте

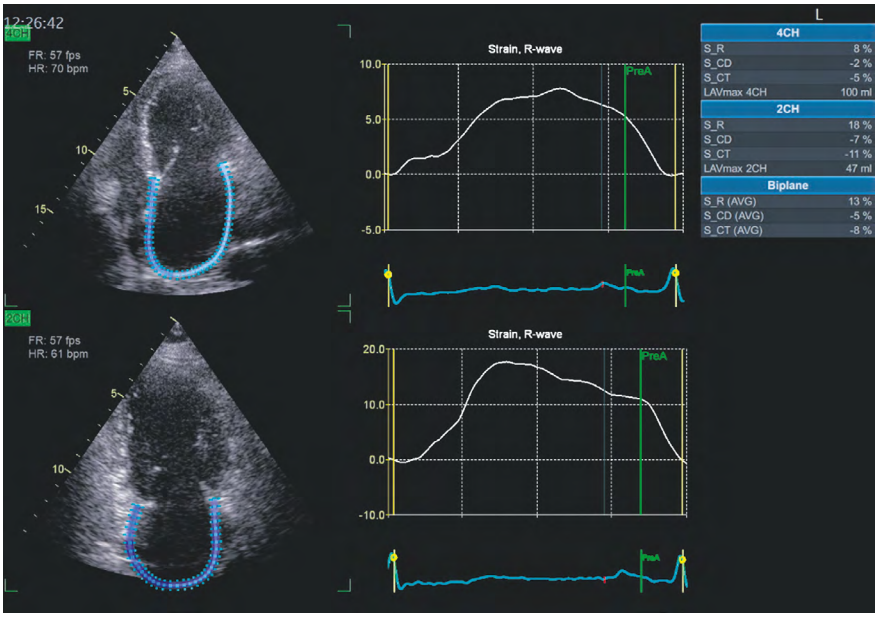

Fig. 3. Assessment of left atrial function in 2022 in 2D-Strain mode. Explanation in the text
Рис. 3. Оценка функции левого предсердия в 2022 году в режиме деформации. Объяснение в тексте

Because the assessment of LA myocardial strain was performed for the first time, it was not possible to ascertain the extent to which LA function had been disturbed previously.

During Holter ECG monitoring, 1,337 (1.5%) PVGCs, 22 runs of non-sustaned VT, and 215 (0.2%) atrial premature complexes were recorded.

Continued therapy was necessary. In September 2023, the patient presented to our facility for the recurrence of chest discomfort during physical exertion exceeding household loads. Stress EchoCG testing was performed repeatedly, with negative results. In accordance with the ESC Guidelines for the Management of Cardiomyopathies, ranolazine 500 mg twice a day [1, 3] was prescribed to control the pain syndrome. The chest discomfort was successfully managed during the medication therapy.

A control EchoCG was performed in February 2024. For other parameters the following results were obtained: EDVI (48 mL/m^2), LAVI (63 mL/m^2), PASP (25 mmHg), *VE/VA* = 1.1, and *VE/Em* (mean) = 10.0 were noted. The dynamics of key EchoCG indices are presented in Table 2. Unfortunately, the global longitudinal LV myocardial strain did not improve, remaining at the level observed in 2022.

In addition to LV diastolic function improvement, the LA volume tended to decrease (Fig. 4). Indices of LA function have improved. Consequently, the proportion of LA myocardial strain increased from 13% to 17% during the reservoir phase, from 5% to 8% during the conduit phase, and from 8% to 9% during the contractile phase. The dynamics of the indices are presented in Table 3.

During Holter ECG monitoring, 73 (0.1%) PVCs, 1 run of non-sustained VT (Fig. 5), 792 (1.0%) atrial premature complexes, and 1 run of non-sustained atrial tachycardia were recorded. The dynamics of the number of ventricular and atrial rhythm disturbances are presented in Table 4.

In this case, the therapy should be continued in accordance with national and international recommendations for the treatment of chronic heart failure, i.e., the therapy, which demonstrated a positive outcome, should be continued

Table 2. Dynamics of key echocardiography parameters during quadruple therapy
Таблица 2. Динамика ключевых эхокардиографических показателей на фоне квадротерапии

Indices	Before quadruple therapy	During quadruple therapy	
	February 2021 года	May 2022 года	February 2024 года
EF, %	40	49	55
EDVI, mL/m^2	75	45	48
LAVI, mL/m^2	68	68	63
PASP, mmHg	52	29	25
VE/VA	2.1	1.1	1.1
VE/Em	16.3	10.3	10.0

Note: ФВ — ejection fraction; ИКДО — end-diastolic volume index; ИОЛП — left atrium volume index; СДЛА — pulmonary artery systolic pressure; *VE* — transmitral blood flow velocity during the rapid filling phase; *VA* — transmitral blood flow velocity at the moment of left atrium systole; *Em* — the average value of the sum of the speeds of movement of the septal and lateral segments of the mitral valve anulus.

Примечание: ФВ — фракция выброса; ИКДО — индекс конечно-диастолического объема; ИОЛП — индекс объема левого предсердия; СДЛА — систолическое давление в легочной артерии; *VE* — скорость трансмитрального кровотока в фазу быстрого наполнения; *VA* — скорость трансмитрального кровотока в момент систолы левого предсердия; *Em* — среднее значение суммы скоростей движения перегородочного и бокового сегментов кольца митрального клапана.

Table 3. Dynamics of indicators of left atrium function during quadruple therapy
Таблица 3. Динамика показателей функции левого предсердия на фоне квадротерапии

Indices	May 2022	February 2024	Normal, mean value, (95% CI) [6]
LASr, %	13	17	39 % (95% CI 38%–41%)
LAScd, %	5	8	23 % (95% CI 21%–25%)
LASct, %	8	9	17 % (95% CI 16%–19%)

Note: ДИ — confidence interval; ЛП — left atrium; *LASr* — left atrium reservoir strain; *LAScd* — left atrium conduit strain; *LASct* — left atrium contractile strain.

Примечание: ДИ — доверительный интервал; ЛП — левое предсердие; *LASr* — деформация левого предсердия во время резервуарной фазы; *LAScd* — деформация левого предсердия во время кондуитной фазы;, *LASct* — деформация левого предсердия во время сократительной фазы

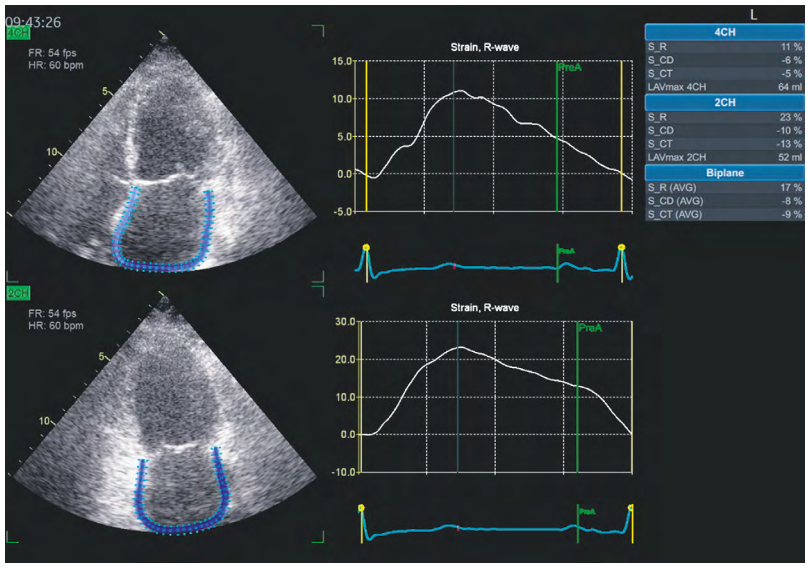

Fig. 4. Assessment of left atrial function over time in February 2024 in 2D-Strain mode. Explanation in the text
Рис. 4. Оценка функции левого предсердия в динамике в феврале 2024 года в режиме деформации. Объяснение в тексте

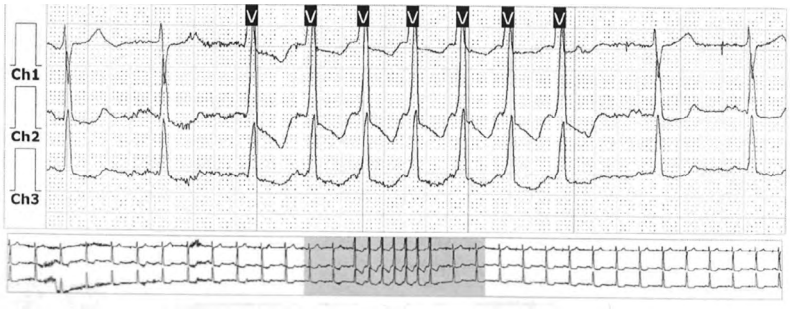

Fig. 5. Fragment of ECG monitoring. Episode of non-sustained ventricular tachycardia
Рис. 5. Фрагмент суточного мониторирования ЭКГ. Эпизод неустойчивой желудочковой тахикардии

Table 4. Dynamics of indicators of ECG monitoring for 2021–2024
Таблица 4. Динамика показателей суточного мониторирования ЭКГ за 2021–2024 годы

Indices	February 2021	May 2022	October 2022	June 2023	February 2024
Number premature ventricular complexes, *n* (%)	5698 (4.4)	1337 (1.5)	520 (0.6)	119 (0.1)	73 (0.1)
Number premature atrial complexes, *n* (%)	9341 (7.3)	215 (0.2)	1380 (1.6)	1833 (2.1)	792 (1.0)
Number of на non-sustained ventricular tachycardia	7	2	1	0	1
Number of non-sustained atrial tachycardia	9	0	0	1	1

to prevent any deterioration in the case of the withdrawal of any [7, 8].

DISCUSSION

Most HCMP cases have genetic causes. The identification of typical genetic mutations facilitates the diagnosis of HCMP. The disease is most often the result of mutations in genes encoding sarcomeric proteins, with mutations in β-myosin heavy chain (MYH7), myosin regulatory light chain (MYL2), essential myosin light chain (MYL3), myosin-binding cardiac protein C (MYBPC3), troponins (TNNI3 and TNNT2), and other proteins accounting for 40%–60% of cases [1, 3, 9].

In the present case, one of the two identified mutations (TNNT2) is typical and relatively common in HCM, whereas the second mutation is more characteristic of dilated CMP (TTN).

The HCMP is diagnosed based on the presence of LV wall thickening, which is extremely rare on the right ventricle. This thickening cannot be explained by increased hemodynamic load, which includes arterial hypertension and valvular heart diseases. In the proband, the quantitative criterion of myocardial thickness of ⩾15 mm is considered diagnostic [1, 3, 9]. Since 2002 until 2021 the patient exhibited the classic phenotype of nonobstructive HCMP, which is characterized by pain syndrome and various rhythm disturbances. HCMP-related heart failure is more often associated with diastolic dysfunction, primarily in the early disease stages. In some patients (5%–8% of those suffering from HCMP), a systolic component may be added due to the burnout phenomenon, which is characterized by a decrease in LV EF ⩽50%, LV wall thinning, and LV cavity dilation [3, 4]. The term "burnout HCMP" has been proposed to distinguish this phenotype, which is novel for the patient and emerged during disease progression, from the phenotype at the time of diagnosis [4]. Currently, no clear criteria can be used to predict the transition from the hypertrophic stage to the burnout phase. However, several potential factors have been identified, including certain mutations of genes encoding the synthesis of sarcomere proteins, family history of a terminal dilated stage of HCMP, AF, and degree of late signal enhancement by gadolinium, which reflects the severity of fibrosis on cardiac MRI [3, 4]. EF is not an optimal method for the early detection of the burnout phenomenon. Changes of myocardial longitudinal strain over time allows an unfavorable prognosis assumed. In recent years, echocardiographic assessment of myocardial longitudinal strain has become a widely used diagnostic tool. D.M. Adamczak et al. revealed an association between myocardial longitudinal strain and burnout [10]. Longitudinal LV myocardial strain was assesed in the patient at the stage of EF restoration in 2022 and 2024. It appeared to be reduced and did not improve significantly in 2024 compared with 2022, whereas EF increased from 49% to 55%. Unfortunately, this parameter was not determined before 2022.

Our patient experienced a transformation of hypertrophic phenotype into dilated phenotype due to several reasons. These include multiple mutations (one of which may lead to both hypertrophic and dilatational phenotypes), cardiac rhythm disorders, including AF, and, possibly, longitudinal deformation disorders of the LV myocardium.

Before the introduction of quadruple therapy in clinical practice, the burnout phase was assumed to represent a terminal stage of HCMP, and patients entering this phase are deemed potential candidates for heart transplantation. Our example illustrates the reversibility of changes with the timely initiation of quadruple therapy involving angiotensin II receptor type 1 and neprilysin ingibitor with sodium-glucose cotransporter type 2 inhibitor, mineralocorticoid receptor antagonist, and β-adrenoblocker. Currently, mavacamten, a selective allosteric inhibitor of cardiac myosin adenosine triphosphatase, for HCMP treatment is registered in some countries [1, 3]. However, no information is available about the effect of mavacamten on the burnout phenomenon.

In patients undergoing quadruple therapy, both systolic and diastolic indices significantly improved. This was accompanied by a tendency for LA myocardial deformation parameters to increase, reflecting an improvement in the state of the LA function.

A separate discussion is warranted regarding cardiac rhythm disorders. The most prevalent rhythm disturbance in HCMP is AF, which occurs following excessive hemodynamic load, leading to LA dilatation.

The treatment and prophylaxis of AF in HCMP are initiated according to the general principles of the recommendations for AF diagnosis and treatment, which may include certain adjustments because of the specifics of the underlying disease. Considering the high incidence of stroke in the setting of AF in HCMP, anticoagulants are recommended regardless of the presence or absence of risk scores for ischemic stroke and systemic embolism [1]. Both warfarin and direct oral anticoagulants (apixaban, dabigatran, and rivaroxaban) are used. Sinus rhythm is preferred to AF in patients with HCMP; therefore, all options should be used to maintain sinus rhythm, including pulmonary vein isolation, which was attempted in this patient with a positive effect. Amiodarone is the optimal drug for sinus rhythm control. However, in the described case, owing to the rapid development of cordarone-induced thyrotoxicosis further therapy with this drug is impossible.

Non-sustained and sustained VT is a common finding in patients with HCMP. Owing to the high risk of SCD in this pathology, risk stratification and determination of indications for ICD placement are essential [1, 3, 11, 12]. In this patient, the sustained VT accompanied by hemodynamic abnormalities necessitated ICD insertion in 2007 and replacements in 2012 and 2020 because of battery depletion. Before each replacement, the risk of SCD must be reevaluated because it may decrease over time.

CONCLUSIONS

The HCMP course in each patient is highly variable, ranging from asymptomatic to severe progressive symptoms,

including Burned-out phase of HCMP, and premature death. In the context of regular follow-up, the physician should promptly identify markers and signs of an unfavorable prognosis and initiate therapy to improve the prognosis. In the presence of risk factors for SCD, ICD implantation is indicated. In patients with signs of burned-out phase and a decreased LV EF, therapies for chronic heart failure, including quadruple therapy, may be beneficial.

ADDITIONAL INFORMATION

Consent for publication. Written consent was obtained from the patient for publication of relevant medical information and all of accompanying images within the manuscript.

Author contribution. Thereby, all authors confirm that their authorship complies with the international ICMJE criteria (all authors have made a significant contribution to the development of the concept, research, and preparation of the article, as well as read and approved the final version before its publication).

Personal contribution of the authors: T.N. Novikova — concept, design, collection and processing of materials, data analysis, text writing, literature review; A.E. Andreeva — collection and processing of echocardiography data; F.I. Bitakova — collection and analysis of daily monitoring data; V.I. Novikov — cprocessing and analysis of echocardiography data, literature review; K.A. Gladysheva — literature review; P.V. Petrova — processing of materials; P.A. Stalnova, N.A. Tokareva — collection of material.

Competing interests. The authors declare that they have no competing interests.

Funding source. This study was not supported by any external sources of funding.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Информированное согласие на публикацию. Авторы получили согласие пациента на публикацию медицинских данных и всех аккомпанирующих изображений.

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Вклад каждого автора. Т.Н. Новикова — концепция, дизайн, сбор и обработка материалов, анализ данных, написание текста, обзор литературы; А.Е. Андреева — сбор и обработка ЭхоКГ данных; Ф.И. Битакова — сбор и анализ данных суточного мониторирования; К.А. Гладышева — обзор литературы; В.И. Новиков — обработка и анализ ЭХОКГ данных, обзор литературы; П.В. Петрова — обработка материалов; П.А. Стальнова, Н.А. Токарева — сбор материала.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

REFERENCES

1. Arbelo E, Protonotarios A, Gimeno JR, et al. 2023 ESC Guidelines for the management of cardiomyopathies. *Eur Heart J.* 2023;44(37):3503–3626. doi: 10.1093/eurheartj/ehad194

2. Raphael CE, Cooper R, Parker KH, et al. 2016 Mechanisms of myocardial ischemia in hypertrophic cardiomyopathy: insights from wave intensity analysis and magnetic resonance. *J Am Coll Cardiol.* 2016;68(15):1651–1660. doi: 10.1016/j.jacc.2016.07.751

3. Novikov VI, Novikova TN. *Cardiomyopathies*. 2nd ed., rev. and supplement. Moscow: MEDpress-Inform; 2024. 144 p. (In Russ.)

4. Brinkley DM, Wells OS, Stevenson LW. Avoiding burnout from hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2020;75(24): 3044–3047. doi: 10.1016/j.jacc.2020.05.009

5. Potter E, Marwick TH. Assessment of left ventricular function by echocardiography: the case for routinely adding global longitudinal strain to ejection fraction. *JACC Cardiovasc Imaging*. 2018;11(2(Pt 1)):260–274. doi: 10.1016/j.jcmg.2017.11.017

6. Pathan F, D'Elia N, Nolan MT, et al. Normal ranges of left atrial strain by speckle-tracking echocardiography: a systematic review and meta-analysis. *J Am Soc Echocardiogr*. 2017;30(1):59–70.e8. doi: 10.1016/j.echo.2016.09.007

7. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of

Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. *Euro Heart J.* 2021;42(36):3599–3726. doi: 10.1093/eurheartj/ehab368

8. Tereshchenko SN, Galyavich AS, Uskach TM, et al. 2020 Clinical practice guidelines for Chronic heart failure. *Russian Journal of Cardiology*. 2020;25(11):311–374. EDN: LJGGQV doi: 10.15829/1560-4071-2020-4083

9. Gabrusenko SA, Gudkova AYa, Koziolova NA, et al. 2020 Clinical practice guidelines for Hypertrophic cardiomyopathy. *Russian Journal of Cardiology*. 2021;26(5):269–334. EDN: MXDYLE doi: 10.15829/1560-4071-2021-4541

10. Adamczak DM, Rogala A, Antoniak M, Oko-Sarnowska Z. New predictors of burned-out phase in hypertrophic cardiomyopathy. *Eur Heart J Cardiovasc Imaging.* 2020;21(Supplement_1). doi: 10.1093/ehjci/jez319.828

11. Zeppenfeld K, Tfelt-Hansen J, de Riva M, et al. 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J.* 2022;43(40):3997–4126. doi: 10.1093/eurheartj/ehac262

12. Novikova TN, Bitakova FI, Ignatieva VS, et al. European guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death 2022: cardiomyopathy. What's new? *Cardiac Arrhythmias.* 2023;3(3):41–62. EDN: DHKBZF doi: 10.17816/cardar56

СПИСОК ЛИТЕРАТУРЫ

1. Arbelo E., Protonotarios A., Gimeno J.R., et al. 2023 ESC Guidelines for the management of cardiomyopathies // Eur Heart J. 2023. Vol. 44, N. 37. P. 3503–3626. doi: 10.1093/eurheartj/ehad194

2. Raphael C.E., Cooper R., Parker K.H., et al. 2016 Mechanisms of myocardial ischemia in hypertrophic cardiomyopathy: insights from wave intensity analysis and magnetic resonance // J Am Coll Cardiol. 2016. Vol. 68, N. 15. P. 1651–1660. doi: 10.1016/j.jacc.2016.07.751

3. Новиков В.И., НовиковаТ.Н. Кардиомиопатии. 2-е изд., перераб. и доп. Москва: МЕДпресс-информ, 2024. 144 с.

4. Brinkley D.M., Wells O.S., Stevenson L.W. Avoiding burnout from hypertrophic cardiomyopathy // J Am Coll Cardiol. 2020. Vol. 75, N. 24. P. 3044–3047. doi: 10.1016/j.jacc.2020.05.009

5. Potter E., Marwick T.H. Assessment of left ventricular function by echocardiography: the case for routinely adding global longitudinal strain to ejection fraction // JACC Cardiovasc Imaging. 2018. Vol. 11, N. 2 (Pt 1). P. 260–274. doi: 10.1016/j.jcmg.2017.11.017

6. Pathan F., D'Elia N., Nolan M.T., et al. Normal ranges of left atrial strain by speckle-tracking echocardiography: a systematic review and meta-analysis // J Am Soc Echocardiogr. 2017. Vol. 30, N. 1. P. 59–70.e8. doi: 10.1016/j.echo.2016.09.007

7. McDonagh T.A., Metra M., Adamo M., et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC // Euro Heart J. 2021. Vol. 42, N. 36. P. 3599–3726. doi: 10.1093/eurheartj/ehab368

8. Терещенко С.Н., Галявич А.С., Ускач Т.М., и др. Хроническая сердечная недостаточность. Клинические рекомендации 2020 // Российский кардиологический журнал. 2020. Т. 25, № 11. С. 1–64. EDN: LJGGQV doi: 10.15829/1560-4071-2020-4083

9. Габрусенко С.А., Гудкова А.Я., Козиолова Н.А., и др. Гипертрофическая кардиомиопатия. Клинические рекомендации 2020 // Российский кардиологический журнал. 2021. Т. 26, № 5. С. 269–334. EDN: MXDYLE doi: 10.15829/1560-4071-2021-454

10. Adamczak D.M., Rogala A., Antoniak M., Oko-Sarnowska Z. New predictors of burned-out phase in hypertrophic cardiomyopathy // Eur Heart J Cardiovasc Imaging. 2020. Vol. 21. (Supplement_1). doi: 10.1093/ehjci/jez319.828

11. Zeppenfeld K., Tfelt-Hansen J., de Riva M., et al. 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death // Eur Heart J. 2022. Vol. 43, N. 40. P. 3997–4126. doi: 10.1093/eurheartj/ehac262

12. Новикова Т.Н., Битакова Ф.И., Игнатьева В.С., и др. Европейские рекомендации по лечению пациентов с желудочковыми аритмиями и профилактике внезапной сердечной смерти 2022 года: кардиомиопатии. Что нового? // Cardiac Arrhythmias. 2023. Т. 3, № 3. С. 41–62. EDN: EDN: DHKBZF doi: 10.17816/cardar56

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