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

Tatsiana I. Balabanovich[1], Valentina S. Golyshko[1], Irina A. Sinkevich[2], Elen S. Shkuta[2], Elizaveta A. Veniadziktava[2], Pavel V. Baliuk[2], Alexei V. Knysh[2]

[1] Grodno State Medical University, Grodno, Belarus;

[2] City Clinical Hospital No. 3 of Grodno, Grodno, Belarus

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

Т.И. Балабанович[1], В.С. Голышко[1], И.А. Синкевич[2], Э.С. Шкута[2], Е.А. Венедиктова[2], П.В. Балюк[2], А.В. Кныш[2]

[1] Гродненский государственный медицинский университет, Гродно, Беларусь;

[2] Городская клиническая больница № 3, Гродно, Беларусь

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.

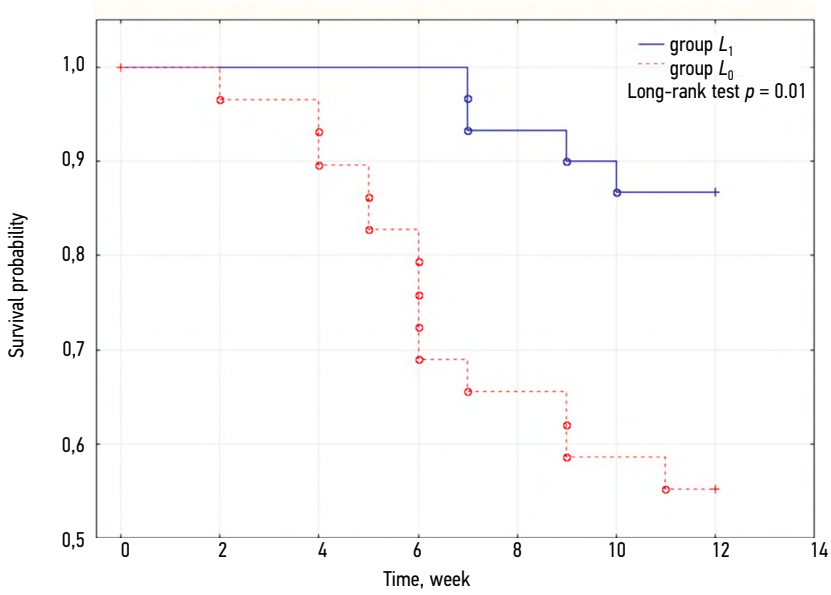

Fig. 1. Kaplan – Meier curves of end-point "atrial fibrillation recurrence"
Рис. 1. Кривые Каплана – Майера для конечной точки «рецидив фибрилляции предсердий»

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

AUTHORS INFO

***Tatsiana I. Balabanovich,** MD, Cand. Sci. (Med.), Associated Professor, Grodno State Medical University, address: Republic of Belarus, Grodno, 230009, Gorky str., 80; eLibrary SPIN: 8776-7636; ORCID: 0000-0002-5552-8764, e-mail: TatiBo1@yandex.ru

Valentina S. Golyshko, MD, Cand. Sci. (Med.), Associated Professor, ORCID: 0000-0001-9907-6192; eLibrary SPIN: 3743-3770; e-mail: vgolyshko@inbox.ru

Irina A. Sinkevich, cardiologist; e-mail: irina5897509@gmail.com

Elen S. Shkuta, clinical pharmacologist; e-mail: ellashkuta@gmail.com

Elizaveta A. Veniadziktova, cardiologist; e-mail: agent.vms@gmail.com

Pavel V. Baliuk, cardiologist; e-mail: pbalyuk98@mail.ru

Alexei V. Knysh, doctor of ultrasound diagnostics; e-mail: alekseiknysh19@ail.com

ОБ АВТОРАХ

***Татьяна Игоревна Балабанович,** канд. мед. наук, доцент, Гродненский государственный медицинский университет, адрес: Республика Беларусь, г. Гродно, ул. Горького, 80, 230009; eLibrary SPIN: 8776-7636, ORCID: 0000-0002-5552-8764, e-mail: TatiBo1@yandex.ru

Валентина Святославовна Голышко, канд. мед. наук, доцент; ORCID: 0000-0001-9907-6192, eLibrary SPIN: 3743-3770, e-mail: vgolyshko@inbox.ru

Ирина Александровна Синкевич, врач-кардиолог; e-mail: irina5897509@gmail.com

Элен Станиславовна Шкута, врач-клинический фармаколог; e-mail: ellashkuta@gmail.com

Елизавета Александровна Венедиктова, врач-кардиолог; e-mail: agent.vms@gmail.com

Павел Валерьевич Балюк, врач-кардиолог; e-mail: pbalyuk98@mail.ru

Алексей Викторович Кныш, врач ультразвуковой диагностики; e-mail: alekseiknysh19@ail.com

* Corresponding author / Автор, ответственный за переписку