можливості оптимізації комплексної терапії даної когорти пацієнтів.

Ключові слова: алкогольна залежність, постійний тип зловживання алкоголем, біоритмологічний статус, реактивна тривога, особистісна тривожність, депресія, індивідуально-психологічні особливості.

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оптимизации комплексной терапии данной когорты пациентов.

Ключевые слова: алкогольная зависимость, постоянный тип злоупотребления алкоголем, биоритмологический статус, реактивная тревога, личностная тревожность, депрессия, индивидуально-психологические особенности.

Рецензент Скрипніков А.М.

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V.P. Ivanov, M.O. Kolesnyk, O.M. Kolesnyk, O.F. Bilonko, T.Y. Niushko
National Pirogov Memorial Medical University, Vinnytsya

CHANGES IN EFFORT TOLERANCE INDICES IN PATIENTS WITH CHRONIC HEART FAILURE AND LATENT IRON DEFICIENCY ON THE BACKGROUND OF THE ORAL FERROTHERAPY

e-mail: mokolesnyk@gmail.com

It is known that iron deficiency (ID) in the case of chronic heart failure (CHF), regardless of the presence of anemia, contributes to the development of the skeletal muscle dysfunction, which results in a reduction of effort tolerance (ET) in patients. The objective of the study was to assess the changes in effort tolerance indices in patients with chronic heart failure, with reduced left ventricular ejection fraction and concomitant latent iron deficiency, on the background of a standard treatment combined with long-term oral ferrotherapy. The data obtained showed that the conducted additional oral ferrotherapy is accompanied by a substantial improvement in effort tolerance indices in patients with CHF as compared to the standard therapy alone. This demonstrates the feasibility of a latent ID 6-month oral ferrocorrection to treat CHF with reduced LV EF in order to improve the patients' condition and working capacity.

Key words: chronic heart failure, latent iron deficiency, oral ferrotherapy

The study is a fragment of the research project "Prediction of the course and efficacy of various cardiovascular diseases treatment in combination with the pathology of other organs and systems", state registration No. 0120U100022.

In recent years, researchers have focused on the comorbidity of chronic heart failure (CHF). This is due to the fact that despite the use of modern treatment methods, the mortality of such patients reaches 30-60% within 3-5 years [14, 15]. Besides, the patients with CHF have a significantly lower quality of life, caused primarily by impairment of their physical activity [5], which, in turn, leads to significant medical, social, and economic challenges [2, 13]. In this regard, the issue of improving their physical condition, quality of life and prognosis remains relevant and can be addressed by improving the comorbidity diagnostics and treatment [2].

In previous years, researchers have focused more on the combination of CHF with a common manifest iron deficiency (ID), i.e. iron deficiency anemia (IDA), whereas the latent ID, even in the absence of anemia, is recorded in 45.6% of patients with CHF [10]. An important clinical aspect is that ID is significantly common among patients with cardiovascular morbidity, having nonspecific symptoms, and can be diagnosed only by determining the biochemical parameters of iron metabolism. Further, it is known that ID is a factor of unfavorable prognosis, impairment of physical activity and quality of life, as well as contributes to an increased number of hospitalizations [8].

ET decrease in these patients is due to the skeletal muscles disorders. In the human body, part of the iron is represented in the protein form – myoglobin, which is used to accumulate oxygen in the muscles. ATP in the muscles is formed by oxidative phosphorylation, which constantly requires a significant amount of oxygen. Accordingly, myoglobin provides oxygen redundancy and provides the ability of the muscles to contract for a long time. Lack of iron leads to the defects in the formation of iron-containing enzymes, which in turn is the cause of muscle hypotrophy and dysfunction, which is of clinical significance, especially in patients with latent iron metabolism disorders [6, 11].

The medicated correction of ID in the case of CHF brings positive changes in patients' condition. However, it has its own peculiarities. In previous studies, the benefits of intravenous administration over oral administration of iron have been demonstrated [9, 3]. However, these studies were conducted in patients with both absolute and functional ID, when known to activate proinflammatory cytokines in the case of functional ID worsen oral iron absorption. The question is whether positive changes in patients' condition with CHF and absolute ID with oral iron formulation will be obtained. Besides, a position of ferrocorrection and its duration in patients with latent ID remains ambiguous. In view of disadvantages of oral ferrocorrection, i.e. slow absorption in the gastrointestinal tract and its decreased level upon a slightest

possible inflammation in the case of CHF and due to blood congestion, in order to improve patients' physical functioning and general condition, oral ferrotherapy in patients with CHF and concomitant latent ID was prolonged in our study.

The purpose of the study was to assess the changes in effort tolerance indices in patients with chronic heart failure with reduced left ventricular ejection fraction and concomitant latent iron deficiency in the background of a standard treatment combined with long-term oral ferrotherapy.

Materials and methods. The study includes 60 patients with CHF with reduced left ventricular (LV) ejection fraction (EF) of the functional class (FC) II-III according to NYHA with concomitant latent ID. The patients with combined hypertensive and ischemic etiology of HF were enrolled in the study. Of them, 41 (68.3%) were men and 19 (37.1%) were women 68.3±0.63 years old. During the enrollment phase, all patients underwent general clinical examination according to 2016 ESC Guidelines for the diagnostics and treatment of acute and chronic heart failure with a compulsory laboratory testing of hemoglobin (Hb), red blood cells (Rbc), Rbc indices: MCV, MCH, MCHC and serum iron levels (SI), ferritin, total iron-binding capacity of serum (TIBC) and transferrin saturation (TS). The following criteria were used to diagnose the latent ID: 1) in the absence of signs of anemia, a decrease in serum iron (SI) in women < 11.5 μmol/l and in men < 13.0 μmol/l; 2) absolute ID – upon a decrease of SI and ferritin level < 100 ng/ml and 3) functional ID – upon a decrease of SI, ferritin levels of 100-300 ng/ml and transferrin saturation (TS) < 20% [7].

According to the study design, all patients received a standard therapy indicated by modern ESC recommendations, taking into account ischemic and hypertensive etiology of CHF and comorbid conditions, such as a trial fibrillation.

In order to avoid the possible impact of base treatment on the ferrotherapy outcomes, standard drug regimens were prescribed. Drug dosages were selected individually, in view of the patients' clinical condition. Two study groups were formed: besides the standard therapy, the patients in the 1stgroup (n=30) were prescribed oral ferrous sulfate at the dose of 320 mg, equivalent to 100 mg of bivalent iron and 60 mg of ascorbic acid, per day for 6 months; the patients in the 2nd group (n=30) received only a standard CHF therapy. The prescription of additional treatment was conducted among patients with absolute ID only. To determine the changes in effort tolerance (ET) indices in patients during treatment, the dynamics of the covered six-minute walk test distance was analyzed.

The groups of patients were compared by gender, age, main clinical characteristics, and treatment regimen.

Statistical processing of the obtained results was performed using Microsoft Office Excel and Statistica. Due to abnormal distribution of data, the obtained measurements are presented as a median (lower, upper quartile). The statistical significance of the difference in the measured parameters among groups was calculated according to Kruskal-Wallis ANOVA & Median test for all groups criterion, and the difference between the results of a 6-month treatment and the baseline values were calculated according to Wilcoxon matched pairs test criterion. The difference in the frequency of signs (%) was calculated by the χ^2 criterion. The difference was considered significant at $p<0.05$.

Results of the study and their discussion. At the end of the study, the distribution of CHF FC according to NYHA among all patients demonstrated a decrease in the number of patients with FC 3 in the background of the prescribed treatment in comparison with the initial distribution of the recording frequency of different FC (Fig. 1). Accordingly, the analysis of the dynamics showed that the overall decrease of FC according to NYHA on month 6 of treatment was reported for 14 (23.3%) patients. It should be noted that the clinical signs of CHF progression were not observed in any patient.

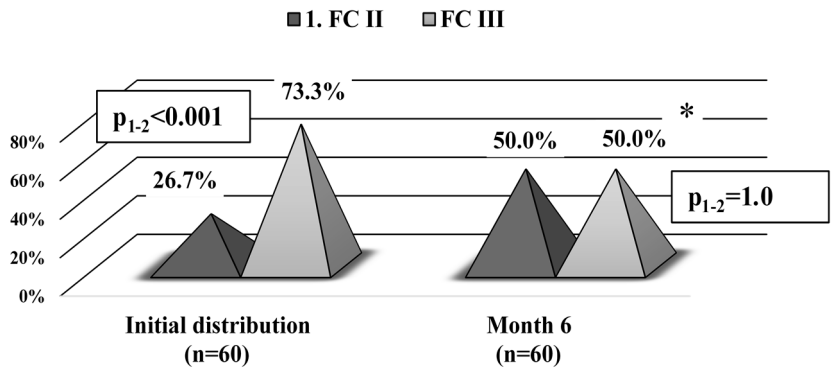

Fig. 1. Changes in CHF FC distribution according to NYHA among patients in the background of treatment. Note: "*" the difference of FC (%) on the background of a 6-month treatment as compared to the initial distribution was calculated by χ2 criterion (p<0.001).

The assessment of FC changes on the background of treatment depending on a 6-month ferrotherapy (Fig. 2) did not identify any significant pattern $p>0.05$, although a trend of increase in the cases of HF FC reduction was observed among patients who received iron supplements.

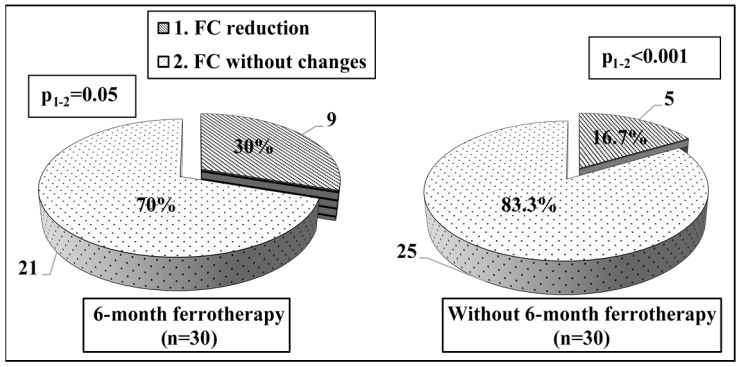

Fig. 2. Frequency of HF FC reduction cases according to NYHA depending on the 6-month ferrotherapy (in %). Note: The cross-group difference in % of cases with FC reduction depending on the 6-month oral ferrotherapy, which was calculated by χ^2 criterion, is insignificant (p>0.05).

Analysis of changes in the hematological indices of patients who received a 6-month ferrotherapy as ferrocorrection effectiveness markers (tables 1-2), demonstrated an increase of all parameters and, accordingly, normalization of iron metabolism indices, whereas the comparison of the studied laboratory indices in patients with latent ID after 6 months of standard treatment without ferrotherapy showed a significant decrease of all parameters, except for ferritin and TIBC (total iron-binding capacity of serum), which have increased over time. The following hematological changes, especially the decrease of SI (serum iron) and TS (transferrin saturation), in the group of patients who did not receive the iron supplements, demonstrate ID progression.

Table 1

Changes in the indicators of red blood growth in patients on the background of 6-months treatment (median, lower and upper quartile)

Hematological parameters	6-month ferrotherapy, n=30	Without 6-month ferrotherapy, n=30	p
Hb, g/l			
Baselinevalue	133 (130; 139)	135 (130; 146)	>0.05
6th month	156 (150; 163)	121 (112; 132)	<0.001
Changes, %	+17.3 (+15.3; +17.2)	-9.7 (-14; -8)	<0.001
p_{iv-6}	<0.001	<0.001	
Rbc, $\times 10^{12}$/l			
Baseline value	4.59 (4.5; 5)	4.65 (4.4; 5)	>0.05
6th month	4.8 (4.6; 5.2)	4.35 (4.2; 4.7)	<0.05
Changes, %	+4.57 (+2.22; +4)	-6 (-7.1; -4.5)	<0.001
p_{iv-6}	<0.001	<0.001	
MCV, fl			
Baseline value	84.6 (81.25; 86.7)	86.2 (81.3; 91.8)	>0.05
6th month	87.4 (84.8; 89.8)	83.3 (80.4; 88.4)	<0.001
Changes, %	+3.3 (+4.3; +3.7)	-2 (-3.8; -1.1)	<0.001
p_{iv-6}	<0.001	0.01	
MCH, pg			
Baseline value	28.3 (27.3; 29.25)	29.4 (27.7; 30.1)	>0.05
6th month	31.5 (29.9; 33.6)	27.4 (25.6; 28.4)	<0.001
Changes, %	+11.3 (+9.5; +14.8)	-4.3 (-7; -2.7)	<0.001
p_{iv-6}	<0.001	<0.001	
MCHC, g/l			
Baseline value	341 (331.1; 347.5)	340.3 (320.9; 351.1)	>0.05
6th month	368.6 (348.8; 379.5)	326.9 (305.9; 343.6)	<0.001
Changes, %	+8.1 (+5.3; +9.2)	-2.1 (-5.7; -1.7)	<0.001
p_{iv-6}	<0.001	0.002	

Note: p_{iv-6} – significance of a difference between baseline values and after a 6-monthtreatment

The ET analysis among all patients with latent ID demonstrated that the indices of the covered six-minute walk test distance, as compared to the baseline values, increased by 10.5% (from 286.5 to 302.5 m, p<0.001) after 6 months of standard treatment.

Despite an overall increase of the covered six-minute walk test distance, 60 patients with latent ID on the background of the proper standard treatment and a half of patients, who received additional ferrotherapy, that is 16 (26.7%) patients, showed the covered distance reduction.

Table 2

Changes in the indicators of iron metabolism in patients on the background of 6-months treatment (median, lower and upper quartile)

Hematological parameters	6-month ferrotherapy, n=30	Without 6-month ferrotherapy, n=30	p
1	2	3	4
SI (serum iron), umol/l			
Baseline value	8.7 (7.9; 9.6)	8.6 (8.5; 9.6)	>0.05
6th month	23 (18; 25.9)	7 (5.9;8)	<0.001
Changes, %	+164 (+127.8; +169.8)	-17.3(-29.9; -7)	<0.001
p_{iv-6}	<0.001	<0.001	
Ferritin, μg/l			
Baseline value	70 (46; 78)	113 (78; 156)	<0.001
6th month	144 (104; 167)	148 (65; 194)	>0.05
Changes, %	+105.7 (+126; +114)	+10.1(-13.9; 48.7)	<0.001
p_{iv-6}	<0.001	>0.05	
TS, %			
Baseline value	12.5 (11.8; 14.6)	13.9 (12.2; 17.6)	>0.05
6th month	37.2 (31; 44.2)	10.5 (9; 15.1)	<0.001
Changes, %	+198 (+162.7; +202.7)	-20.7 (-36.4; -5.9)	<0.001
p_{iv-6}	<0.001	<0.001	
TIBC, umol/l			
Baseline value	67.5 (62.5; 73)	62.3 (56.4; 66)	>0.05
6th month	58 (55.4; 64)	63 (55; 72)	>0.05
Changes, %	-13.4 (-11.36; -12.3)	3.6 (-8.9; 11.9)	<0.005
p_{iv-6}	<0.001	>0.05	

Note: p_{iv-6} – significance of a difference between baseline values and after a 6-monthtreatment

The changes in the covered six-minute walk test distance in 30 patients with latent ID on the background of a standard treatment and additional ferrotherapy over 6 months demonstrated an increase in the actual distance by 13.8% (from 273.5 to 307 m, p<0.001) (Fig. 3). The analysis of changes in the covered distance among patients, who did not receive a 6-month therapy, did not demonstrate significant positive changes. Thus, as compared to the baseline values, the covered distance increased by 5.3% after 6 months (from 288.5 to 298 m, p=0.067) (Fig. 3).

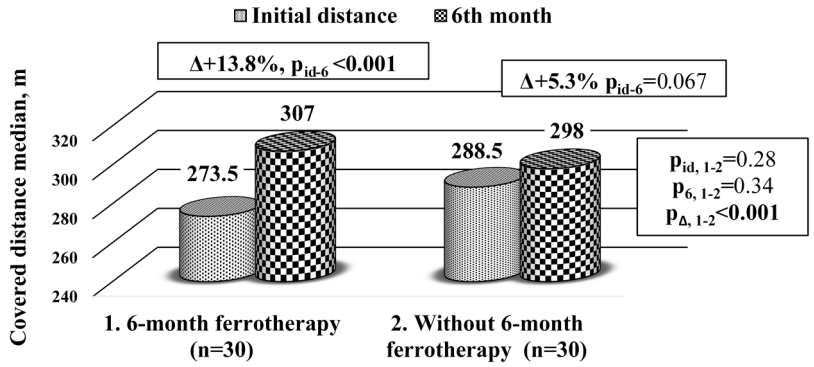

Fig. 3. The changes in the covered six-minute walk test distance in patients with CHF, with reduced LV EF and concomitant latent ID, on the background of 6-months treatment, median (lower, upper quartile). Notes: p_{id-6}– significance of differences between the initial and post-treatment distance; $p_{id, 1-2}$–significance of initial distance differences between two treatment groups; $p_{6, 1-2}$– significance of distance differences after 6 months of observations between two treatment groups; $p_{\Delta, 1-2}$– significance of changes difference between two treatment groups.

From a practical point of view, the analysis of frequency of the cases in decrease in the covered six-minute walk test distance on the background of the prescribed treatment is rather interesting. It was identified that a greater frequency of cases with negative changes in the six-minute walk test occurred in the group of patients who received a standard treatment without ferrotherapy, namely 14 (46.7%) versus 2 (6.7%) patients, who received oral iron supplements, p<0,001 (Fig. 4).

Thus, this study shows that despite adequate standard treatment in patients with CHF with concomitant latent ID without ferrocorrection compared to patients who received iron supplementation noted a smaller percentage of frequency reduction of the HF FC by NYHA, less positive dynamics of the covered distance of 6-minute walk test, higher incidence of covered distance, which demonstrates lack of effective treatment in view of improving ET. The results obtained are probably due to negative changes in the indicators of red blood growth and iron metabolism, which took place due to the lack of ferrocorrection with the development of the above-mentioned mechanisms of influence of ID on the potentiation of skeletal muscle dysfunction. According to the hematological picture, not only a decrease in iron metabolism in patients who did not receive iron preparations was demonstrated, but also the progression of ID, in some

cases, with the development of manifestation – the appearance of anemic syndrome (as evidenced by a significant decrease in hemoglobin levels), which in turn also affects the reduction of ET in patients [4].

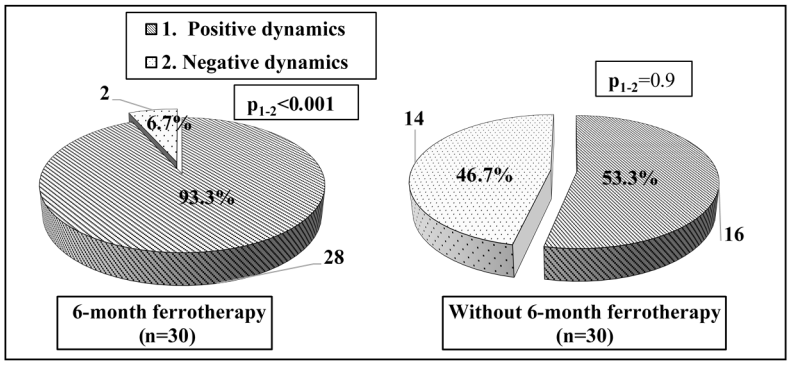

Fig. 4. Frequency of cases with negative changes in the six-minute walk test depending on whether a 6-month ferrotherapy was conducted or not (in %). Notes: The significance of intergroup differences in % of cases with negative changes in the six-minute walk test distance, depending on whether the 6-month oral ferrotherapy was conducted or not, was calculated by χ^2 criterion ($p<0,001$).

However, hematological changes in patients receiving iron sulfate at a dose of 320 mg in combination with 60 mg of ascorbic acid for 6 months, indicate sufficient and effective ferrocorrection, so these patients were determined to have a more pronounced positive ET dynamics.

Few clinical studies have shown a positive hematological and clinical result of ID correction in patients with CHF with reduced LV EF, but with parenteral iron agents [9]. The number of papers devoted to peroral ferrotherapy in CHF with differentiation of hematological variants is limited. It is known that due to reduced absorption of iron in the gastrointestinal tract, to replenish its reserves in the body, peroral ferrotherapy should last more than 3 months [1]. Despite this disadvantage, due to its availability, peroral iron therapy remains an alternative method of correcting ID [3], which is confirmed in our study.

Conclusion

The conducted additional oral ferrotherapy was accompanied by a more substantial improvement of effort tolerance indices in patients with CHF as compared to the use of the standard therapy alone. This demonstrates the feasibility of the latent ID 6-month oral ferrocorrection to treat CHF with reduced LV EF in order to improve the patients' condition and working capacity.

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Реферати

ЗМІНИ ПОКАЗНИКІВ ТОЛЕРАНТНІСТІ ДО ФІЗИЧНОГО НАВАНТАЖЕННЯ У ХВОРИХ З ХРОНІЧНОЮ СЕРЦЕВОЮ НЕДОСТАТНІСТЮ ТА ЛАТЕНТНИМ ЗАЛІЗОДЕФІЦИТОМ НА ТЛІ ПЕРОРАЛЬНОЇ ФЕРОТЕРАПІЇ

Іванов В.П., Колесник М.О., Колесник О.М., Білонько О.Ф., Нюшко Т.Ю.

Відомо, що залізодефіцит (ЗД) при хронічній серцевій недостатності (ХСН), незалежно від наявності анемії, сприяє розвитку дисфункції скелетних м'язів, що приводить до зниження толерантності до фізичного навантаження (ТФН) у пацієнтів. Метою дослідження було оцінити зміни показників ТФН у хворих з ХСН зі зниженою фракцією викиду лівого шлуночка та супутнім латентним ЗД на тлі стандартного лікування в комбінації з тривалою пероральною феротерапією. Отримані дані продемонстрували, що проведена пероральна феротерапія супроводжується більш суттєвим покращенням показників ТФН у пацієнтів з ХСН, порівняно із застосуванням лише стандартного лікування. Це свідчить про доцільність 6-місячної ферокорекції латентного ЗД при лікуванні ХСН зі зниженою ФВ ЛШ, з метою покращення стану і працездатності таких пацієнтів.

Ключові слова: хронічна серцева недостатність, латентний залізодефіцит, оральна феротерапія

Стаття надійшла 20.06.2019 р.

ИЗМЕНЕНИЕ ПОКАЗАТЕЛЕЙ ТОЛЕРАНТНОСТИ К ФИЗИЧЕСКОЙ НАГРУЗКЕ У БОЛЬНЫХ С ХРОНИЧЕСКОЙ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТЬЮ И ЛАТЕНТНЫМ ЖЕЛЕЗОДЕФИЦИТОМ НА ФОНЕ ПЕРОРАЛЬНОЙ ФЕРРОТЕРАПИИ

Иванов В.П., Колесник М.О., Колесник О.М., Билонько О.Ф., Нюшко Т.Ю.

Известно, что железодефицит (ЖД) при хронической сердечной недостаточности (ХСН), независимо от наличия анемии, способствует развитию дисфункции скелетных мышц, что приводить к снижению толерантности к физической нагрузке (ТФН) у пациентов. Целью исследования было оценить динамику показателей толерантности к физической нагрузке у больных с хронической сердечной недостаточностью со сниженной фракцией выброса левого желудочка и сопутствующим латентным ЖД на фоне стандартного лечения в сочетании с длительной пероральной ферротерапией. Полученные данные продемонстрировали, что проведенная дополнительная пероральная ферротерапия сопровождается более существенным улучшением показателей толерантности к физической нагрузке у пациентов с ХСН по сравнению с применением только стандартной терапии. Это свидетельствует о целесообразности 6-месячной феррокорекции латентного ЖД при лечении ХСН со сниженной ФВ ЛЖ, с целью улучшения состояния и работоспособности таких пациентов.

Ключевые слова: хроническая сердечная недостаточность, латентный железодефицит, оральная ферротерапия

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A.P. Kazmirchuk, O.I. Lashin, O.V. Druz, I.O. Chernenko
National Military Medical Clinical Center "Main Military Clinical Hospital", Ministry of Defense of Ukraine, Kyiv

BASIC PREDICTORS OF POST-TRAUMA STRESS DISORDER FORMATION AMONG COMBATANTS

e-mail: super-passa@ukr.net

In the present work, the authors identify predictors of the post-traumatic stress disorder (PTSD) formation among combatants. The study results include: a) tendency to express negative feelings through the form and content of verbal answers; b) unstable balance between the simultaneous desire for truthfulness and aggravation of PTSD symptoms, which provides a PTSD prognosis at the level of ΣD□ = 20.59> 20; □) □□mb□n□t□□n □f h□gh l□v□l □n□□t□wth □n□rm□l l□v□l □f s□□nt□n□t□, wh□□h □nsur□s a PTSD forecast of ΣDK = 15, 82> 13. Thus, an important component of the rehabilitation for combatants with PTSD is the creation of an appropriate therapeutic environment based on a patient-centered approach to potentiate the psychological, psychotherapeutic work aimed at restoring the relations between combatants, at the level of micro- and macro-environment.

Key words: combatants, post-traumatic stress disorder, post-stress mental disorder, combat mental trauma.

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The peculiarity of wars and military conflicts of today has become a manifestation of characteristic specific symptoms in many of its participants and in those occurring in the battle area, that are associated with the complex influence of physical, psychological, informational and other factors of war and related informational and cognitive influences on people. According to the WHO, 16.2% and 12.5% (out of 10% of citizens in 21 countries) suffer the consequences of war or traumatic injuries, respectively [1, 3, 9, 10]. Combat mental trauma (CMT) causes major disorders in combatant serviceman - mental maladaptation states - in 80% of cases, and among the wounded, according to the experience of local armed conflicts, mental disorders make almost 50% [2, 4, 5].

Stress-related mental disorders occurring during military operations are one of the major internal barriers to combativity and efficient performance of professional duties by combatants (up to the reduced