11. Schonmann Y, Ashcroft DM, Iskandar IY, Parisi R, Sde-Or S, Comaneshter D, et al. Incidence and prevalence of psoriasis in Israel between 2011 and 2017. Journal of the European Academy of Dermatology and Venereology. 2019; 33(11):2075–81. doi: 10.1111/jdv.15762
12. Springate DA, Parisi R, Kontopantelis E, Reeves D, Griffiths CEM, Ashcroft DM. Incidence, prevalence and mortality of patients with psoriasis: a U.K. population-based cohort study. Br J Dermatol. 2017; 176:650–8. doi: 10.1111/bjd.15021
13. Takeshita J, Gelfand JM, Li P, Pinto L, Yu X, Rao P, et al. Psoriasis in the US Medicare population: prevalence, treatment, and factors associated with biologic use. Journal of Investigative Dermatology. 2015; 135(12):2955–63. doi: 10.1038/jid.2015.296
14. Yemchenko YaA, Ishhejkin KYe, Kaidashev IP. Dynamics of clinical and laboratory indicators in the treatment of patients with psoriasis and concomitant alimentary obesity. World of Medicine and Biology. 2021; 1(75): 55–8. doi: 10.26724/2079-8334-2021-1-75-55-58
15. Yeung H, Takeshita J, Mehta NN, Kimmel SE, Ogdie A, Margolis DJ, et al. Psoriasis severity and the prevalence of major medical comorbidity: a population-based study. JAMA dermatology. 2013;149(10):1173–9. doi: 10.1001/jamadermatol.2013.5015

Стаття надійшла 12.01.2021 р.

DOI 10.26724/2079-8334-2022-1-79-130-134
UDC 614.2:355.72:616.12-02

N.M. Sydorova, O.V. Druz[1], V.L. Savytskyi, I.A. Chernenko[1], L.L. Sydorova[1]
Ukrainian Military Medical Academy, Kyiv
[1]National Military Medical Clinical Center "Main Military Clinical Hospital", Kyiv

PRIMARY AND SECONDARY PREVENTION OF CARDIOVASCULAR PATHOLOGY IN INJURED WITH COMBAT TRAUMA

e-mail: synanik@gmail.com

The purpose of the study was to develop and implement measures for primary and secondary prevention of cardiovascular pathology in injured with combat trauma. The data of 448 injured with combat trauma who were admitted to the National Military Medical Clinical Center «Main Military Clinical Hospital» were analyzed. Analysis of the average values of biochemical blood parameters showed the presence among injured with combat trauma and signs of cardiovascular disease more pronounced metabolic disorders, cytolysis and inflammation compared with injured without such complication: high levels of fibrinogen (by 11.1 %, p=0.0294), glucose (by 11.1 %, p=0.0004), asparagine transaminase (by 74.6 %, p=0.0005), alanine transaminase (by 58.4 %, p=0.0013), and lower levels of total protein (by 7.1 %, p=0.0008). The obtained results allowed us to offer hypermetabolism syndrome as one of the mechanisms of cardiovascular pathology development in injured with combat trauma, as well as to develop and implement approaches for prevention of this syndrome associated with the secondary pathology of the cardiovascular system.

Key words: metabolism, psychological support, military medicine, cardiology.

Н.М. Сидорова, О.В. Друзь, В.Л. Савицький, І.А. Черненко, Л.Л. Сидорова

ПЕРВИННА ТА ВТОРИННА ПРОФІЛАКТИКА СЕРЦЕВО-СУДИННОЇ ПАТОЛОГІЇ У ПОСТРАЖДАЛИХ, ЯКІ ОТРИМАЛИ БОЙОВУ ТРАВМУ

Метою роботи було розробити та запровадити заходи первинної та вторинної профілактики ураження серцево-судинної системи у постраждалих, які перенесли бойову травму. Були проаналізовані дані 448 постраждалих з бойовою травмою, які поступали до Національного військово-медичного клінічного центру «Головний військовий клінічний госпіталь». Аналіз середніх величин біохімічних показників крові показав наявність у постраждалих з бойовою травмою та ознаками ураження серцево-судинної системи більш виражених метаболічних порушень, цитолізу та запалення порівняно з постраждалими, які не мали цього ускладнення травмування: вищі рівні фібриногену (на 11,1 %, p=0,0294), глюкози (також на 11,1 %, p=0,0004), аспарагінової трансамінази (на 74,6 %, p=0,0005) та аланінової трансамінази (на 58,4 %, p=0,0013), та нижчі – загального білку (на 7,1 %, p=0,0008). Отримані результати дозволили запропонувати в якості одного з механізмів розвитку ураження серцево-судинної системи у постраждалих з бойовою травмою синдрому гіперметаболізму, а також обґрунтувати, розробити та запровадити заходи профілактики цього синдрому, асоційованого з розвитком вторинної патології серцево-судинної системи у постраждалих, які перенесли бойову травму.

Ключові слова: метаболізм, психологічна підтримка, військова медицина, кардіологія.

The work is a fragment of the research project "Development of modern methods of diagnosis and treatment of purulent-septic complications in combat surgical trauma", state registration No. 0120U101834.

Studies of the last 7 years show that people who have suffered a combat trauma in the area of the Anti-Terrorist Operation (ATO)/Joint Forces Operation (JFO), in addition to health problems directly related to the injury, may experience secondary pathology of internal organs. The frequency of such complications according to various data can reach 40 % [8]. Most often in the first 2 weeks after injury, there are signs of the pathology of the cardiovascular system (15.4 %) and hepatopathy (9.9 %) [8]. Moreover, the incidence of secondary pathology of the cardiovascular system reaches 92.5 % among patients who were treated for combat trauma in the intensive care units [4].

Secondary pathology of the cardiovascular system as a consequence of combat trauma is defined as cardiovascular abnormalities in the wounded outside the area of injury, due to impaired neuroendocrine

regulation, hypoxia, systemic and local response to injury, dysregulation of the autonomic nervous system, stress – a set of effects of the damage and compensatory reactions to injury, as well as nature, location and severity of trauma. A special role in the development of secondary pathology of the cardiovascular system after combat trauma is given to metabolic disorders, anaemia and hypoproteinemia [4], post-traumatic stress disorder and mental trauma. It should be noted that post-traumatic stress disorder and mental trauma are also accompanied by increased metabolism, activation of lipid peroxidation, slowing down the recombination of free radicals in the body [12–14].

It is known that secondary pathology of the cardiovascular system as a consequence of combat trauma can adversely affect the prognosis of patients due to the development of both organic (myocardial necrosis, acute myocarditis, dilated cardiomyopathy, etc.) and functional signs of the lesion (systolic and/or diastolic dysfunction of the left ventricle, congestive heart failure, heart rhythm and conduction disorders, including fatal arrhythmias) [9, 14], and lead to disability of patients [7]. Timely detection of a group of injured with combat trauma who are at high risk of secondary pathology of the cardiovascular system as well as the implementation of measures to prevent this complication at the stage of providing qualified medical care will significantly improve the prognosis of such patients and reduce the cost of their treatment.

However, despite the urgency of the problem of secondary pathology of the cardiovascular system, the genesis of this pathological condition is insufficiently studied, as verification of the nature of heart disease is almost impossible without a myocardial biopsy, whereas laboratory and instrumental changes are usually nonspecific.

Recently, methods of probabilistic-statistical modelling and multidimensional statistical analysis are increasingly used in medical and biological research to predict various processes. The advantage of such methods is the ability to identify the nature and interdependence between the features that describe the process under study. Multidimensional methods of regression, discriminant analysis, Bayesian classification methods, etc. are most often used for this purpose [2, 10].

The purpose of the study was to develop and implement measures of primary and secondary prevention of secondary pathology of the cardiovascular system as a consequence of combat trauma on the basis of substantiation of the genesis of its development in injured with combat trauma, using mathematical methods of processing routine biochemical blood parameters in the first three days after injury.

Materials and methods. The data of the injured in the area of Anti-Terrorist Operation/Joint Forces Operation (ATO/JFO), who were admitted to the specialized (fourth) level of medical care – to the National Military Medical Clinical Center "Main Military Clinical Hospital" (NMMCC "MMCH") were analyzed.

The inclusion of injured in the analysis was based on a study protocol approved according to the Helsinki Declaration by the Ethics Committee of the NMMCC "MMCH", which is sufficient for retrospective analysis of patient data from the Data Registry.

In order to determine the characteristics of biochemical blood parameters in servicemen with combat trauma, the data of 448 injured who were admitted to the NMMCC "MMCH" in 2014–2016 were analyzed. According to the chosen design and purpose of the study, injured with combat trauma were allocated to two groups depending on the presence of signs of secondary pathology of the cardiovascular system, which appeared in the first two weeks after receiving combat trauma.

Group I included 260 injured (58.0 % of subjects), in whom the examination on the 10^{th}–14^{th} day after receiving combat trauma did not show any signs of secondary pathology of the cardiovascular system (mean age 31.72±0.53). Group II included 188 patients (42.0 % of subjects, mean age 31.77±0.69), in whom signs of secondary pathology of the cardiovascular system were diagnosed. According to the main clinical characteristics, patients of both groups did not differ.

The laboratory tests were performed by the Clinic of Laboratory Diagnostics of NMMCC "MMCH". The results of the study were processed on IBM-compatible computers using Excel computer software.

For each sample of indicators studied, we calculated and analyzed the average value (M), the standard error of the average value (m), the variance (σ) [1].

According to the values of the coefficients of asymmetry (As) and excess (Ex), all samples had a normal distribution (As and Ex <2) [6]. Analysis and verification of the equality of the mean populations analyzed in this study confirmed that the samples had a normal distribution and were independent, the variances of the samples differed ($\sigma 12 \neq \sigma 22$, $p\sigma$ in all cases ≤ 0.025). In this regard, parametric methods were used for samples with different variances [6]. The statistical significance of the difference between the mean sample values of groups studied was determined by the results of a two-sample t-test with different variances [6]. Differences at p-value <0.05 were considered statistically significant.

Results of the study and their discussion. According to the results of our analysis, patients from Group II more often had gunshot wounds (29.8 % compared to 21.5 % of those from Group I, p <0.05) and less often – closed injuries (10.6 and 23.1 %, respectively, p <0.001). Patients from Group II had multiple or combined injuries more often (35.1 and 25.5 %, respectively) compared with the frequency of these indicators in Group I (28.1 and 16.2 %, respectively, p for both cases <0.05). Patients in both groups had a moderate injury in almost half of the cases, however, patients from Group II have diagnosed a severe injury more often than in Group I, (42.6 *vs.* 23.1 %, p<0.001) and less often – minor injury (13.83 *vs.* 28.08 %, p<0.001).

Analysis of the average values of blood parameters of injured with signs of secondary pathology of the cardiovascular system showed the presence of more severe metabolic disorders, cytolysis and inflammation in the early period after combat trauma compared with parameters in injured who did not have signs of secondary pathology of the cardiovascular system (Table 1).

Table 1

Biochemical blood parameters (M±m) of injured in the area of ATO/JFO

Parameter	Group I (n=260)	Group II (n=188)	P value
Fibrinogen, g/L	4.77±0.18	5.30±0.2256	0.0294
Bilirubin, μmol/L	11.62±0.66	13.66±0.80	>0.05
Total protein, g/L	63.41±0.99	58.90±1.07	0.0008
Glucose, mmol/L	5.22±0.09	5.80±0.16	0.0004
Asparagine transaminase, U/L	40.70±2.55	71.07±7.59	0.0005
Alanine transaminase, U/L	32.04±1.81	50.74±5.40	0.0013
Prothrombin index, %	90.05±1.11	88.92±1.14	>0.05
Creatinine, μmol/L	81.73±1.91	86.69±1.62	>0.05
Urea, mmol/L	5.05±0.29	5.47±0.24	>0.05
Iron, mmol/L	10.19±2.82	5.37±0.24	>0.05
Total cholesterol, mmol/L	3.93±0.34	4.08±0.34	>0.05
Low density lipoprotein cholesterol, mmol/L	2.14±0.44	2.36±0.38	>0.05
High density lipoprotein cholesterol, mmol/L	1.22±0.08	1.19±0.04	>0.05
Triglycerides, mmol/L	1.46±0.16	1.45±0.22	>0.05

Patients in Group II had higher blood levels of fibrinogen (by 11.1 %, p=0.0294), glucose (also by 11.1 %, p=0.0004), asparagine transaminase (AST, by 74.6 %, p=0.0005), alanine transaminase (ALT, by 58.4 %, p=0.0013), and lower – total protein (by 7.1 %, p=0.0008) compared with such parameters in Group I.

Our new data on the development of hypermetabolism syndrome in injured with combat trauma, and further clinical observation of this contingent allowed us to justify and develop measures for the prevention of this syndrome associated with the development of secondary pathology of the cardiovascular system in injured with combat trauma (table 2).

We earlier using the methods of mathematical modeling [8] proved the role of metabolic disorders in the genesis of secondary pathology of the cardiovascular system. According to the proposed binomial logistic regression, the model of the impact of laboratory blood parameters determined in the first three days after injury, on the risk of developing secondary pathology of the cardiovascular system had the form [8]:

$$y=0.71–0.013 \text{ total protein (g/L)}+0.099 \text{ glucose (mmol/L)}.$$

The prognosis of the event development (secondary pathology of the cardiovascular system in this case) is positive at y>0.5 and negative at y <0.5 (0=<y>=1).

This model suggests that combatants, who have lower blood levels of total protein and higher serum levels of glucose in the first three days after combat trauma are at high risk of secondary pathology of the cardiovascular system. This finding also supports our previous concept of hypermetabolism syndrome as a main cause of secondary pathology of the cardiovascular system.

Thus, in the series of our studies, we have confirmed the role of metabolic disorders in the development of secondary pathology of the cardiovascular system as a consequence of combat trauma, which revealed one of the possible mechanisms of myocardial damage in injured with combat trauma and justify measures for its prevention.

Classical studies of the early century have shown that systemic inflammation, the presence of which in patients with combat trauma is essential, is accompanied by secondary toxic damage due to absorption of tissue breakdown products, both neuroendocrine and metabolic response – the so-called hypermetabolism syndrome [3, 5, 8].

Because of hypermetabolic energy consumption and activation of catabolic processes (proteolysis, protein oxidation, activation of acute protein synthesis) due to hypermetabolism syndrome, there is a decrease in reparative processes and increased secondary immunodeficiency. Energy deficiency, which is formed as a result of these disorders, leads to the dysfunction of membrane cell pumps with the replacement of intracellular K + to Na +, followed by intracellular hyperhydration [3].

Table 2

Measures of primary and secondary prevention of secondary pathology of the cardiovascular system in injured with combat trauma

Time after combat trauma	Features of the period, measures of primary and secondary prevention
Days 1–10	Signs: Signs of secondary pathology of the cardiovascular system are usually absent. Measures: Stabilization of the condition, treatment of anemia and life-threatening conditions. Control of the blood levels of total protein and glucose, detection of persons at high risk of secondary pathology of the cardiovascular system developing. Psychological support (desirable)
10 days–1 month	Signs: Manifestation of secondary pathology of the cardiovascular system is possible. The appearance of signs of sympathetic nervous system hyperactivation as well as microcirculation disorders. Measures: ECG registration, in the presence of changes – echocardiography is recommended. Metabolic support according to the clinical situation (medication, dietary support). Psychological support (required)
1–12 months	Signs: Manifestation of symptoms of secondary pathology of the cardiovascular system and signs is possible, including myocarditis and pericarditis, syndrome of the prolonged QT interval on the ECG, hypertension, and structural changes in the microcirculatory tract. Measures: Clinical observation Prescribing beta-blockers to correct sympathicotonia. Monitoring the QT interval on the ECG and control of drugs that may affect its duration. Consider the optimal individual metabolic support program. Psychological support (required). Rehabilitation measures.
>1 year	Measures: Solving expert issues (ability to work/combat readiness). Decision-making regarding the continuation of sympathicotonia correction, metabolic support. Psychological support (mandatory), special attention during periods vulnerable to psychological disorders, in particular in the 5^{th} and 7^{th} years after receiving combat trauma. Active rehabilitation and treatment of conditions diagnosed at this stage, periodic monitoring of screening indicators of cardiovascular disease.

When developing measures for primary and secondary prevention of secondary pathology of the cardiovascular system in injured with combat trauma, we considered the high frequency of post-traumatic stress disorder in this group of patients (25–35 % of cases among persons with psychological trauma) [15]. The presence of this syndrome has an additional contribution to the development of secondary pathology of the cardiovascular system, as it can play a significant role in the formation of myocardial and vascular damage in injured with combat trauma. Some adverse effects on the myocardium and blood vessels have been described in patients with post-traumatic stress disorder [8, 9, 11–14]:

– increased levels of adrenaline and noradrenaline (increased activity of the sympathetic nervous system);
– increase in blood pressure and heart rate;
– increase in platelet aggregation capacity;
– disorders of lipid metabolism.

The presented above measures were introduced as a clinical component to the new functional and organizational model of providing medical care to injured with combat trauma. They are implemented in the work of field hospitals, military hospitals and military medical clinical centres, in particular NMMCC “MMCH”, civilian institutions that provide medical care to the specified contingent (acts of implementation), and received a high expert assessment.

Conclusion

Secondary pathology of the cardiovascular system was detected in 42.0 % of patients, confirming the high frequency of such pathology, which is manifested usually on days 10–14 after injury.

Injured with combat trauma and secondary pathology of the cardiovascular system are characterized by greater severity of metabolic disorders, cytolysis and inflammation, namely, higher blood levels of fibrinogen (by 11.1 %, p=0.0294), glucose (by 11.1 %, p=0.0004), asparagine transaminase (by 74.6 %, p=0.0005), alanine transaminase (by 58.4 %, p=0.0013), and lower – total protein (by 7.1 %, p=0.0008).

The revealed changes of biochemical indicators allow us to offer hypermetabolism syndrome as one of the mechanisms of cardiovascular pathology development in injured with combat trauma. Our findings as well as results of further clinical monitoring allowed us to justify, develop and implement a comprehensive program of measures for the prevention of hypermetabolism syndrome associated with the development of secondary pathology of the cardiovascular system in injured with combat trauma.

The presence of metabolic disorders in injured with combat trauma requires preventive measures both in the early stages after injury (as the primary prevention of secondary pathology of the cardiovascular system), and subsequent medical and psychological support of such patients to minimize the effects of combat trauma on the cardiovascular system in the long-term perspective.

References

1. Boyarintsev VV, Yevseyev MA. Metabolizm i nutritivnaya podderzhka khirurgicheskogo patsiyenta: Rukovodstvo dlya vrachey. SPb.: Onli-Press. 2017; 260 s. ISBN 978-5-906042-10-1. [in Russian]

2. Baraz VR, Pegashkin VF. Ispolzovanie MS Excel dlya analiza statisticheskikh dannykh. Nizhniy Tagil: Nizhnetagilskiy tehnologicheskiy institut (filial) Uralskogo federalnogo universiteta; 2014; 181 s. [in Russian]

3. Bolukh VA. Suchasni matematychni modeli v termodynamitsi biolohichnykh protsesiv. Medytsyna osvita. 2018; 4 :127-131. doi: 10.11603/me.2414–5998.2018.4.9007. [in Ukrainian]

4. Enikeev DA, Hisamov JeN, Pavlov VN, Nurgaleeva EA, Farshatova ER, Srubilin DV, et al. Vvedenie v klinicheskuju patofiziologiju. Tipovye patologicheskie processy: uchebnoe posobie. Ufa: Izd-vo FGBOU VO BGMU Minzdrava Rossii; 2017; 164 s. [in Russian]

5. Zvonarev SV. Osnovy matematicheskogo modelirovaniya: uchebnoe posobie. Ekaterinburg: Izdatelstvo Uralskogo universiteta; 2019. 112 s. [in Russian]

6. Petri A, Sebin K. Naglyadnaya meditsinskaya statistika: uchebnoye posobiye.; Leonov VP, redactor. Moskva: GEOTAR-Media; 2019; 216 s. [in Russian]

6. Sydorova NM, Halushka AM, Voronko AA, Kazmirchuk AP, Tretyak DD, Spaska HO, et al. Suchasni voyenni konflikty ta vtorynna patolohiya sertsevo-sudynnoyi systemy: statystyka, mozhlyvosti prohnozuvannya ta poperedzhennya. Suchasni aspekty viyskovoyi medytsyny. 2019; 26(2):70–79. doi: 10.32751/2310-4910-2019-26-29. [in Ukrainian]

7. Sydorova NM, Peshkova MI, Voronko AA, Khomenko IV, Tretiak DD. Rozrakhunok ryzyku rozvytku sertsevo-sudynnoi patolohii, shcho maie tryvalyi perebih, u postrazhdaloho z boiovoiu travmoiu: klinichnyi vypadok. World Science. 2020; 54 :35–42. Available at: doi:https://doi.org/10.31435/rsglobal_ws/28022020/6928. [in Ukrainian]

8. Kholod AH. Patolohichni zminy sertsevo-sudynnoi systemy u vazhkoporanenykh. Suchasni aspekty viiskovoyi medytsyny. 2015; 22(1) :166–168. [in Ukrainian]

9. Shevchuk VI, Beliaieva NM, Yavorovenko OB, Kurylenko IV, Haliutyna OIu. Sotsialni naslidky urazhennya vnutrishnikh orhaniv v uchasnykiv antyterorystychnoyi operatsii. Zbirnyk naukovykh prats spivrobitnykiv NMAPO imeni P.L. Shupyka. 2016; 25 :77–83. [in Ukrainian]

10. Edmondson D, von Känel R. Posttraumatic Stress Disorder and Cardiovascular disease. The Lancet Psychiatry. 2017; 4(4) :P320–329. doi:10.1016/S2215-0366(16)30377-7.

11. Karanikas E, Daskalakis NP, Agorastos A. Oxidative Dysregulation in Early Life Stress and Posttraumatic Stress Disorder: A Comprehensive Review. Brain Sci. 2021; 11(6) :723. doi: 10.3390/brainsci11060723.

12. Koenen, K., Sumner, J., Gilsanz, P., Glymour, M., Ratanatharathorn, A., Rimm, E., et al. Post-traumatic stress disorder and cardiometabolic disease: Improving causal inference to inform practice. Psychological Medicine. 2017; 47(2) :209–225. doi:10.1017/S0033291716002294.

13. O'Donnell CJ, Longacre LS, Cohen BE, Fayad AA, Liberzon I, et al. Posttraumatic Stress Disorder and Cardiovascular Disease: State of the Science, Knowledge Gaps, and Research Opportunities. JAMA Cardiol. 2021; 6(10) :1207–1216. doi:10.1001/jamacardio.2021.2530.

14. Xue C, Ge Y, Tang B, Liu Y, Kang P, Wang M, et al. A Meta-Analysis of Risk Factors for Combat-Related PTSD among Military Personnel and Veterans. PLoS ONE. 2015; 10(3): e0120270. https://doi.org/10.1371/journal.pone.0120270.

Стаття надійшла 18.02.2021 р.