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Research Article

Correction of protein and lipid spectra of erythrocyte membranes as a pathogenetic supplement to the therapy of coronary heart disease

Svetlana G. Dorofeeva[1], Eugenia N. Konoplya[1], Oksana V. Mansimova[1]

1 Kursk State Medical University, 3 Karl Marx St., Kursk 305041 Russia

Corresponding author: Svetlana G. Dorofeeva (Swet.naumova@yandex.ru)

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Abstract

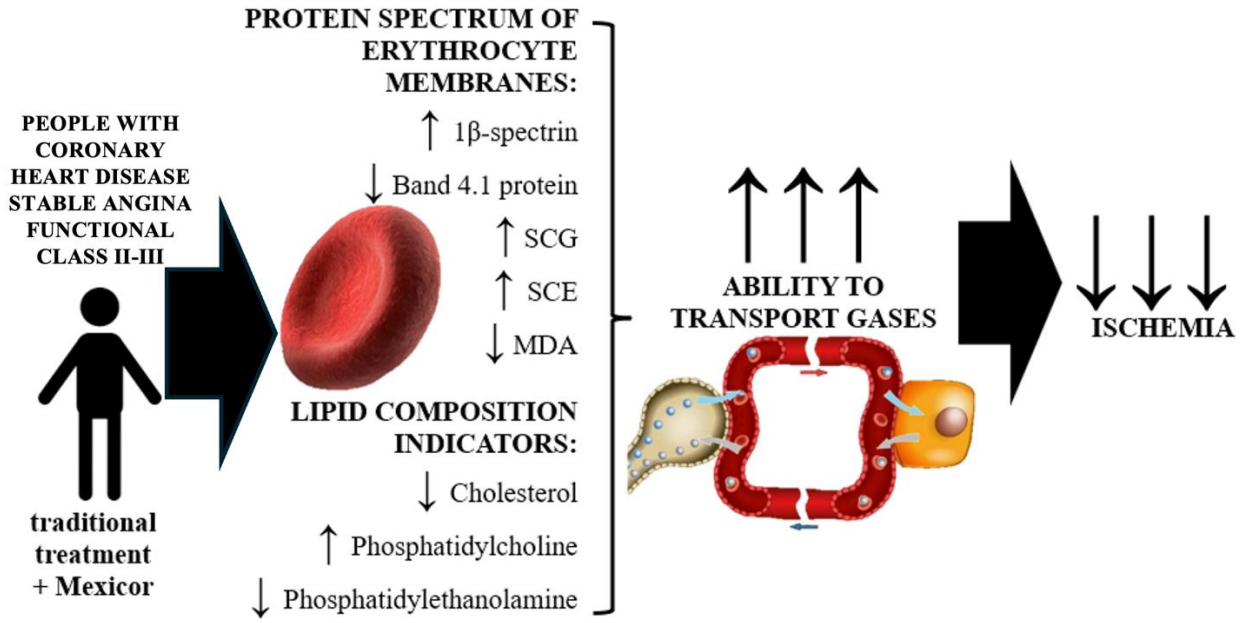
Introduction: Coronary heart disease is currently a pressing problem in the medical and scientific community. The hemic component, which is a disruption of the ability of red blood cells to effectively exchange gases, is of great importance in ischemic myocardial damage. Oxidative stress, through functional and structural changes in red blood cells, can significantly impair the efficiency of oxygen delivery to tissues.

Materials and Methods: In this clinical study, 80 patients suffering from coronary heart disease (stable angina pectoris functional class II-III) were selected. They were divided into two groups, one of which received traditional treatment, and the other – traditional treatment in combination with Mexicor. Before the start of taking the drugs and 11 days after the start of therapy, the clinical condition of the patients, bicycle ergometry indicators and the values of protein and lipid spectra of erythrocyte membranes were assessed.

Results: Addition of Mexicor, a drug with antioxidant and endothelioprotective properties, to the classical approach to therapy resulted in correction of various clinical parameters by values from 11% to 58.82%; bicycle ergometry – from 20.29% to 70.31%; protein spectrum of erythrocyte membranes – from 3.08% to 75.41%; and lipid spectrum – from 8.67% to 35.83%. Moreover, most of the studied parameters statistically significantly differed from those both in the control group and the traditional treatment group.

Conclusion: The combination of traditional treatment with single daily intravenous injections of 5 mL of Mexicor (ethylmethylhydroxypyridine succinate 50 mg/mL), made it possible not only to improve the clinical course and functional indicators, but also to positively influence the pathogenetic causes of ischemia development through significant, statistically reliable correction of the indicators of the protein and lipid spectrum of red blood cell membranes.

Graphical abstract



Keywords oxidative stress, cardiovascular diseases, clinical trial, Mexicor, antioxidant

Introduction

Cardiovascular diseases are the leading cause of both morbidity and mortality. The World Health Organization notes that 18 million people died from these diseases in 2019. At the same time, the cause of death for more than 40% of those who died from cardiovascular pathology is coronary heart disease (CHD) (Rethy et al. 2020; Agienko et al. 2022; Cardiovascular Diseases 2024).

The pathogenesis of most cardiovascular diseases is based on circulatory insufficiency in the tissues supplied with blood due to changes in the walls of blood vessels and/or the impossibility or insufficiency of blood perfusion through them. The hemic component, which is a disruption of the ability of red blood cells to effectively exchange gases, may be of the utmost importance in these mechanisms (Suslin et al. 2024).

Despite the polyetiology of cardiovascular diseases, oxidative stress as a manifestation of endothelial dysfunction and aberrant inflammatory reactions is considered as an increasingly significant pathogenetic mechanism of their development in the scientific community (Shcheblykin et al. 2022; Zhang and Dhalla 2024). Dysfunction of endothelial cells with this mechanism leads to discoordination of the release of pro- and anti-inflammatory cytokines, as well as pro- and anticoagulants, which, together with a decrease in the synthesis of nitric oxide, potentiates free radical oxidation (Shilov et al. 2017). Such discordant biochemical effects are capable of significantly altering the protein and lipid composition of erythrocyte membranes, thus reducing their metabolic activity. Such disturbances in erythrocyte membranes, combined with changes in the walls of blood vessels, create circulatory failure and, as a consequence, ischemic tissue damage, which underlie the most socially significant forms of cardiovascular pathology.

Traditional therapy of CHD has repeatedly proven itself as a method of treatment that significantly improves the quality of life and prognosis of patients with such diseases. However, the epidemiology of CHD, morbidity and mortality rates show that it is necessary to continue searching for new approaches to therapy in this area, including pathogenetic (Kosolapov and Yarmonova 2021).

The drug Mexicor, which has antioxidant and endothelioprotective properties, is able to

suppress oxidative stress and, therefore, restore the biochemical structure and gas exchange function of erythrocyte membranes, which can significantly complement traditional systems of therapy for cardiovascular diseases and CHD in particular.

Materials and Methods

Experimental groups

Based on the purpose of the study, 40 healthy individuals (control group) and 80 patients who periodically underwent inpatient treatment for CHD (stable angina functional class II-III) were selected. The criteria for inclusion and exclusion of patients are given in Table 1.

Table 1. Inclusion and exclusion criteria for patients

Inclusion criteria for patients	Exclusion criteria for patients
Men and women aged 40-65 years	Patients are under 40 and over 65 years old
Voluntary informed consent of patients for the study	Hemodynamically significant rhythm and conduction disturbances
Coronary heart disease, stable angina pectoris functional class II-III	Echocardiography data: left ventricular ejection fraction <40%
Confirmed clinically characteristic pain syndrome and bicycle ergometry data (ST segment depression >1 mm lasting more than 0.08 sec)	Progressive angina or unstable angina, angina of effort IV functional class
Regular intake of antianginal medications prior to the study	Need for intensive care
Absence of alcohol and drug addiction	The presence of chronic diseases, other than coronary heart disease, requiring dispensary observation
Patient's ability to independently fill out a questionnaire in Russian	Renal, hepatic and respiratory failure
	The presence of contraindications to the administration or hypersensitivity to any of the drugs used in the study
	Participation in another clinical drug trial within the last 3 months
	The presence of an inflammatory process of any etiology and localization or its relief less than 7 days before blood sampling for participation in the study

All patients were initially divided into 2 experimental groups comparable in age, gender, clinical data, and threshold load level in bicycle ergometry (BEM). The age of the patients ranged from 40 to 65 years (mean age 51.18±0.63). Among the subjects, 41 were women (51.3%) and 39 were men (48.7%). The characteristics of the groups are presented in Table 2.

Table 2. Characteristics of the experimental groups participating in the study

№	Group	Therapy	Purpose of the study
1	19 men, 21 women; average age 51.01±0.11 years	Traditional treatment	Study of the influence of traditional treatment on the protein and lipid spectrum, metabolic activity of erythrocyte membranes; clinical course of angina in patients with coronary heart disease.
2	20 men, 20 women; average age 51.18±0.75 years	Traditional treatment + Mexicor	Study of the effect of the antioxidant Mexicor as part of complex treatment on the protein and lipid spectrum, metabolic activity of erythrocyte membranes; clinical course of angina in patients with coronary heart disease.

Patients of the 1st group (40 people) received standard therapy, including β-blockers (metoprolol 50±25 mg/day (Egilok, Egis, Hungary), antiplatelet agents (aspirin 75±25 mg/day) to improve the rheological properties of the blood, ACE inhibitors (perindopril at a dose of 8 mg/day) (Prestarium, Servier, France) to influence the processes of remodeling and lowering blood pressure, and nitrates (Nitroglycerin 0.5 mg, sublingually) (JSC Pharmstandard-Leksredstva, Russia) were added to the treatment on demand.

Patients of the 2nd group (40 people) were additionally prescribed Mexicor (EcoPharmInvest LLC, Russia) (ethylmethylhydroxypyridine succinate 50 mg/mL), which was administered by injection of 5.0 mL intravenously once a day for 10 days in the morning between 10:00-11:00 am.

Parameters studied

The collection of complaints was carried out in the form of a conversation with the subsequent use of a clinical diary. Every day, patients independently noted the number of angina attacks per day,

the number of nitroglycerin tablets used per day and the rate of relief of attacks in minutes, the value of systolic blood pressure (SBP) and diastolic blood pressure (DBP), as well as other manifestations that patients associated with the therapy. Quality control of treatment was based on the analysis of clinical dynamics (reduction of pain syndrome, reduction in the need for nitroglycerin, the rate of relief of attacks) after 11 days of taking the drugs.

The patients also underwent daily monitoring of the electrocardiogram (ECG) using Holter. The study was performed using the Polispektr-SM hardware and software package (Neurosoft, Russia). The recording duration was 24 hours. During the daily monitoring, the number of ST-segment depression episodes, the duration of ST-segment depression episodes, and the daily duration of myocardial ischemia were assessed.

Patients' tolerance to physical activity was assessed using the method of paired BEMs using an intermittent, stepwise increasing scheme. The study was conducted on an empty stomach in the morning or 1.5-2 hours after eating. Submaximal loads were calculated using the R. Shephard nomogram, taking into account the patient's gender, age, and weight. The total duration of the load was limited to 16 minutes, the duration of each stage and the pause between them were 4 minutes. The following indicators were calculated: threshold load power (Wth, W), total load power (Wt, W), load duration in minutes, and the rate-pressure product (RPP) in accordance with generally accepted methods.

Blood was taken from the patients in the morning after a 12-hour fast. To isolate pure membrane fractions, erythrocytes were destroyed by osmotic "shock" using the G.T. Dodge method (Gavrilyuk 2011).

The protein component of the erythrocyte membrane was determined using a modified one-dimensional electrophoresis in the presence of sodium dodecyl sulfate according to the Laemmli method. To obtain the analyzed sample for electrophoresis, 50 μL of erythrocyte membranes and 20 μL of equilibration buffer were collected with the composition (per 10 mL): 3 g of urea, 0.2 mL of sodium dodecyl sulfate, 1.25 mL of 0.5 M TRIS-HCl solution (pH = 6.8 ± 0.5), 0.5 mL of mercaptoethanol, and 5 μL of bromophenol blue dye. Electrophoresis was carried out at a current of 35 mA until the voltage increased to 300 V, then stabilized at this voltage and electrophoresis was carried out in the mode until the main dye reached 1 cm to the edge of the plate. Electropherograms were stained with Coomassie G-255 dye using a modified Fairbanks method.. Identification and counting of protein fractions according to the Stack-Fairbanks classification were performed on an IBM PA/AT PVM using the OneDscan software package (Demyanov et al. 2013). The amount of protein in the fractions was calculated based on the known mass of the marker protein human serum albumin, excluding the mass of hemoglobin, and was expressed in micrograms per 1 milligram of total membrane protein.

To study the parameters of lipid metabolism, erythrocyte membranes and high-density lipoproteins (HDL) were used. HDL was isolated from blood plasma by heparin-manganese precipitation of apo-B-containing lipoproteins. The erythrocyte mass was obtained by three-fold washing from blood plasma with isotonic sodium chloride solution followed by centrifugation at 3000 rpm. The spectra of neutral lipids of HDL and erythrocyte membranes were obtained by thin-layer chromatography.

Statistical data processing

Statistical analysis was performed using IBM SPSS Statistics 26 and Microsoft Excel 2010 software (USA). Using descriptive statistics methods, the data were checked for normal distribution using the Shapiro-Wilk criterion. With a normal distribution, the data were presented as the mean and standard deviation (M±SD), with a distribution different from normal; the median and interquartile range were calculated. When analyzing data, intergroup differences were determined by parametric or nonparametric methods, depending on a type of distribution. In the case of a normal distribution, when analyzing differences between two samples, the Student criterion was used, when comparing more than two samples, the methods of variance analysis with a check for the equality of variances and performing post hoc tests were used. For distributions different from normal, the Mann and Whitney U-test was used when comparing two independent samples, the Wilcoxon test – when comparing two dependent samples, and for multiple comparisons, the Kruskal-Wallis H-test – for independent samples or Friedman – in case of dependent samples, with recalculation of the critical significance level. Differences were considered significant at $p<0.05$.

Results

When analyzing the effect of traditional therapy on the clinical course of CHD, it was found that all the studied parameters decreased, subjectively improving the condition of patients. Thus, the frequency of angina attacks statistically significantly decreased by 28.11%; the time

of attack relief – by 39.22%; SBP – by 10.73%; the number of ST segment depression episodes – by 12.28%; and daily duration of myocardial ischemia – by 12.81%. At the same time, the inclusion of Mexicor in the treatment regimen led to statistically significant improvements in most of the studied parameters both in relation to the group that did not receive treatment and the traditional therapy group: the number of angina attacks decreased by 42.35% in relation to the control group; the time of attack relief – by 58.82%; SBP – by 11% ($p>0.05$ when compared with the traditional therapy group); the number of ST segment depression episodes – by 24.56%; daily duration of myocardial ischemia – by 24.51%; and duration of ST depression episodes – by 14.33%.

The results of clinical characteristics in patients with CHD when Mexicor was included in the complex therapy are presented in Table 3.

Table 3. Dynamics of clinical characteristics in patients with CHD stable angina functional class II-III, with the inclusion of Mexicor in the complex therapy (M±m)

Indicators	Patients with CHD: Before treatment n=80	Patients with CHD: After traditional treatment n=40	Patients with CHD: After traditional treatment + Mexicor n=40
Angina attacks per day, attack/day.	2.81±0.21	2.02±0.26*	1.62±0.28*#
Daily use of Nitroglycerin, tablets/day.	2.17±1.27	1.98±1.03	1.54±0.77
Time to stop attacks, min	5.1±0.3	3.1±0.3*	2.1±0.5*#
SBP, mmHg	148.2±6.7	132.3±9.1*	131.9±6.4*
DBP, mmHg	90.5±12.8	87.0±11.7	85.5±9.9
Number of ST depression episodes, episode/day.	5.7±1.3	5.0±0.61*	4.3±0.55*#
Daily duration of myocardial ischemia, min	35.9±2.52	31.3±2.11*	27.1±1.89*#
Duration of ST depression episodes, sec	592.3±142.9	572.4±113.3	507.4±85.7*#

Note: * – $p<0.05$ in comparative analysis with the group before treatment, # – $p<0.05$ in comparative analysis with the group receiving traditional therapy. SBP – systolic blood pressure, DBP – diastolic blood pressure.

The study noted a significant decrease in the BEM test values in patients before treatment relative to the group of healthy individuals. The use of traditional therapy statistically significantly led to an increase in the studied parameters relative to the group before treatment: Wth increased by 17.77%; Wt – by 58.57%; load time – by 45.31%; and RPP – by 9.28%. The addition of Mexicor to the traditional treatment regimen also improved the BEM test results: Wth increased by 43.07%; Wt – by 70.31%; load time – by 64.06%; and RPP – by 20.29%. It should be noted that all the studied parameters in the group of patients receiving Mexicor were significantly higher than in patients receiving only traditional therapy, but did not reach the parameters of the group of healthy individuals.

The results of the BEM test indicators in patients with CHD depending on the treatment are presented in Table 4.

Table 4. Dynamics of changes in BEM indices in patients with CHD stable angina functional class II-III during therapy with Mexicor (M±m)

Indicators	Healthy individuals n=40	Patients with CHD: Before treatment n=80	Patients with CHD: After traditional treatment n=40	Patients with CHD: After traditional treatment + Mexicor n=40
W_{th}, W	120.0±1.64	74.3±2.9#	87.5±2.6*#	106.3±1.6*#a
W_t, W	800.3±22.9	448.9±37.5#	711.8±49.4*#	764.5±45.1#a
Load duration, min	20.0±0.1	6.4±0.4#	9.3±0.4*#	10.5±0.3*#a
RPP, conv. units	268.5±5.5	174.5±3.5#	190.7±5.3*#	209.9±5.1*#a

Note: * – $p<0.05$ in comparative analysis with the group before treatment, # – $p<0.05$ in comparative analysis with the control group of healthy individuals; a – $p<0.05$ in comparative analysis with the group receiving traditional therapy. Wth – threshold load power, Wt – total load power, RPP – rate-pressure product.

When studying the indicators of the protein status of erythrocytes using traditional treatment in patients with CHD, the identified indicators remained virtually unchanged compared to the group of patients before treatment.

In the group of patients receiving traditional treatment, relative to the group that did not receive therapy, a partial statistically significant correction of a number of indicators of the protein spectrum of erythrocyte membranes was noted: the value of 1α-spectrin was higher by 9.84%; anion transport protein (ATP) – by 4.34%; ankyrin – by 10.26%; band 4.5 protein – by 6.65%; and G-3-PD – by 11.79%.

When using the drug Mexicor in patients with CHD, stable angina functional class II-III, a slightly more pronounced statistically significant correction of a significantly wider range of parameters of the protein spectrum of erythrocyte membranes was recorded: the value of 1α-spectrin was higher by 18.06%; 1β-spectrin – by 8.05%; АТБ – by 3.08% (p>0,05 when compared with the traditional therapy group); ankyrin – by 16.72%; band 4.5 protein – by 16.16%; G-3-PD – by 17.69%, G-S-T – by 11.67%; sorption capacity of erythrocytes (SCE) – by 75.41%; and sorption capacity of glycocalyx (SCG) – by 11.67%. The level of band 4.1 protein decreased by 7.28%; intracellular concentrations of malondialdehyde (MDA) were 7.84% lower.

It should be noted that the use of both traditional therapy and its combination with Mexicor did not allow achieving the indicators of the group of healthy individuals. The results of the study of the protein spectrum of erythrocyte membranes in patients with CHD with stable angina functional class II-III against the background of pharmacological correction are presented in Table 5.

Table 5. Protein spectrum of erythrocyte membranes in patients with CHD stable angina functional class II-III (mg%, M±m) against the background of pharmacological correction using Mexicor in complex therapy

Indicators	Healthy individuals n=40	Patients with CHD: Before treatment n=80	Patients with CHD: After traditional treatment n=40	Patients with CHD: After traditional treatment + Mexicor n=40
1α-spectrin	109.3±4.9	74.2±3.9*	81.5±3.22*#	87.6±4.2*#a
1β-spectrin	92.1±4.29	79.5±4.3*	80.3± 4.8*	85.9±4.05*#a
ATP	168.7±6.21	142.7±5.47*	148.9± 4.8*#	147.1±5.91*#
Ankyrin	42.71±3.17	34.1±3.66*	37.6±2.05*#	39.8±1.08*#a
Band 4.1 protein	81.4±4.1	96.1±5.3*	95.6±4.7*	89.1±3.14*#a
Pallidin	61.2±4.08	74.7±4.8*	74.6± 5.2*	73.2±4.91*
Band 4.5 protein	68.8±3.14	52.6±3.82*	56.1±1.7*#	61.1±2.92*#a
Dematin	41.2±2.04	45.6±3.33*	45.6±2.6*	44.9±4.72*
Actin	101.2±4.14	117.7±5.64*	117.7±4.2*	116.6±8.22*
Band 6 protein (G-3-PD)	53.4±1.9	40.7±3.14*	45.5±1.06*#	47.9±1.12*#a
Tropomyosin	65.3±3.08	56.2±3.81*	56.6±3.16*	57.1±4.2*
Band 8 protein (G-S-T)	58.9±2.46	44.3±2.91*	44.3±3.3*	49.1±3.0*#a
SCG	2.3±0.12	1.8±0.09*	1.8±0.08*	2.01±0.02*#a
SCE	45.2±2.9	12.2±4.84*	12.6±3.21*	21.4±2.28*#a
MDA	3.22±0.08	7.27±0.39*	7.07±0.25*	6.7±0.3*#a

Note: *– p<0.05 in comparative analysis with the control group of healthy individuals, #– p<0.05 in comparative analysis with the group of patients before treatment; a – p<0.05 in comparative analysis with the group receiving traditional therapy. ATP – anion transport protein, SCG – sorption capacity of glycocalyx, SCE – sorption capacity of erythrocytes, MDA – malondialdehyde.

When studying the composition of neutral lipids of erythrocyte membranes, no statistically significant effect of traditional treatment was found. Adding Mexicor to the treatment regimen led to a decrease in cholesterol levels by 8.67%. Moreover, traditional therapy also did not have a statistically significant effect on the fractional composition of phospholipids of erythrocytes. At the same time, the use of Mexicor in the complex treatment of patients led to a decrease in the values of phosphatidylethanolamine and sphingomyelin (by 9.69% and 15.21%, respectively) and an increase in the level of phosphatidylcholine by 35.83%.

It should be noted that the obtained lipid spectrum indices did not reach similar values in healthy individuals. Table 6 shows the lipid composition indices in patients with CHD depending on the treatment regimen.

Table 6. Lipid composition indicators in patients with CHD stable angina functional class II-III depending on the treatment regimen (mg%, M±m)

Indicators	Healthy individuals n=40	Patients with CHD: Before treatment n=80	Patients with CHD: After traditional treatment n=40	Patients with CHD: After traditional treatment + Mexicor n=40
Cholesterol	47.2±2.68	77.2±3.5*	77.0±2.1*	70.5±1.73*#a
Cholesterol esters	25.9±1.4	32.5±1.09*	32.3±1.98*	31.2±1.8*
Triglycerides	18.9±0.55	41.9±0.5*	40.6±0.9*	40.0±0.31*
Free fatty acids	11.8±0.2	20.6±0.18*	19.9±0.31*	18.0±0.71*
Mono- and diglycerides	7.06±0.35	12.9±0.5*	12.3±0.51*	11.8±0.3*
Phosphatidylcholine	43.0±0.62	17.3±1.1*	19.4±0.93*	23.5±0.8*#a
Phosphatidylethanol amine	24.6±1.3	52.6±1.82*	52.1±1.17*	47.5±1.34*#a
Lysophosphatidylch oline	2.12±0.31	6.9±2.04*	5.6±2.6*	5.4±1.72*
Sphingomyelin	23.7±0.52	44.7±1.14*	41.5±1.24*	37.9±1.05*#

Note: *– $p<0.05$ in comparative analysis with the control group of healthy individuals, #– $p<0.05$ in comparative analysis with the group of patients before treatment; a – $p<0.05$ in comparative analysis with the group receiving traditional therapy.

Discussion

Endothelial dysfunction and oxidative stress are key processes in the pathogenesis of various vascular lesions (Solus et al. 2010). By disrupting the pro- and anticoagulant, as well as pro- and anti-inflammatory activities of the vascular endothelium, these processes lead to atherogenic changes in the vascular wall and a significant increase in the risk of intravascular thrombosis (Dorofeeva et al. 2024). Free radical oxidation as a manifestation of oxidative stress, in turn, leads to structural and functional changes in erythrocyte membranes, which can significantly affect their ability to gas exchange. The combination of changes in vascular permeability, increased thrombogenicity and decreased oxygen availability (due to decreased gas exchange activity) can lead to ischemia of the tissue supplied with blood, which underlies the macroscopic manifestations of CHD and many other cardiovascular diseases.

In connection with such data, in recent decades, one of the most promising scientific directions in the field of CHD therapy are drugs with antioxidant and anti-inflammatory properties (Huo et al. 2021). Such an effect can significantly reduce the pathological synergy described above and, due to the complex effect, slow down the progression of cardiovascular pathology and improve the clinical condition of patients with such diseases.

The effectiveness of Mexicor in patients with cardiovascular diseases was first identified more than 20 years ago (Golikov et al. 2004) and has been repeatedly confirmed in later studies (Aleinikova et al. 2021). The results of our work are also consistent with those previously performed and indicate an improvement in clinical and laboratory parameters in patients with CHD stable angina functional class II-III when Mexicor is added to the treatment regimen.

Conclusion

In this study, it was shown that the use of traditional treatment regimens in patients with CHD stable angina functional class II-III leads to an improvement in the clinical parameters of such patients. At the same time, reliable improvements in the studied biochemical markers of oxidative stress were isolated or absent altogether.

Supplementation of traditional treatment with single daily intravenous injections of 5 mL of Mexicor (ethylmethylhydroxypyridine succinate 50 mg/mL), a drug with antioxidant and endothelioprotective activity, for 10 days contributed not only to a more significant improvement in the clinical picture of patients with CHD stable angina functional class II-III, but was also characterized by statistically significant correction of metabolic and gas exchange parameters of erythrocytes, thereby affecting one of the most important mechanisms of development of ischemic myocardial damage. Such a corrective effect was reflected in a significant improvement in the parameters of the protein and lipid spectrum of red blood cell membranes.

Thus, it can be concluded that it is advisable to supplement classical conservative treatment regimens with antioxidant drugs and Mexicor in particular to suppress the hemic factor of ischemia and dissociate pathogenetic chains in various forms of cardiovascular diseases.

Additional information

Conflict of interest

The authors declare the absence of a conflict of interests.

Funding

The authors have no funding to report.

Data availability

All of the data that support the findings of this study are available in the main text.

Ethics Statements

All the procedures with animals were considered and approved by the Local Ethics Committee, Kursk State Medical University (Minutes № 2 of 18 February 2013).

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Author Contribution

- **Svetlana G. Dorofeeva**, Assistant of the Department of Propaedeutics of Internal Diseases, Kursk State Medical University, Kursk, Russia; e-mail: Swet.naumova@yandex.ru; **ORCID ID:** https://orcid.org/0009-0008-1507-0569. The author had the primary role in the data collection, statistical data processing, analysis, and interpretation of the study results, prepared a draft version of the article, and translated the final version of the article into English.
- **Eugenia N. Konoplya**, Doctor of Medical Sciences, Professor of the Department of Propaedeutics of Internal Diseases, Kursk State Medical University, Kursk, Russia; e-mail: Konopljaen@kursksmu.net; **ORCID ID:** https://orcid.org/0009-0002-6861-3500. The author was the research program supervisor and contributed to the concept of the study.
- **Oksana V. Mansimova**, Candidate of Medical Sciences, Associate Professor of the Department of Propaedeutics of Internal Diseases, Kursk State Medical University, Kursk, Russia; e-mail: manoks555@mail.ru; **ORCID ID:** https://orcid.org/0009-0000-6689-4797. The author contributed to the data collection and statistical processing.