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Combined treatment of neurovegetative disorders in patients with ischemic heart disease with Long COVID-19 syndrome

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The aim of the study. To assess the dynamics of neurovegetative disorders in patients with coronary artery disease (CAD) with Long COVID-19 syndrome under the influence of combined treatment with the inclusion of exogenous L-arginine and phenibut in basic therapy.

Materials and methods. A prospective study with parallel distribution and elements of randomization included 31 patients with CAD: stable angina of exertion of functional class II–III (age 69.0 (64.0; 76.0) years)), who had suffered from moderate or severe COVID-19 coronavirus disease with manifestations of Long COVID-19 syndrome. Patients were divided into two groups depending on the prescribed treatment: group I (n = 15) – basic therapy for CAD was used; in group II (n = 16) a combination of L-arginine and phenibut was additionally prescribed against the background of basic therapy. Heart rate variability (HRV) parameters were assessed using 24-hour Holter ECG monitoring, degree of cognitive impairment – MoCa scale, anxiety-depressive – HADS scale, as well as their dynamics under the influence of the treatment.

Results. The use of combination therapy with the inclusion of exogenous L-arginine and phenibut in patients of group II contributed to an increase in the average integral indicator of cognitive status by 9.47 %, as well as a significant decrease in the level of anxiety-depressive symptoms: in the "Anxiety" subscale by 35.97 %, in the "Depression" subscale – by 20.81 % ($p < 0.05$). In the group receiving combination therapy with exogenous L-arginine and phenibut, a significant positive dynamics of most indicators of total HRV was determined: an increase in SDNNi by 1.22 times and 1.42 times, rMSSD, % by 1.56 times and 1.66 times, HRVT by 1.46 times and 1.40 in the daytime and nighttime periods, respectively. Analysis of HRV spectral indicators showed restoration of sympatho-parasympathetic balance and a significant decrease in the stress index by 1.89 and 2.03 times in the active and passive periods.

Conclusions. Adding exogenous L-arginine and phenibut to the basic therapy in patients with CAD who have had COVID-19 contributes to a significant reduction in anxiety and depressive symptoms, improvement of cognitive function, and stabilization of autonomic regulation of cardiac activity, which indicates a positive neuromodulatory effect of the combination therapy.

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Комбіноване лікування нейровегетативних порушень у хворих на ішемічну хворобу серця з Long COVID-19 синдромом

Н. С. Михайловська, С. М. Мануйлов, О. О. Лісова, О. В. Шершньова, Г. В. Грицай

Мета роботи – оцінити динаміку нейровегетативних порушень у хворих на ішемічну хворобу серця (ІХС) із Long COVID-19 синдромом під впливом комбінованого лікування із включенням до базисної терапії екзогенного L-аргініну та фенібуту.

Матеріали і методи. До проспективного дослідження з паралельним розподілом та елементами рандомізації залучено 31 пацієнта з ІХС: стабільною стенокардією напруження II–III функціонального класу (вік – 69,0 (64,0; 76,0) року)), які перенесли коронавірусну хворобу COVID-19 середнього або тяжкого ступеня із проявами Long COVID-19 синдрому. Пацієнтів поділили на дві групи залежно від призначеного лікування: у групі I (n = 15) застосовували базисну терапію ІХС; у групі II (n = 16) на фоні базисної терапії додатково призначено комбінацію L-аргініну та фенібуту. Оцінювали параметри варіабельності серцевого ритму (ВСР) за допомогою добового моніторування ЕКГ за Холтером, ступінь когнітивних порушень – шкали MoCa, тривожно-депресивних – шкали HADS, а також їхню динаміку під впливом проведеного лікування.

Результати. Застосування комбінованої терапії з додаванням екзогенного L-аргініну та фенібуту у пацієнтів II групи сприяло підвищенню середнього інтегрального показника когнітивного статусу на 9,47 %, а також суттєвому зниженню рівня тривожно-депресивної симптоматики: у підшкалі «Тривога» – на 35,97 %, у підшкалі «Депресія» – на 20,81 % ($p < 0,05$). У групі, пацієнти якої отримували комбіновану терапію екзогенним L-аргініном та фенібутом, визначено достовірну позитивну динаміку більшості показників загальної ВСР: збільшення SDNNi в 1,22 раза та 1,42 раза, rMSSD, % – у 1,56 раза та 1,66 раза, HRVT

– в 1,46 та 1,40 раза в денний і нічний періоди відповідно. Аналіз спектральних показників ВСР показав відновлення симпато-парасимпатичного балансу та достовірне зниження стрес-індексу (SI) в 1,89 та 2,03 раза в активний і пасивний періоди відповідно.

Висновки. Додавання до базисної терапії екзогенного L-аргініну та фенібуту у хворих на ІХС, які перенесли COVID-19, сприяє достовірній редукції тривожно-депресивних проявів, покращенню когнітивної функції, стабілізації автономної регуляції серцевої діяльності, що свідчить про позитивний нейромодулювальний ефект комбінованої терапії.

Сучасні медичні технології. 2026. Т. 18, № 2(69). С. 97-104

Coronary artery disease (CAD) remains one of the predominant causes of disability and mortality in the population. In Ukraine, cardiovascular diseases remain the main cause of mortality – according to the Ministry of Health, they account for about 67 % of all deaths, and a significant share of them is CAD [1]. The COVID-19 pandemic has also caused a significant shift in mortality patterns: according to WHO estimates, in two years (2020–2021), excess mortality associated directly or indirectly with COVID-19 amounted to about 14.9 million people worldwide [2]. In 2021, COVID-19 became the third leading cause of death after cardiovascular disease and cancer [3,4].

In patients with CAD who have had COVID-19, there is often a deterioration in the course of the main disease and neurocognitive status, which is manifested by a decrease in memory, concentration, as well as the development of anxiety-depressive and autonomic disorders [5]. One of the lead mechanisms for the occurrence of such symptoms is hypoxic-ischemic, when prolonged systemic hypoxemia caused by lung damage, against the background of pre-existing coronary disorders, leads to a decrease in cerebral perfusion and persistent cognitive disorders. Endothelial dysfunction also plays an important role: SARS-CoV-2 penetration into the endothelium of cerebral vessels contributes to the formation of microthrombi, impaired microcirculation and the development of chronic cerebral ischemia. An additional factor is systemic neuroinflammation, mediated by a cytokine storm with excessive production of IL-6, TNF-α and other pro-inflammatory mediators, which trigger neurodegenerative processes and are associated with encephalopathy and long-term cognitive impairment. Neurovegetative disorders, which are manifested by an imbalance between the sympathetic and parasympathetic divisions of the nervous system, heart rhythm lability, and sleep regulation disorders, are also of significant importance. These changes impair the adaptive capabilities of the cardiovascular system and further reduce the cognitive potential of patients with CAD [6,7].

An equally important component is psycho-emotional stress caused by the severity of COVID-19, isolation and fear of complications, which contributes to the development of anxiety and depressive disorders. These, in turn, are closely related to a decrease in cognitive functions and a deterioration in the quality of life of patients [8].

Thus, COVID-19 in patients with CAD forms a complex syndrome that combines the worsening of the underlying disease with neurocognitive and autonomic disorders. This justifies the need for a multidisciplinary approach to the treatment of such patients, which includes not only standard cardiological therapy, but also means for the correction of cognitive and psychoemotional disorders. However, there are currently no unified clinical protocols or international guidelines that would regulate approaches to the diagnosis and treatment of CAD in patients during the Long COVID-19 period. Given the common pathogenetic mechanisms of CAD and post-COVID syndrome, the possibility of using metabolic and neuromodulatory agents, such as exogenous L-arginine and phenibut, as part of complex therapy is of particular scientific and practical interest.

Both drugs demonstrated vasodilating, cardio- and neuroprotective properties, contributing to the improvement of microcirculation, normalization of cerebral circulation and restoration of metabolic activity of the myocardium affected by both direct and indirect effects of SARS-CoV-2. Thus, the study of the effectiveness of the combined use of L-arginine and phenibut against the background of basic therapy of CAD in patients with Long-COVID is a relevant direction in modern cardiology. This paves the way for optimizing treatment strategies, minimizing complication rates, and enhancing the quality of life for these patients [9,10].

Aim

To assess the dynamics of neurovegetative disorders in patients with coronary artery disease with Long-COVID-19 syndrome under the influence of combined treatment with the inclusion of exogenous L-arginine and phenibut in basic therapy.

Materials and methods

A prospective study with parallel distribution and elements of randomization included 31 patients with CAD: stable angina pectoris of functional class II–III (age 69.0 (64.0; 76.0) years) with manifestations of Long COVID-19 syndrome. Patients were divided into two groups depending on the prescribed treatment: in group I (n = 15), basic therapy for CHD was used, which included antiplatelet agents, statins, β-blockers, ACE inhibitors or sartans, as well as long-acting nitrates according to indications; in group II (n = 16), a combination of L-arginine (1000 mg twice a day) and phenibut (500 mg twice a day) was additionally prescribed for three months against the background of basic therapy.

The diagnosis of coronary heart disease was established in accordance with the current recommendations of ESC (2021) for the diagnosis and treatment of chronic coronary syndromes, as well as on the basis of the current unified clinical protocol for providing medical care for stable CAD (Order of the Ministry of Health of Ukraine No. 2857, December 23, 2021). The presence of COVID-19 coronavirus infection was confirmed based on the

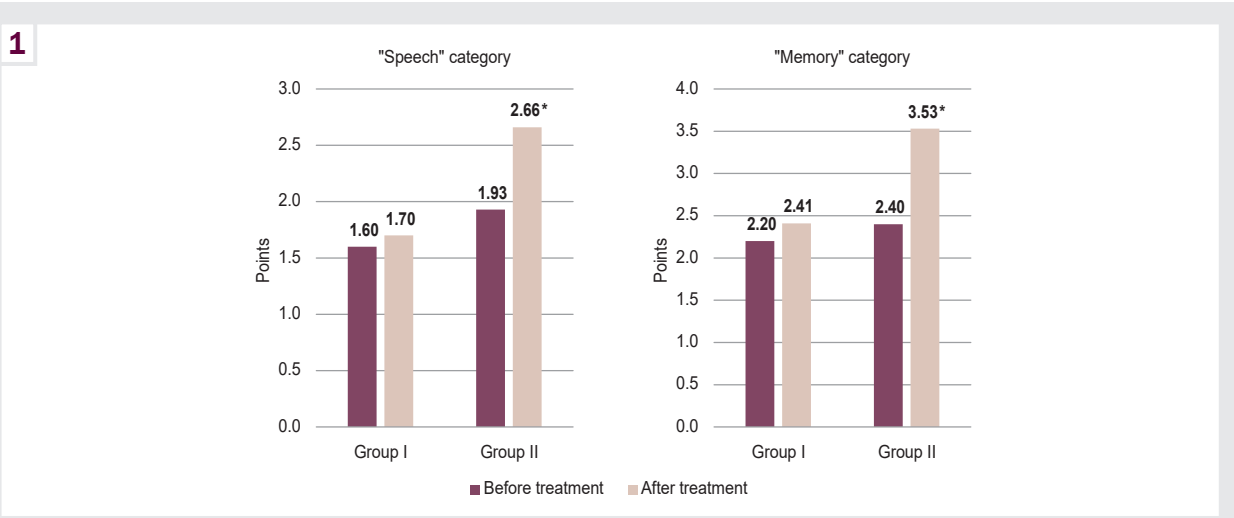

Fig. 1. Dynamics of cognitive indicators of the "Speech" and "Memory" sections on the MoCa scale in patients with CAD, after COVID-19, under the influence of treatment.

***:** significance of difference in indicators compared to the initial level ($p < 0.05$).

results of the analysis of medical documentation (case histories, discharge epicrits), as well as positive testing for SARS-CoV-2 by the polymerase chain reaction method during hospitalization with subsequent identification of the series and study number.

The inclusion criteria for the study included: confirmed coronary artery disease with a clinical picture of stable exertional angina of functional class II–III, moderate or severe COVID-19 at least 12 weeks after the acute period.

Exclusion criteria were: chronic heart failure stage IIB–III; heart defects; previous stroke; bronchial asthma or COPD; oncological, psychiatric, hematological or systemic pathologies; renal or hepatic failure; alcohol abuse; patient refusal to receive therapy.

The study was conducted in compliance with the principles of bioethics and moral and ethical norms with the mandatory signing of informed consent by patients.

To identify and assess the severity of anxiety and depressive disorders, the Hospital Anxiety and Depression Scale (HADS) was used. Cognitive state was assessed using the MoCA scale. Heart rate variability (HRV) was recorded using the "Cardiosense K" 24-hour ECG monitoring system (KHAI MEDIKA, Ukraine). Recording was performed for 24 hours during the day and night. The analysis included temporal and spectral parameters recommended by the ESC Working Group on HRV.

The work was carried out in accordance with the principles of bioethics, regulated by the following documents: the Council of Europe Convention on Human Rights and Biomedicine (1997), GCP (1996), the Declaration of Helsinki on the Ethical Principles of Conducting Scientific Medical Research with Human Participation (1964–2000), Order of the Ministry of Health of Ukraine dated 01.11.2000 No. 281. The compliance of the conducted research with the accepted ethical standards was confirmed by the conclusion of the Bioethics Commission of the Zaporizhzhia State Medical and Pharmaceutical University No. 1 dated 13.01.2025. All patients provided written informed consent to voluntarily participate in the study.

Statistical data processing was performed in the software Statistica 13.0 (license No. JPZ804I382130ARCN10-J) in accordance with modern requirements. The normal distribution of quantitative variables was assessed using the Shapiro–Wilk test. Due to the lack of normal distribution, the data are presented as median and interquartile range – Me (Q25; Q75). Qualitative variables are presented as absolute numbers and percentages – n (%). To assess the reliability of changes in dynamics, the Wilcoxon test for related samples was used. Comparison of intergroup differences by qualitative characteristics and analysis of event frequency were carried out using the χ^2 test using conjugation tables. A p-value of less than 0.05 was regarded as indicative of statistical significance.

Results

In patients with CAD who have had coronavirus infection (COVID-19), there was an increase in the frequency and intensity of manifestations of anxiety-depressive and cognitive disorders, signs of autonomic dysfunction, as well as tension in the functional-adaptive potential of the cardiovascular system with a predominance of the activity of central regulatory mechanisms over autonomous ones, which was demonstrated in our previous works [11,12].

The use of combination therapy with the addition of exogenous L-arginine and phenibut in patients in the group II contributed to an increase in the integral indicator of cognitive status by 9.47 % (from 24.09 to 26.61 points). The most pronounced positive effect was observed in the domains "Speech" and "Memory" *(Fig. 1)*: the average score in the "Speech" category increased by 27.44 % (from 1.93 to 2.66; $p < 0.05$), and in the "Memory" category – by 32.01 % (from 2.40 to 3.53; $p < 0.05$).

Three months after combined therapy using exogenous L-arginine and phenibut, a more pronounced decrease in anxiety and depressive symptoms was observed compared to the group

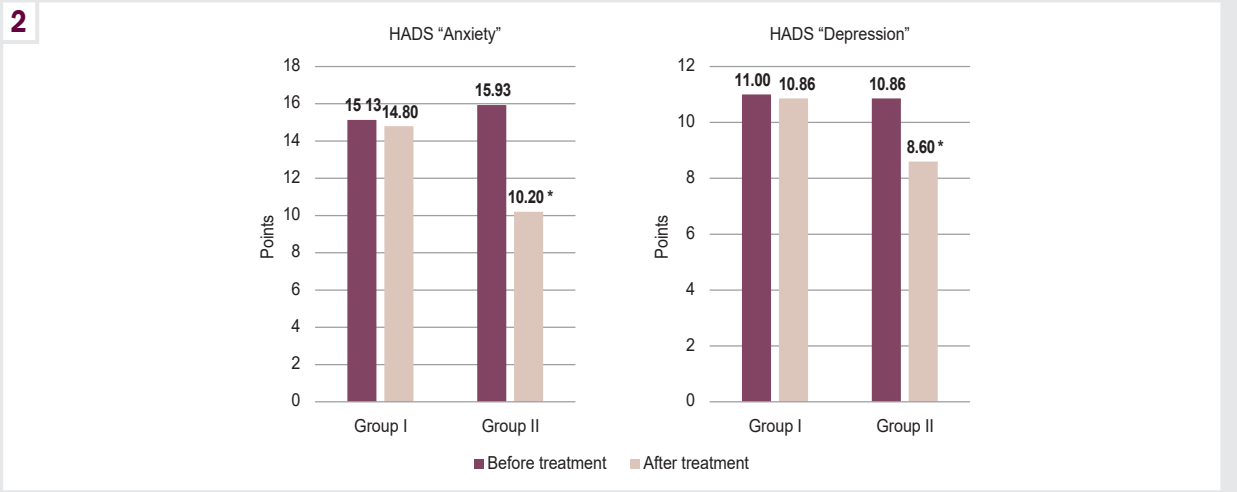

Fig. 2. Dynamics of ADD manifestations according to the HADS scale in patients with CAD after COVID-19, under the influence of treatment.

***:** significance of difference in indicators compared to the initial level ($p < 0.05$).

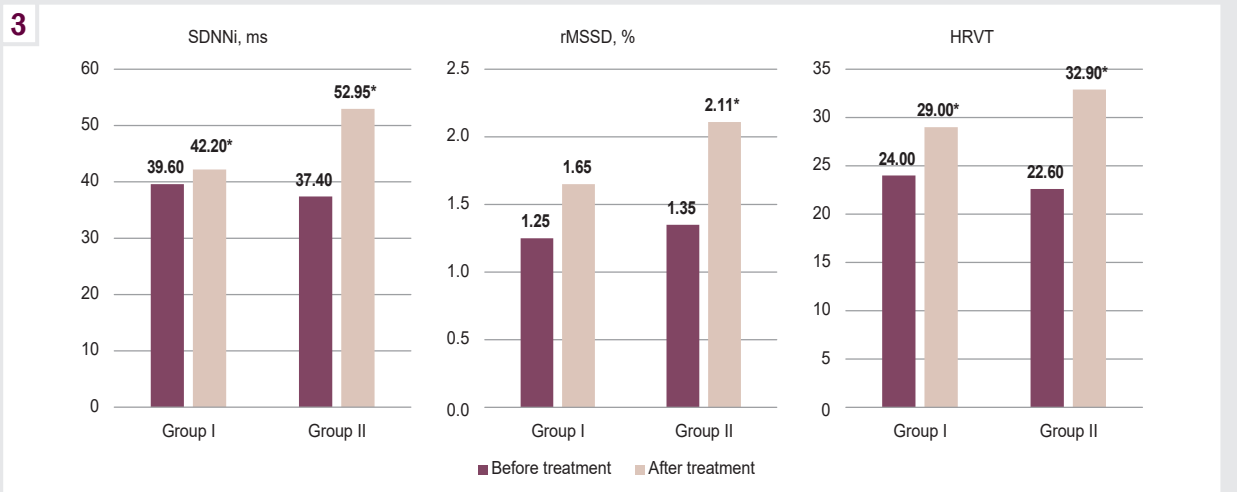

Fig 3. Daytime dynamics of temporal parameters of HRV in patients with CAD, after COVID-19, under the influence of treatment.

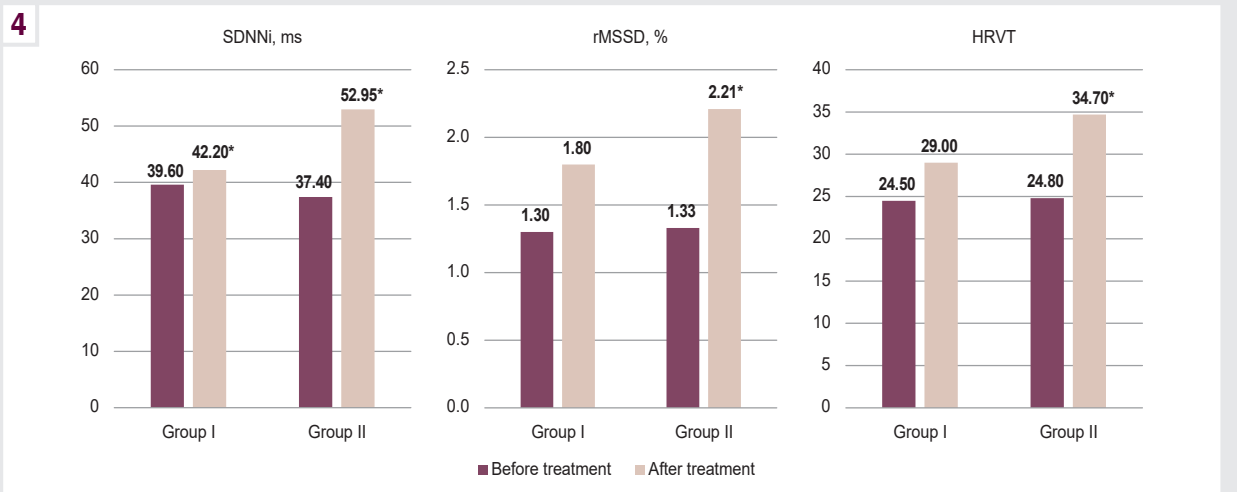

Fig 4. Night-time dynamics of temporal parameters of HRV in patients with CAD, after COVID-19, under the influence of treatment.

***:** significance of difference in indicators compared to the initial level ($p < 0.05$).

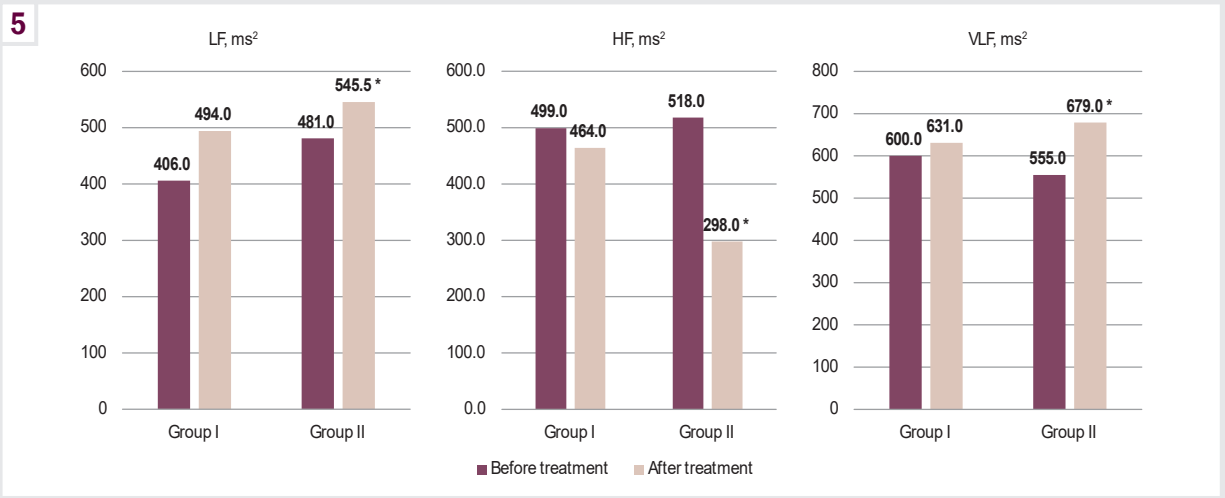

Fig. 5. Daytime changes of HRV spectral parameters in patients with CAD, after COVID-19, under the influence of treatment.

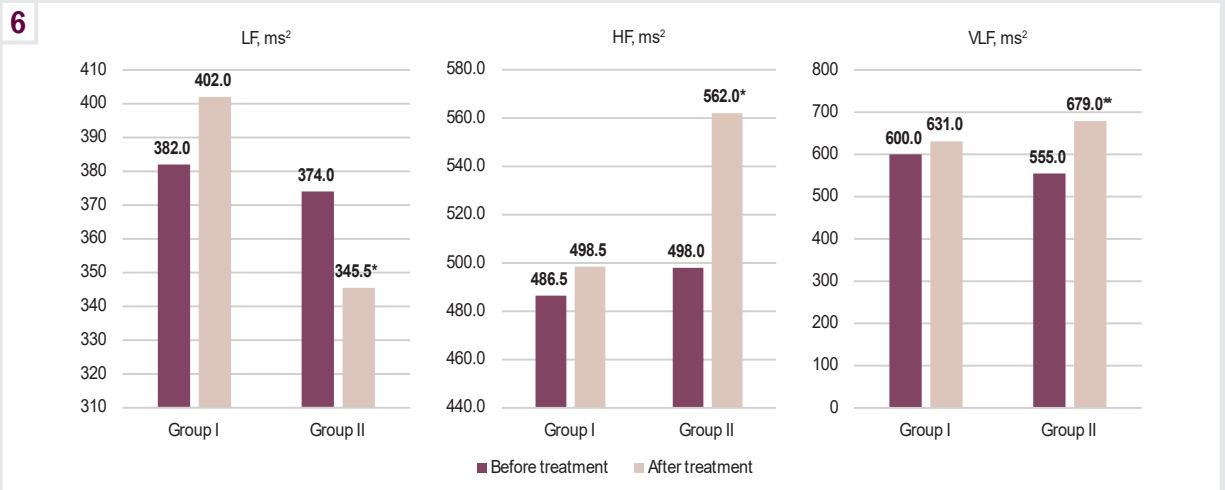

Fig. 6. Night-time changes of HRV spectral parameters in patients with CAD, after COVID-19, under the influence of treatment.

*: significance of difference in indicators compared to the initial level ($p < 0.05$).

receiving only basic CHD therapy *(Fig. 2)*. Patients in the second group showed a significant ($p < 0.05$) decrease in the average score in the "Anxiety" subscale by 35.97 % (from 15.93 to 10.20) compared to 2.18 % (from 15.13 to 14.80) in patients in the first group. Similar dynamics were observed in the "Depression" subscale, where in patients of the second group the average score decreased by 20.81 % (from 10.86 to 8.60; $p < 0.05$), while in the group with standard basic therapy the changes were minimal – only 1.27 % (from 11.00 to 10.86).

Changes in temporal parameters of HRV in patients with CAD after COVID-19 under the influence of treatment are shown in *Fig. 3, 4*.

In patients with CAD after COVID-19 infection who received only basic therapy, moderate positive dynamics of individual HRV indicators were determined. Thus, during the daytime period, an increase in SDNNi was noted by 1.18 times ($p < 0.05$), HRVT by 1.08 times ($p < 0.05$). During the night, only the changes in the parameter rMSSD, % by 1.39 times ($p < 0.05$) were statistically significant. In the group receiving combined therapy with exogenous L-arginine and phenibut, positive dynamics of most indicators of total HRV were determined: an increase in SDNNi by 1.22 times and 1.42 times ($p < 0.05$), rMSSD, % by 1.56 times and 1.66 times ($p < 0.05$), HRVT by 1.46 times and 1.40 ($p < 0.05$) in the daytime and night-time periods, respectively.

A positive effect of combined treatment with exogenous L-arginine and phenibut on spectral analysis parameters was observed, as shown in *Fig. 5, 6*.

In patients of group I, who received only basic therapy, a significant increase in spectral indicators was detected during the daytime: the LF component by 1.22 times ($p < 0.05$) and the LF/HF ratio by 1.23 times ($p < 0.05$). At the same time, there was a tendency to decrease in HF indicators ($p \approx 0.08$) and stress index ($p \approx 0.06$). During the analysis of spectral characteristics in the passive period, an increase in the activity of the sympathetic division of the autonomic nervous system was detected: the LF value increased by 1.05 times ($p < 0.05$), and the LF/HF ratio

increased by 1.13 times ($p < 0.05$). However, even with such changes, the obtained indicators did not reach the reference limits inherent in the state of adequate autonomic regulation, which indicates the preservation of heart rate variability disorders in patients receiving only basic therapy.

In patients receiving combination therapy, analysis of spectral indices of heart rate variability showed significant positive dynamics towards restoration of sympatho-parasympathetic balance. During the active period, there was a significant increase in the low-frequency component LF by 1.05 times ($p < 0.05$) against the background of a significant decrease in the high-frequency indicator of parasympathetic activity HF – by 1.13 times ($p < 0.05$). At the same time, there was an increase in the LF/HF ratio by 1.78 times ($p < 0.05$) and the very low frequency component VLF by 1.22 times ($p < 0.05$), which indicates the activation of central mechanisms of heart rate regulation. In the passive period, on the contrary, there was a decrease in sympathetic activity (LF) by 1.08 times ($p < 0.05$) with a simultaneous increase in the parasympathetic component HF by 1.13 times ($p < 0.05$) and a significant increase in the LF/HF ratio by 1.97 times ($p < 0.05$). Such dynamics indicate a tendency to normalize the regulatory effects of the autonomic nervous system. In both periods – both active and passive – a significant decrease in the stress index (SI) was observed, respectively, by 1.89 ($p < 0.05$) and 2.03 times ($p < 0.05$), while the centralization index (IC) tended to decrease in both phases of observation ($p \approx 0,07$), which further confirms the stabilization of the autonomic regulation of cardiac activity.

Therefore, in patients with coronary heart disease who had COVID-19, the use of combination therapy with the inclusion of exogenous L-arginine and phenibut contributed to a decrease in anxiety-depressive spectrum indicators, an improvement in cognitive functions according to the MoCA scale, and an optimization of the autonomic regulation of the cardiovascular system.

Discussion

We have found that in patients with CAD and Long COVID-19 syndrome, combined treatment with exogenous L-arginine and phenibut resulted in a reduction in anxiety and depression spectrum indicators, as well as an improvement in cognitive status according to the MoCA scale.

The effect of GABA-agonists on neurohumoral and psychoemotional disorders in patients with ischemic heart disease was also confirmed in a study by Q. Liu et al. According to the results obtained by the authors, the use of β-phenyl-γ-aminobutyric acid contributed to increasing the body's adaptive capabilities, reducing the level of anxiety and depression, and decreasing the frequency of adverse cardiovascular events [13].

The positive effects of phenibut can be explained by its ability to modulate GABAergic neurotransmission, reduce neurovegetative dysfunction, and restore the balance between excitation and inhibition in the central nervous system. This, in turn, contributes to the stabilization of the psychoemotional state, the reduction of stress-induced sympathetic activation, and the improvement of autonomic control of cardiac activity. An important pharmacological feature of phenibut is its ability to penetrate the blood-brain barrier, which ensures high bioavailability of the drug and determines the effectiveness of its action in lesions of the central nervous system, in particular those associated with the direct or indirect neurotropic effect of the SARS-CoV-2 virus [14].

According to a recent study by Thomas Prévot et al., a key role in the development of cognitive symptoms is played by changes in the γ-aminobutyric acid (GABA) system, in particular, impaired function of GABA-ergic interneurons that express somatostatin (SST+). Such neurons are involved in the transmission of excitatory signals to pyramidal cells in cortical brain circuits. It has been experimentally proven that a decrease in the activity of SST+ neurons disrupts the signal-to-noise ratio, reduces neuronal synchronization and coherence, which, in turn, leads to cognitive disorders and impaired executive functions [15].

Phenibut, as a derivative of γ-aminobutyric acid, has a multifactorial effect on the central nervous system: it normalizes GABAergic neurotransmission, increases the resistance of neurons to hypoxia, reduces the level of excessive sympathetic activation and improves the integrative activity of the brain. In addition, phenibut promotes the release of dopamine, which has a positive effect on the motivational sphere, emotional state and cognitive performance. Due to these properties, phenibut not only reduces anxiety levels and promotes the restoration of cognitive functions in patients with post-COVID neuropsychiatric disorders, but also exhibits a pronounced neuroprotective and adaptogenic effect, which increases its therapeutic value in the complex treatment of patients with ischemic heart disease after COVID-19 infection [16].

The choice of a three-month continuous course of phenibut was based on available scientific data and the positive tolerability profile in the included patients. A systematic review of clinical trials (E. Kupats et al., 2020) demonstrates that the average duration of therapeutic use of phenibut in clinical practice was up to 12 weeks, which corresponds to the 3-month regimen we chose [17]. Thus, the proposed duration of treatment is scientifically justified and corresponds to clinical data on the efficacy and tolerability of the drug with longer-term use under medical supervision.

L-arginine as part of complex therapy also plays an important role in restoring the cognitive status of patients due to its multifaceted pharmacological properties. The drug exhibits antihypoxic, membrane-stabilizing, cytoprotective and antioxidant effects, contributes to the normalization of cell energy supply processes and the maintenance of hormonal homeostasis in the body. In addition, L-arginine has a pronounced neuroprotective effect, reduces the manifestations of anxiety-depressive syndrome, improves the functional state of the limbic system and promotes increased neuroplasticity of the brain. These properties determine its potential in preventing and slowing the development of neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease [18].

L-arginine is the main substrate for the synthesis of nitric oxide (NO), which is a key mediator in the regulation of cerebral blood flow, interneuronal communication and neuronal growth. Under the influence of NO, the formation of new neuronal connections is stimulated, which contributes to improving the brain's ability to learn, the formation of long-term memory and adaptation mechanisms. The results of experimental and clinical studies [18,19] indicate that normalization of cerebral blood

circulation and maintenance of neurotransmitter balance under the influence of exogenous L-arginine contribute to improving the emotional state, reducing anxiety levels, and increasing cognitive performance of patients.

In patients with coronary heart disease and with Long COVID-19 syndrome, who received combination therapy with the inclusion of exogenous L-arginine and phenibut, a pronounced positive dynamics of changes in total HRV, as well as temporal and spectral parameters, was noted in both the active and passive observation periods, which indicates a gradual restoration of sympatho-parasympathetic balance. The obtained results may be due to the modulatory effect of phenibut on slow GABAergic receptors of the cerebral cortex, hypothalamus and limbic-reticular complex. It is known that activation of these receptors contributes to the reduction of excessive sympathetic activity, normalization of inhibition processes in the central nervous system and improvement of neurovegetative regulation of cardiac activity [20].

According to the results of research by P. Hepsomali et al., the use of GABA agonists has a positive effect on autonomic regulation, which is manifested by an improvement in the integral state of HRV due to an increase in the centralization index, an increase in RR-interval indicators (rMSSD, pNN50) and total spectrum power, simultaneously with a decrease in the triangular index and the restoration of sympatho-parasympathetic balance [21].

The results of the study by O. M. E. Abdel-Salam et al. confirm the positive antiarrhythmic effect of L-arginine, which is manifested by stabilization of R–R intervals, normalization of QRS complex duration and reduction of the frequency of extrasystoles during the day. These data indicate a pronounced cardioprotective and vegetotropic effect of L-arginine, which is realized through improvement of HRV indicators and normalization of the ratio of sympathetic and parasympathetic influences [22].

Additionally, the effectiveness of exogenous L-arginine in restoring heart rate variability, reducing the frequency of arrhythmic disorders, and normalizing sympatho-parasympathetic balance has been confirmed by other modern studies [18,23].

Conclusions

1. In patients with CAD and Long COVID-19 syndrome, under the influence of combination therapy with the adding of exogenous L-arginine and phenibut, a significant decrease in the severity of anxiety and depressive disorders was observed, as well as an improvement in cognitive functions assessed by the MoCA scale, which indicates a positive neuromodulatory effect of complex treatment.

2. The combined use of L-arginine and phenibut in patients with CAD and Long COVID-19 syndrome was associated with a statistically significant increase in total heart rate variability, a decrease in autonomic imbalance, and a decrease in the stress index in both active and passive periods of daily monitoring, indicating normalization of sympatho-parasympathetic regulation of cardiac activity.

Prospects for further research. A further direction is to conduct long-term observations to assess the impact of combination therapy using exogenous L-arginine and phenibut in patients with CAD and COVID-19 on the risk of recurrent cardiovascular events.

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