DOI 10.29254/2077-4214-2022-3-166-277-282
UDC 616.12-005.4+616.155.194:546.172.6]-085.22-036.8

[1]Khanyukov O. O., [2]Zaiats I. O.

NITRIC OXIDE DONATORS IN COMPLEX TREATMENT OF PATIENTS WITH CORONARY HEART DISEASE AND ANEMIA: ANTIISCHEMIC AND ANTIARRHYTHMIC EFFECTS

[1]Dnipro State Medical University (Dnipro, Ukraine)
[2]Dnipro Medical Institute of Traditional and Non-Traditional Medicine (Dnipro, Ukraine)
khanyukov.al@gmail.com

The most common cardiovascular disease in the world is coronary heart disease (CHD). The course of CHD against the background of anemia is associated with a more severe clinical condition. Purpose: to evaluate the clinical and functional parameters of ischemia, the presence of pathological cardiac arrhythmias and the clinical efficacy of treatment with nitric oxide donors in patients with coronary artery disease and anemia. 95 patients with IHD were examined. 53 patients with CHD and iron-deficiency anemia of main group, were divided into two subgroups. 24 patients of the first subgroup were recommended standard therapy for CHD and anemia. 29 patients of the second subgroup additionally took L-arginine. The control group consisted of 42 patients with CHD without anemia who received standard therapy. At the beginning of the study, compared to the control group, patients in the main group had more pronounced ischemic changes and heart failure; significantly lower median circadian index (CI) of heart rate; a greater number of extrasystoles; greater total number of patients with atrial fibrillation. Against the background of therapy, the index of "total burden of ischemia", CI, the percentage of changes in the number of extrasystoles in the dynamics in the second subgroup was comparable to the indicators of the control group and differed from the first subgroup.

Key words: *coronary heart disease, anemia, heart rhythm disorder, treatment.*

Communication of the publication with planned research work. The study is a fragment of the research work of the Department of Internal Medicine 3 of the Dnipro State Medical University «Clinical, functional and morphological changes in the cardiovascular system in patients with acute and chronic coronary heart disease, arterial hypertension and heart failure in combination with concomitant pathology» State registration number 0120U102731

Introduction. Ischemic heart disease (CHD) is considered the most common pathology among heart diseases both worldwide and in Ukraine. Mortality from complications of coronary artery disease is also very high. According to the World Health Organization (WHO), in the structure of mortality from cardiovascular diseases (CVD), the proportion of coronary artery disease and strokes is 85% [1, 2, 3].

According to statistics, 649,999 deaths were recorded in Ukraine in 2021. A greater number of deaths were caused by diseases of the cardiovascular system (429,291 cases), including coronary heart disease – 300,406 cases [4].

Structural changes in the heart are more common in middle-aged and older patients and underlie cardiovascular complications in general and sudden cardiac death (SCD) in particular. CVD is one of the most important causes of death in the world. Up to 20% of all cases of SCD are associated with arrhythmias [5].

The role of multifactorial influence on the risk of complications cannot be overestimated, especially in aged patients. After all, comorbidity increases with age [6-10].

Among comorbid conditions in cardiology, IHD, arrhythmias (including supraventricular and ventricular extrasystole, atrial fibrillation), arterial hypertension (AH), chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD) are more common; iron deficiency) [6, 11-19].

As with CAD, the prevalence of anemia increases with age and is associated with a more severe condition. It is known that coronary artery disease and anemia, independently of each other, have a negative impact on a person's condition, worsening the quality of life and reducing performance. At the same time, a number of studies have confirmed the negative combined effect of coronary artery disease and anemia on the risk of complications, including SCD [20-27].

The "total severity of ischemia", detected by Holter ECG monitoring (HM ECG), is an objective criterion for the severity of IHD, associated with an unfavorable prognosis (an increase in the number of acute myocardial infarctions and mortality), if it exceeds 60 minutes per day. The concept of total ischemic load includes all types of ischemia, including symptomatic and asymptomatic episodes, and should be taken into account in patients with stable angina [28].

Changes in heart rate (HR) per day can also signal an increased risk of fatal and non-fatal cardiovascular complications. Thus, changes in the circadian index (CI) may indicate insufficient activity of the vagus nerve or, conversely, excessive activation of the sympathoadrenal system, which increases the likelihood of life-threatening cardiac arrhythmia [28].

Hypoxia and nitric oxide deficiency play a significant role in the pathogenesis of ischemia [29-37], but there is insufficient data on the effect of mild and moderate anemia on the clinical and functional parameters of ischemia in middle-aged and older patients with coronary artery disease.

The therapeutic potential and safety of L-arginine for the correction of oxide deficiency have long been known [38-45], but require a more detailed study of its effect on the clinical and functional parameters of ischemia in middle-aged and older patients with coronary artery disease and anemia.

Purpose of the study – assessment of clinical and functional indicators of ischemia, the presence of pathological cardiac arrhythmias and the clinical efficacy of

Table 1 – General characteristics of the examined patients at the beginning of the study

Indicator		Main group (n=53)	Control group (n=42)	Difference between groups(p)
gender, абс. /%	male	18/ 34,0%	16/ 38,1%	>0,05
	female	35/ 66,0%	26/ 61,9%	>0,05
Age,years, M±m		73,1±1,2	72,8±1,3	>0,05
Hemoglobin, g/l, M±m		113,4±1,3	135,3±1,7	<0,001
Atrial fibrillation in history, abs. /%		19/ 35,8%	7/ 16,7%	<0,05
The average number of supraventricular extrasystoles per day, Me (LQ; HQ)		1721 (0; 4252)	79,5 (0; 315)	<0,001
Average number of ventricular extrasystoles per day, Me (LQ; HQ)		1478 (729; 3649)	434,5 (43; 1048)	<0,001
Circadian index, M±m		1,125±0,005	1,21±0,009	<0,001
* «total burden of ischemia» (min.) according to HM-ECG, Me (LQ; HQ)		135 (108; 138,0)	103,0 (48,0; 127,5)	<0,001
* «total burden of ischemia» for XM-ECG, abs. /%:		53/ 100%	42/ 100%	>0,05
FC II		11/ 20,7%	18/ 42,9%	<0,05
FC III		38/ 71,7%	20/ 47,6%	
FC IV		4/ 7,6%	4/ 9,5%	
Clinical stage of heart failure (HF):				
HF I		24/ 45,3%	26/ 61,9%	>0,05
HF II A		21/ 39,6%	11/ 26,2%	
HF II B		8/ 15,1%	5/ 11,9%	

Notes: * – «total burden of ischemia» (only for patients with angina pectoris) according to HM-ECG: FC I – less than 1% (total duration of ischemia less than 14,5 minutes); FC II – 1-4% (15-59 minutes); FC III – 5-10% (60-142 minutes); FC IV – more than 10% (total duration of ischemia more than 143 minutes) [28].

treatment with nitric oxide donors in patients with coronary artery disease and anemia.

Object and methods of research. We examined 95 patients with coronary artery disease who were hospitalized in the departments of cardiology and therapeutic profile in the city of Dnipro. The main group consisted of 53 patients (from 56 to 85 years old, on average – 73,1±1,2 years), coronary heart disease in combination with iron deficiency anemia (IDA) of mild and moderate severity (hemoglobin level – 113,4±1,3 g/l). Patients were randomly divided into two subgroups. The first subgroup of the main group consisted of 24 patients who received standard therapy for coronary artery disease and anemia (beta-blockers, ACE inhibitors or sartans, statins, aspirin; if necessary, antiarrhythmics, diuretics, calcium channel blockers; iron preparations to correct anemia). The second subgroup of the main group included 29 patients, in addition to standard therapy, they additionally received L-arginine (orally and intravenously according to the scheme: intravenously for 7-10 days (100 ml/day), followed by oral administration of 5 ml 3 times a day, 3 courses according to 30 days The control group consisted of 42 patients (from 58 to 86 years old, mean age 72,8±1,2 years) with coronary heart disease without anemia, who received standard therapy.At the beginning of the study, all groups and subgroups were statistically comparable (p>0,05) by gender, age, and main clinical and laboratory parameters [46]. The period of observation of patients was 6 months.

Statistical processing of the study materials was performed using parametric and nonparametric statistical methods implemented in the STATISTICA software package version 6.1 (Statsoft Inc., USA) (serial no. AGAR909E415822FA). To characterize and compare quantitative data distributed according to the normal law (Shapiro-Wilk and Liliefors tests), we used the arithmetic mean (M), its standard error (±m), Student's t-tests for dependent (T) and independent (t) samples, and the test Tukey's multiple comparison (Tukey's HSD); with abnormal distribution – median (Me), quartile (LQ; HQ) and the corresponding tests of Wilcoxon (W), Mann-Whitney (U) and Dunn (Dunn's Q test). Comparison of relative indicators was carried out according to Pearson's Chi-square test ($\chi 2$). Differences in indicators between groups were considered statistically significant at $p \leq 0,05$.

Results of the study and their discussion. At the beginning of the study, during Holter ECG monitoring (HM ECG), atrial fibrillation was recorded in 19 patients with coronary artery disease on the background of anemia and 7 of patients with coronary artery disease ($p<0,05$ between groups). The heart rate parameters at the beginning of the study also differed in the main and control groups: the average heart rate levels in the active/passive period of the day in patients of the main group were 82,2±1,6/73,1±1,4 bpm, and in control – 78,5±1,6/64,2±1,3 beats/min. ($p>0,05/p<0,001$). A decrease in the circadian index (the ratio of heart rate in the active period of the day to the heart rate in the passive period of the day; the norm is 1,22-1,45) was observed in 24 (57,1%) patients with coronary artery disease without anemic syndrome and in 53 (100,0%) patients IHD with anemic

Table 2 – Dynamics of the circadian index in patients of the study groups

Indicators	Control group (n=42)	1st group (n=24)	2nd group (n=29)	Differences between groups (p)
Average level of CI, M±m:				
- before treatment	1,210±0,009	1,138±0,008	1,115±0,007	$p_{к-1}<0,001$; $p_{к-2}<0,001$; $p_{1-2}>0,05$
- after 6 months*	1,277±0,007	1,231±0,010	1,282±0,010	$p_{к-1}<0,01$; $p_{к-2}>0,05$; $p_{1-2}<0,001$
Number of patients with deviations from the norm, abs./%				
- before treatment	24/ 57,1%	24/ 100%	29/ 100%	$p_{к-1}<0,001$; $p_{к-2}<0,001$; $p_{1-2}>0,05$
- after 6 months*	1/ 2,4%	11/ 45,8%	2/ 6,9%	$p_{к-1}<0,001$; $p_{к-2}>0,05$; $p_{1-2}<0,001$

Notes: *significant changes compared to the indicator for treatment in the corresponding group ($p<0,001$); $p_{к-1}$, $p_{к-2}$, p_{1-2} – the level of statistical significance of differences in indicators between the respective groups.

syndrome (p<0,001). The relevant data are shown in **table 1**.

When comparing the dynamics of the circadian heart rate index in patients of the main group – the first subgroup (patients who received only iron preparations), the second subgroup (patients who received iron preparations and L-arginine), and the control group (CHD without anemia), it was found that in patients of the control group, on the background of standard therapy of coronary artery disease, the circadian index increased significantly and reached normal values in 97,6% of patients **(table 2)**.

In the patients of the first subgroup of the main group against the background of standard therapy of coronary heart disease and anemia, the CI heart rate normalized in half (54,2%) of the patients, while in the patients of the second subgroup (with the addition of L-arginine), the restoration of the CI heart rate to normal values was noted in 93,1% of patients.

Extrasystole (both supraventricular and ventricular) is more pronounced in patients with coronary artery disease on the background of iron deficiency anemia than without it. When comparing the results of treatment of patients of both subgroups of the main group, it turned out that a greater antiarrhythmic effect was found in the second subgroup (with the addition of L-arginine). The results are shown in **table 3**.

Total severity of ischemia» (total duration of episodes of symptomatic and asymptomatic ischemia) is considered an objective measure of the severity of CAD. The initial duration of all episodes of ischemia (symptomatic and asymptomatic) was longer in the main group compared to the control group. Against the background of IHD and anemia therapy in the main group, the dynamics of the anti-ischemic effect (the percentage of changes in the indicator over time (Δ%)) was more pronounced in the second subgroup than in the first subgroup. The results are shown in **table 4**.

Table 3 – Dynamics of indicators of manifestations of arrhythmia in patients of study groups

Indicators	Control group (n=42)	1st group(n=24)	2nd group (n=29)	differences between groups(p)
The average number of extrasystoles per day, Me (LQ; HQ):				
-before treatment	880,5 (233; 1531)	4232,5 (2355; 7880)	4849 (2808; 7792)	$p_{к-1}$<0,001; $p_{к-2}$<0,001; p_{1-2}>0,05
-after 6 months*	263,5 ^^ (87; 442)	2267,5 ^^ (1243; 5105)	1832 ^^ (821; 2924)	$p_{к-1}$<0,001; $p_{к-2}$<0,001; p_{1-2}<0,05
Percentage of indicator changes in dynamics (Δ,%)	-70,9 (-78,9; -61,4)	-39,9 (-49,8; -29,5)	-65,6 (-70,7; -55,7)	$p_{к-1}$<0,001; $p_{к-2}$>0,05; p_{1-2}<0,001
The average number of supraventricular extrasystoles per day, Me (LQ; HQ):				
-before treatment	79,5 (0; 315)	1036,5 (0; 4061)	1760 (0; 4277)	$p_{к-1}$<0,01; $p_{к-2}$<0,01; p_{1-2}>0,05
-after 6 months*	21,5 (0; 87) ^^	828 (0; 3021) ^	789 (366; 1725) ^^	$p_{к-1}$<0,001; $p_{к-2}$<0,01; p_{1-2}>0,05
The average number of ventricular extrasystoles per day, Me (LQ; HQ):				
-before treatment	434,5 (43; 1048)	1603 (731; 3508,5)	1456 (728; 3892)	$p_{к-1}$<0,001; $p_{к-2}$<0,001; p_{1-2}>0,05
-after 6 months*	156 (12; 434) ^^	654 (243; 1748) ^^	450 (16; 1227) ^^	$p_{к-1}$<0,001; $p_{к-2}$>0,05; p_{1-2}<0,05

Notes: * The effectiveness of antiarrhythmic therapy – the number of cases with a decrease in the dynamics of the total number of extrasystoles per day by 50% or more; significant changes compared to the indicator for treatment in the corresponding group (^ – p<0,05; ^^ – p<0,001); $p_{к-1}$, $p_{к-2}$, p_{1-2} – the level of statistical significance of differences in indicators between the respective groups.

Table 4 – Dynamics of indicators of ischemia manifestations in patients of study groups

indicators	Control group (n=28)	1st group(n=16)	2nd group (n=20)	difference between groups(p)
The average level of «total burden of ischemia», min., Me (LQ; HQ):				
- before treatment	103,0 (48,0; 127,5)	127,0 (110,0; 138,5)	136,0 (106,0; 142,0)	$p_{к-1}$<0,01; $p_{к-2}$<0,01; p_{1-2}>0,05
– after 6 months	46,5 ^^^ (36,0; 63,0)	76,0 ^^^ (58,5; 97,0)	60,0 ^^^ (43,0; 72,0)	$p_{к-1}$<0,01; $p_{к-2}$<0,05; p_{1-2}<0,05
Percentage of indicator changes in dynamics (Δ,%)	-54,8 (-63,8; -50,6)	-40,2 (-46,8; -29,1)	-55,9 (-59,4; -49,2)	$p_{к-1}$<0,001; $p_{к-2}$>0,05; p_{1-2}<0,001

Notes: * The effectiveness of anti-ischemic therapy is the number of cases with a decrease in the dynamics of the «total burden of ischemia» by 50% or more; significant changescompared to the indicator for treatment in the corresponding group (^ – p<0,05; ^^ – p<0,01; ^^^ – p<0,001); $p_{к-1}$, $p_{к-2}$, p_{1-2} – the level of statistical significance of differences in indicators between the respective groups.

Conclusions.

1. In patients with coronary artery disease and concomitant anemia, the severity of ischemic changes, cardiac arrhythmias, and heart failure were significantly higher than in patients with coronary artery disease without anemia;

2. The median circadian heart rate index was less than normal in both groups, but in the group of patients with anemia, this indicator was significantly lower;

3. A decrease in the circadian heart rate index in iron deficiency anemia is associated with an increase in the number of supraventricular and ventricular extrasystoles and the incidence of atrial fibrillation;

4. During therapy, the “total burden of ischemia” decreased in both groups, was comparable in the second subgroup (with L-arginine) and the control group (pk-2>0,05), but remained higher in the first subgroup (pk-1 <0 ,01; p1-2<0,05);

5. The dynamics of the circadian HR index was similar: in all groups there was a decrease in HR CI, but in the first subgroup the effect was lower than the control group and the second subgroup (pk-2>0,05; pk-1<0,01; p1-2<0,001).

6. The number of extrasystoles decreased in both groups. The percentage of changes in the indicator of the number of extrasystoles in dynamics in the second subgroup was significantly higher than in the first, and then comparable with the indicator of the control group (pk-1<0,001; pk-2>0,05; pk-1<0,001).

Prospects for further research. The prospect of further research is to analyze the effect of iron metabolism on the clinical and functional parameters of ischemia in patients with coronary heart disease.

References

1. WHO. WHO reveals leading causes of death and disability worldwide: 2000-2019 [Internet]. Available from: https://www.who.int/news/item/09-12-2020-who-reveals-leading-causes-of-death-and-disability-worldwide-2000-2019.
2. WHO. World health statistics 2021: a visual summary [Internet]. Available from: https://www.who.int/data/gho/publications/world-health-statistics.
3. WHO. WHO/Health topics/Cardiovascular diseases [Internet]. Available from: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds).
4. Derzhstat Ukrayiny, 1998-2022 [Internet]. Dostupno: https://ukrstat.gov.ua/ operativ/operativ2021/ds/kpops/arh_kpops2021_u.html.
5. Zheng J, Zheng D, Su T, Cheng J. Sudden Unexplained Nocturnal Death Syndrome: The Hundred Years' Enigma. J Am Heart Assoc. 2018 Mar 3;7(5):e007837. DOI: 10.1161/JAHA.117.007837.
6. Hanyukov AA, Pesockaya LA, Sapozhnichenko LV, Pampuha AA. Rasprostranennost i patogenez anemii u pacientov s hronicheskoj serdechnoj nedostatochnostyu. Gematologiya. Transfuziologiya. Vostochnaya Evropa. 2021;7(2):219-228.
7. Sharma YP, Kaur N, Kasinadhuni G, Batta A, Chhabra P, Verma S, et al. Anemia in heart failure: still an unsolved enigma. Egypt Heart J. 2021 Aug 28;73(1):75. DOI: 10.1186/s43044-021-00200-6.
8. Ponikowski P, Anker SD, AlHabib KF, Cowie MR, Force TL, Hu S, et al. Heart failure: preventing disease and death worldwide. ESC Heart Fail. 2014;1(1):4-25. DOI: 10.1002/ehf2.12005.
9. van Veldhuisen DJ, Anker SD, Ponikowski P, Macdougall IC. Anemia and iron deficiency in heart failure: mechanisms and therapeutic approachers. Nat Rev Cardiol. 2011;8(9):485-493. DOI: 10.1038/nrcardio.2011.77.
10. Culleton BF, Manns BJ, Zhang J, Tonelli M, Klarenbach S, Hemmelgarn BR. Impact of anemia on hospitalization and mortality in older adults. Blood. 2006 May 15;107(10):3841-6. DOI: 10.1182/blood-2005-10-4308.
11. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, 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 Feb 1;42(5):373-498. DOI: 10.1093/eurheartj/ehaa612.
12. Paolillo S, Scardovi AB, Campodonico J. Role of comorbidities in heart failure prognosis Part I: Anaemia, iron deficiency, diabetes, atrial fibrillation. Eur J Prev Cardiol. 2020 Dec;27(2):27-34. DOI: 10.1177/20474873209602 88.
13. Tanaka S, Kamiya K, Saito H, Saito K, Ogasahara Y, Maekawa E, et al. Prevalence and prognostic value of the coexistence of anaemia and frailty in older patients with heart failure. ESC Heart Fail. 2021 Feb;8(1):625-633. DOI: 10.1002/ehf2.13140.
14. Pizzini A, Aichner M, Sonnweber T, Tancevski I, Weiss G, Löffler-Ragg J. The Significance of iron deficiency and anemia in a real-life COPD cohort. Int J Med Sci. 2020 Aug 19;17(14):2232-2239. DOI: 10.7150/ijms.46163.
15. Goh VJ, Tromp J, Teng TK, Tay WT, Van Der Meer P, Ling LH, et al; ASIAN-HF investigators. Prevalence, clinical correlates, and outcomes of anaemia in multi-ethnic Asian patients with heart failure with reduced ejection fraction. ESC Heart Fail. 2018 Aug;5(4):570-578. DOI: 10.1002/ehf2.12279.
16. Anand IS, Gupta P. Anemia and Iron Deficiency in Heart Failure: Current Concepts and Emerging Therapies. Circulation. 2018 Jul 3;138(1):80-98. DOI: 10.1161/CIRCULATIONAHA.118.030099.
17. Kiani FZ, Ahmadi A. Prevalence of different comorbidities in chronic obstructive pulmonary disease among Shahrekord PERSIAN cohort study in southwest Iran. Sci Rep. 2021 Jan 15;11(1):1548. DOI: 10.1038/s41598-020-79707-y.
18. Batchelor EK, Kapitsinou P, Pergola PE, Kovesdy CP, Jalal DI. Iron Deficiency in Chronic Kidney Disease: Updates on Pathophysiology, Diagnosis, and Treatment. J Am Soc Nephrol. 2020 Mar;31(3):456-468. DOI: 10.1681/ASN.2019020213.
19. Nowakowska M, Zghebi SS, Ashcroft DM, Buchan I, Chew-Graham C, Holt T, et al. The comorbidity burden of type 2 diabetes mellitus: patterns, clusters and predictions from a large English primary care cohort. BMC Med. 2019 Jul 25;17(1):145. DOI: 10.1186/s12916-019-1373-y.
20. Khan MA, Hashim MJ, Mustafa H, Baniyas MY, Al Suwaidi SKBM, AlKatheeri R, et al. Global Epidemiology of Ischemic Heart Disease: Results from the Global Burden of Disease Study. Cureus. 2020;12(7):e9349. DOI: 10.7759/cureus.9349.
21. Meng H, Wang Y, Ruan J, Chen Y, Wang X, Zhou F, et al. Decreased Iron Ion Concentrations in the Peripheral Blood Correlate with Coronary Atherosclerosis. Nutrients. 2022 Jan 13;14(2):319. DOI: 10.3390/nu14020 319.
22. Stahl-Gugger A, de Godoi Rezende Costa Molino C, Wieczorek M, Chocano-Bedoya PO, Abderhalden LA, Schaer DJ, et al. Prevalence and incidence of iron deficiency in European community-dwelling older adults: an observational analysis of the DO-HEALTH trial. Aging Clin Exp Res. 2022 Sep;34(9):2205-2215. DOI: 10.1007/s40520-022-02093-0.
23. Martens P, Verbrugge FH, Nijst P, Dupont M, Mullens W. Limited contractile reserve contributes to poor peak exercise capacity in iron-deficient heart failure. Eur J Heart Fail. 2018 Apr;20(4):806-808. DOI: 10.1002/ejhf.938.
24. Lanser L, Fuchs D, Scharnagl H, Grammer T, Kleber ME, März W, et al. Anemia of Chronic Disease in Patients With Cardiovascular Disease. Front Cardiovasc Med. 2021 Aug 12;8:666638. DOI: 10.3389/fcvm.2021.666638.
25. Rymer JA, Rao SV. Anemia and coronary artery disease: pathophysiology, prognosis, and treatment. Coron Artery Dis. 2018 Mar;29(2):161-167. DOI: 10.1097/MCA.0000000000000598.
26. González-D'Gregorio J, Miñana G, Núñez J, Núñez E, Ruiz V, García-Blas S, et al. Iron deficiency and long-term mortality in elderly patients with acute coronary syndrome. Biomark Med. 2018 Sep;12(9):987-999. DOI: 10.2217/bmm-2018-0021.
27. Colombo MG, Kirchberger I, Amann U, Heier M, Thilo C, Kuch B, et al. Association between admission anemia and long-term mortality in patients with acute myocardial infarction: results from the MONICA/KORA myocardial infarction registry. BMC Cardiovasc Disord. 2018 Mar 9;18(1):50. DOI: 10.1186/s12872-018-0785-5.
28. Bobrov VO, Zharinov OY, Kuts VO, Sorokivskyy MS, Chernyaga-Royko UP, Tkhor NV, at al. Ambulatorne monitoruvannya EKG. Lviv: Vydavnytstvo «Medytsyna svitu»; 2004. s. 67. [in Ukrainian].
29. Abe H, Semba H, Takeda N. The Roles of Hypoxia Signaling in the Pathogenesis of Cardiovascular Diseases. J Atheroscler Thromb. 2017 Sep 1;24(9):884-894. DOI: 10.5551/jat.RV17009.
30. Zheng J, Zhou C, editors. Hypoxia and Human Diseases [Internet]. London: IntechOpen; 2017 [cited 2022 Aug 24]. Chapter 11, Hypoxia and Pulmonary Hypertension. Available from: https://www.intechopen.com/chapters/53817. DOI: 10.5772/67151.
31. Liu ML, Xing SJ, Liang XQ, Luo Y, Zhang B, Li ZC, et al. Reversal of Hypoxic Pulmonary Hypertension by Hypoxia-Inducible Overexpression of Angiotensin-(1-7) in Pulmonary Endothelial Cells. Mol Ther Methods Clin Dev. 2020 Apr 18;17:975-985.
32. Babapoor-Farrokhran S, Gill D, Alzubi J, Mainigi SK. Atrial fibrillation: the role of hypoxia-inducible factor-1-regulated cytokines. Mol Cell Biochem. 2021 Jun;476(6):2283-2293. DOI: 10.1007/s11010-021-04082-9.
33. Hanna RM, Streja E, Kalantar-Zadeh K. Burden of Anemia in Chronic Kidney Disease: Beyond Erythropoietin. Adv Ther. 2021 Jan;38(1):52-75. DOI: 10.1007/s12325-020-01524-6.
34. Kaplan JM, Sharma N, Dikdan S. Hypoxia-Inducible Factor and Its Role in the Management of Anemia in Chronic Kidney Disease. Int J Mol Sci. 2018 Jan 29;19(2):389. DOI: 10.3390/ijms19020389.
35. Ostrakhovitch EA, Tabibzadeh S. Homocysteine and age-associated disorders. Ageing Res Rev. 2019 Jan;49:144-164. DOI: 10.1016/j.arr. 2018.10.010.
36. Erkens R, Suvorava T, Sutton TR, Fernandez BO, Mikus-Lelinska M, Barbarino F, et al. Nrf2 Deficiency Unmasks the Significance of Nitric Oxide Synthase Activity for Cardioprotection. Oxid Med Cell Longev. 2018 Apr 30;2018:8309698. DOI: 10.1155/2018/8309698.
37. Zinellu A, Zinellu E, Pau MC, Fois AG, Mellino S, Piras B, et al. A systematic review and meta-analysis of homocysteine concentrations in chronic obstructive pulmonary disease. Clin Exp Med. 2022 May 5. DOI: 10.1007/s10238-022-00833-0.

38. Ahmad A, Dempsey SK, Daneva Z, Azam M, Li N, Li PL, et al. Role of Nitric Oxide in the Cardiovascular and Renal Systems. Int J Mol Sci. 2018 Sep 3;19(9):2605. DOI: 10.3390/ijms19092605.
39. Yalovenko MI, Khaniukov OO. Vybir optymalnoi medykamentoznoi terapii u khvorykh z fibryliatsiieiu peredserd i komorbidnoiu palohiieiu. Morphologia. 2018;12(4):104-115. DOI: 10.26641/1997-9665.2018.4.104-115. [in Ukrainian].
40. Totzeck M, Hendgen-Cotta UB, Rassaf T. Nitrite-Nitric Oxide Signaling and Cardioprotection. Adv Exp Med Biol. 2017;982:335-346. DOI: 10.1007/978-3-319-55330-6_18.
41. Tejero J, Shiva S, Gladwin MT. Sources of Vascular Nitric Oxide and Reactive Oxygen Species and Their Regulation. Physiol Rev. 2019 Jan 1;99(1):311-379. DOI: 10.1152/physrev.00036.2017.
42. Wu G, Meininger CJ, McNeal CJ, Bazer FW, Rhoads JM. Role of L-Arginine in Nitric Oxide Synthesis and Health in Humans. Adv Exp Med Biol. 2021;1332:167-187. DOI: 10.1007/978-3-030-74180-8_10.
43. Najafi H, Abolmaali SS, Heidari R, Valizadeh H, Jafari M, Tamaddon AM, et al. Nitric oxide releasing nanofibrous Fmoc-dipeptide hydrogels for amelioration of renal ischemia/reperfusion injury. J Control Release. 2021 Sep 10;337:1-13. DOI: 10.1016/j.jconrel.2021.07.016.
44. Cziráki A, Lenkey Z, Sulyok E, Szokodi I, Koller A. L-Arginine-Nitric Oxide-Asymmetric Dimethylarginine Pathway and the Coronary Circulation: Translation of Basic Science Results to Clinical Practice. Front Pharmacol. 2020 Sep 29;11:569914. DOI: 10.3389/fphar.2020.569914.
45. Liu C, Liang MC, Soong TW. Nitric Oxide, Iron and Neurodegeneration. Front Neurosci. 2019 Feb 18;13:114. DOI: 10.3389/fnins.2019.00114.
46. Khaniukov OO, Zaiats IO. Vplyv donatoriv oksydu azotu na klinichnyi perebih ishemichnoi khvoroby sertsia z suputnoiu anemiieiu. Ukr Zh Med Biol Sport. 2022;3(37):192-199. DOI: 10.26693/jmbs07.03.192. [in Ukrainian].

ДОНАТОРИ ОКСИДУ АЗОТУ В КОМПЛЕКСНОМУ ЛІКУВАННІ ХВОРИХ З ІШЕМІЧНОЮ ХВОРОБОЮ СЕРЦЯ І АНЕМІЄЮ: АНТИІШЕМІЧНІ ТА АНТИАРИТМІЧНІ ЕФЕКТИ

Ханюков О. О., Заяць І. О.

Резюме. Ішемічна хвороба серця (ІХС) є найбільш поширеним серцево-судинним захворюванням у світі, частота виявлення якого зростає з віком. Росповсюдженість анемії також підвищується з віком і асоціюється з більш тяжким станом пацієнтів, що хворіють на ІХС. У цієї категорії хворих також зростає ризик ускладнень, у тому числі і раптової серцевої смертності (РСС). Мета: оцінка клініко-функціональних показників ішемії, наявності патологічних порушень ритму серця та клінічної ефективності лікування донаторами оксиду азоту у хворих на ІХС і анемію. Обстежено 95 хворих на ІХС. Основну групу склали 53 хворих на ІХС із залізо-дефіцитною анемією, які були поділені на дві підгрупи. 24 пацієнтам першої підгрупи була рекомендована стандартна терапія ІХС та анемії. 29 пацієнтів другої підгрупи додатково приймали L-аргінін. Контрольну групу склали 42 пацієнти з ІХС без анемії, які отримували стандартну терапію. На початку дослідження вираженість ішемічних змін та серцевої недостатності у пацієнтів основної групи була більшою, ніж у контрольній. Медіана циркадного індексу ЧСС була менша за норму в обох групах, але в основній групі цей показник був достовірно нижчим. Більша середня кількість ектрасистол (як суправентрикулярних, так і шлуночкових) зареєстрована в основній групі. Загальна кількість пацієнтів з фібриляцією передсердь була також більшою в основній групі.

На фоні терапії показник «загального тягаря ішемії» знизився в обох групах і був зіставним в другій підгрупі (з L-аргініном) і групі контролю ($p_{к-2}$>0,05), але залишався вищим у першій підгрупі ($p_{к-1}$<0,01; p_{1-2}<0,05). Динаміка циркадного індексу була схожою: у всіх групах відзначалося зниження ЦІ, але в перщій підгрупі ефект був нижчим за контрольну групу і другу підгрупу ($p_{к-2}$> 0,05; $p_{к-1}$<0,01; p_{1-2}<0,001). Кількість екстрасистол зменшилася в обох групах. Відсоток змін показника кількості екстрасистол у динаміці у другій підгрупі був достовірно вищим, ніж у першій, та був співставним з показником контрольної групи ($p_{к-1}$<0,001; $p_{к-2}$>0,05, $p_{к-1}$<0,001).

Ключові слова: ішемічна хвороба серця, анемія, порушення ритму серця, лікування.

NITRIC OXIDE DONATORS IN COMPLEX TREATMENT OF PATIENTS WITH CORONARY HEART DISEASE AND ANEMIA: ANTIISCHEMIC AND ANTIARRHYTHMIC EFFECTS

Khanyukov O. O., Zaiats I. O.

Abstract. Coronary artery disease (CHD) is the most common cardiovascular disease in the world, the incidence of which increases with age. The prevalence of anemia also increases with age and is associated with a more severe condition in patients with CAD. This category of patients also has an increased risk of complications, including sudden cardiac death (RCD). Purpose: to evaluate the clinical and functional parameters of ischemia, the presence of pathological cardiac arrhythmias and the clinical efficacy of treatment with nitric oxide donors in patients with coronary artery disease and anemia. 95 patients with IHD were examined. The main group consisted of 53 IHD patients with iron deficiency anemia, which were divided into two subgroups. 24 patients of the first subgroup were recommended standard therapy for coronary artery disease and anemia. 29 patients of the second subgroup additionally took L-arginine. The control group consisted of 42 patients with coronary artery disease without anemia who received standard therapy. At the beginning of the study, the severity of ischemic changes and heart failure in patients of the main group was greater than in the control group. The median circadian heart rate index was less than normal in both groups, but in the main group this indicator was significantly lower. A greater average number of extraistols (both supraventricular and ventricular) was registered in the main group. The total number of patients with atrial fibrillation was also higher in the main group.

During therapy, the indicator of «total ischemia burden» decreased in both groups and was comparable in the second subgroup (with L-arginine) and the control group (p_{k-2}>0,05), but remained higher than the first subgroup (p_{k-1}<0, 01; p_{1-2}<0,05). The dynamics of the circadian index was similar: in all groups there was a decrease in CI HCC, but in the first subgroup the effect was lower than the control group and the second subgroup (p_{k-2}>0,05; p_{k-1}<0,01; p_{1-2}<0,001). The number of extrasystoles decreased in both groups. The percentage of changes in the indicator of the number of extrasystoles in dynamics in the second subgroup was significantly higher than in the first, and then comparable with the indicator of the control group (p_{k-1}<0,001; p_{k-2}>0,05, p_{k-1}<0,001).

Keywords: ischemic heart disease, anemia, heart rhythm disorder, treatment.

ORCID and contributionship:
Khaniukov O. O.: 0000-0003-4146-0110 [AEF]
Zaiats I. O.: 0000-0001-8225-5901 [ABCDE]

Conflict of interest:
The authors of the paper confirm the absence of conflict of interest.

Corresponding author
Khaniukov Oleksii Oleksandrovych
Dnipro State Medical University
Ukraine, 49044, Dnipro, 9 Vernadsky str.
Tel: +380503208261
E-mail: khanyukov.al@gmail.com

A – Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article.

Received 22.03.2022
Accepted 16.08.2022

DOI 10.29254/2077-4214-2022-3-166-282-286
UDC 159.944.4:616-036.1]-085-092.9:159.929

[1]Kharchenko Y. V., [2]Abramov S. V., [2]Kryzhanovskyi D. G., [2]Fedchenko M. P., [2]Chernenko G. P., [2]Filipenko V. V., [2]Tereshchenko N. M.

INFLUENCE OF CHRONIC MILD STRESS ON RAT BEHAVIOR UNDER EXPERIMENTAL PHARMACOTHERAPY

[1]Dnipro State Medical University (Dnipro, Ukraine)
[2]Dnipro Medical Institute of Traditional and Non-Traditional Medicine (Dnipro, Ukraine)
vincarose@gmail.com

Vulnerability to the development of mood disorders, such as anxiety disorders and depression, depends on a combination of genetic and environmental factors, among which stress plays a significant role. Not everyone who experiences stress develops a mood disorder. Stress resistance is the ability to experience stressful events without the development of chronic stress (psychological and / or biological) and related changes in emotional behavior. Susceptibility to stress is associated with psychological factors such as passive coping skills and high emotional reactivity, but is also associated with biological factors such as hypo- or hypersensitivity to the stress response system, sex hormones, central and peripheral immune activation and glucocorticoid resistance. Interestingly, the level of biological response to stress and related neuroendocrine systems influences stress management, active stress management is enhanced by antidepressants. This suggests that drugs that affect the biological side of stress resistance may increase the effectiveness of existing treatments and preventive care. Intestinal microbiome is a biological factor that can affect resistance to stress. The widespread impact of gut microbiota on human health, including mental health, has come to be understood over the last decade. The gut-brain axis is a bidirectional link between the gut and the central nervous system, which plays an important role in maintaining nervous, hormonal, and immunological homeostasis. With the advent of evidence that gut microbiome can affect symptoms of depression and anxiety, it is now seen as a key component of this gut-brain cross-interaction, and the term has been extended to the gut-brain-brain axis. Stress also alters the intestinal microbiota, and the effects of early life stress on the microbiota can extend to adulthood.

This work covers the study of the effect of chronic mild stress on behavioral responses in experimental conditions.

Key words: *stress, microbiota, probiotics, vitamin D_3.*

Relationship of the publication with the planned research works. This work is a fragment of the planned scientific work of the Dnipro State Medical University «Pharmacological analysis of organ and endotheliprotection of experimental pathological conditions». State registration number 0118U006631.

Introduction. Today, no one denies the existence of the so-called intestinal nervous system, which is located between the esophagus and intestines and consists of 100 million nerve cells; there are more of them in it than in the spinal cord [1-4]. This is the second most difficult cluster of nerves in the human body after the brain, which is tentatively called «gut brain» [5-7]. Moreover, our brain with all its feelings, emotions and thoughts constantly communicates with the «gut brain». This process of communication is called the «gut-brain axis» [8, 9].

Recently, scientists have shown that the presence of intestinal microbiome at an early stage of development affects the topology of neurons (a set of properties of entire areas of the brain) associated with anxiety and depression [10]. Intestinal microbiome is associated with specific behavior, stress and disease. Changes in the intestinal microbiome can affect the development of