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INDICATORS OF NONSPECIFIC SYSTEMIC INFLAMMATION AS CRITERIA FOR DESTABILIZATION OF THE COURSE OF CORONARY ARTERY DISEASE

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173 patients with various variants of coronary artery disease course were examined to determine both the presence and severity of non-specific systemic inflammation and the possibility of diagnosing the exacerbation of the atherosclerotic process in such patients by determining of the activity of inflammation. It was established that patients with an unstable course of coronary artery disease were characterized by a more pronounced inflammatory reaction, as evidenced by a significant increase in biochemical markers of inflammation: high-sensitivity C-reactive protein and tumor necrosis factor-α – not only relative to the control group, but also to patients with stable coronary artery disease. Therefore, these markers can be considered as criteria of atherosclerotic process destabilization. Based on determining the limit values of nonspecific systemic inflammation indicators in coronary artery disease patients, groups with reliable and possible ("gray zone") destabilization and without destabilization were selected. Levels of hsCRP ≥4.20 mg/l and TNF-α ≥3.45 ng/ml became the basis for including patients in the group of patients with destabilization of the disease even in the absence of clinical manifestations.

Key words: coronary artery disease, nonspecific systemic inflammation, highly sensitive C-reactive protein, tumor necrosis factor-α.

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ПОКАЗНИКИ НЕСПЕЦИФІЧНОГО СИСТЕМНОГО ЗАПАЛЕННЯ ЯК КРИТЕРІЇ ДЕСТАБІЛІЗАЦІЇ ПЕРЕБІГУ ІШЕМІЧНОЇ ХВОРОБИ СЕРЦЯ

З метою визначення наявності і виразності неспецифічного системного запалення у хворих на ішемічну хворобу серця та можливості діагностики загострення атеросклеротичного процесу у таких пацієнтів шляхом визначення активності запалення, обстежено 173 пацієнти з різними варіантами перебігу захворювання. Встановлено, що пацієнти з нестабільним перебігом ішемічної хвороби серця характеризувалися більш виразною запальною реакцією, свідченням чого було достовірне зростання біохімічних маркерів запалення: високочутливого С-реактивного протеїну і фактора некрозу пухлин-α – не лише відносно контрольної групи, а й відносно хворих зі стабільною ішемічною хворобою серця. Тому вказані маркери можна розцінювати в якості критеріїв дестабілізації атеросклеротичного процесу. На підставі визначення граничних величин показників неспецифічного системного запалення у хворих на ішемічну хворобу серця виділені групи з достовірною і можливою («сіра зона») дестабілізацією та без дестабілізації. Величини показників hsCRP ≥4,20 мг/л і TNF-α ≥3,45 нг/мл стали підставою для включення пацієнтів в групу хворих з дестабілізацією захворювання навіть за відсутності клінічних проявів.

Ключові слова: ішемічна хвороба серця, неспецифічне системне запалення, високочутливий С-реактивний протеїн, фактор некрозу пухлин-α.

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Diseases of the cardiovascular system, primarily coronary artery disease (CAD), are the main cause of premature death and disability throughout the world, including Ukraine [3, 13]. Annually, cardiovascular pathology "kills" about 4 million people in Europe and leads to direct and indirect economic losses of about 192 billion euros [13].

The prognosis of a patient with CAD is largely dependent on the destabilization of the atherogenic process due to the activation of atherothrombogenesis, which is clinically manifested by acute coronary syndrome (ACS). The methods used to establish ACS are based on the detection of foci necrosis or transient myocardial dysfunction. However, the search for laboratory markers that should grant early diagnostics of ACS, at least before the onset of irreversible changes in the myocardium is extremely important.

The main pathophysiological mechanism of CAD progression is the discrepancy between the myocardial oxygen demand and its insufficient supply. It is mostly caused by coronary atherosclerosis.

At present, atherosclerosis is considered not only as a disease caused by disturbances in metabolism and transport of lipids but as a long, indolent chronic inflammation of the vascular wall with periods of stable course and exacerbation of the process [8, 11]. The balance between pro-inflammatory and anti-inflammatory cytokines is crucial for the progression of atherosclerosis [15].

A lot of authors found an increase of a commonly accepted indicator of inflammation in the damaged plaque – high-sensitivity C-reactive protein (hsCRP) [11, 12] and proved in such a way the role

of inflammation in the destabilization of atherosclerotic plaque. The results of population studies contributed to the ideas about hsCRP as an independent risk factor, an independent predictor of ischemic events in various vascular basins both in patients with atherosclerosis-related cardiovascular diseases and in healthy individuals [10].

A meta-analysis of 31 studies involving a total of more than 150,000 people conducted by the Fibrinogen Studies Collaboration expert group, showed that when the level of fibrinogen in the blood plasma increases by 1.0 g/l, the risk of cardiovascular death increases by 3.1 times, development of myocardial infarction and unstable angina – 1.8 times, stroke – also 1.8 times [5].

Vascular inflammation is accompanied by the expression of genes that cause the synthesis of proinflammatory cytokines, including tumor necrosis factor-α (TNF-α) with the most pronounced proatherogenic action [6, 14]. It was found that the concentration of TNF-α is higher in atherosclerotic plaques than in the intact vascular wall, and significantly increased in plaques with high inflammatory activity [9, 15].

The purpose of the study was to determine the levels of indicators of non-specific systemic inflammation in patients with different courses of coronary artery disease and to establish their threshold values for the exacerbation of the atherosclerotic process.

Materials and methods. The study included 173 patients with coronary heart disease (mean age – 57.24±5.12 years), who were treated as an inpatient in the cardiology department of the Vinnytsia Regional Clinical Hospital named after M.I. Pirogov and the department for myocardial infarction patients of the community institution "Vinnytsia Regional Clinical Treatment and Diagnostic Center of Cardiovascular Pathology". The patients were divided into 2 main clinical groups based on the examination results: 92 patients with stable CAD (45 of II and 47 of III functional classes, respectively) and 81 patients who were admitted to the hospital with ACS (unstable angina (UA) was established later in 43 of them, and acute myocardial infarction (AMI) – in another 38).

The control group consisted of 30 practically healthy persons of comparable age and male/female ratio.

Blood samples from the cubital vein for clinical and biochemical examination were taken on the day of admission to the hospital (in ACS patients – within 2 hours after admission). In 82 patients (47.4 %) CAD was combined with essential hypertension.

The diagnosis of stable CHD and variants of ACS was established following the Recommendations of the European Society of Cardiology of 2012, 2013, and 2015 and the Orders of the Ministry of Health of Ukraine No. 455 dated 07.02.2014, No. 164 dated 03.03.2016 and No. 152 dated 02.03. 2016.

The study did not include people older than 75 years, with chronic heart failure of III-IV functional classes according to NYHA, malignant neoplasms, secondary arterial hypertension, acute inflammatory or exacerbation of chronic diseases at the time of examination, obesity of II-III degrees, liver and kidney diseases with impairment of their functions, diseases causing secondary dyslipidemias (diabetes, hypothyroidism, nephrotic syndrome, cholestasis).

General blood and urine analysis, as well as blood lipid spectrum, glucose level, blood electrolyte composition (K+, Na+), urea and creatinine levels, total protein, fibrinogen, prothrombin index or MVN, total bilirubin level and its fractions, the activity of alanine and aspartate aminotransferases, was completed in all patients before the start of observation.

Markers of non-specific systemic inflammation in the blood serum of patients with CHD were determined by the ELISA method using special reagent kits ("hsCRP ELISA" manufactured by "DRG", USA and "TNF-α ELISA test kit" manufactured by "Diaclone", France).

The results were gathered in Excel-2010 spreadsheets and processed by the statistical software Statistica v. 6.0 and 10.0 by StatSoft Company. The significance of differences was determined using the Student's t-test and the Mann-Whitney test. The limit values were calculated according to the formula of Antomonov M.Yu. [1].

Results of the study and their discussion. A comparative assessment of inflammatory biomarkers in groups of patients with stable and unstable CAD showed significant differences in the values of indicators with a high degree of reliability for the levels of hsCRP and TNF-α ($p<0.001$). These results give us grounds for associating their increase with a destabilization of the process. Although the degree of differences in fibrinogen levels was somewhat smaller, it was also reliable ($p<0.05$). The parameters of the blood lipid spectrum were not significantly different in patients with different disease courses, except for the level of HDL-C, which was slightly, but significantly higher in patients with stable CAD than in patients with ACS ($p<0.05$) (Table 1).

Table 1

Biochemical indicators in patients with various variants of the course of coronary heart disease

Parameter	Stable course (n=92)	ACS (n=81)	p
Fibrinogen, g/l	3.52±0.18	4.09±0.22	<0.05
hsCRP, mg/l	3.27±0.16	7.58±0.21	<0.0001
TNF-α, pg/мл	3.00±0.17	5.74±0.14	<0.0001
TC, mmol/l	5.99±0.13	6.01±0.17	ns
TG, mmol/l	1.80±0.05	1.90±0.07	ns
LDL-C, mmol/l	4.05±0.12	4.07±0.14	ns
VLDL-C, mmol/l	0.80±0.03	0.85±0.04	ns
HDL-C, mmol/l	1.14±0.02	1.07±0.02	<0.05
IA	4.25±0.21	4.62±0.19	ns

Notes: p is the significance of the difference of parameters between groups with a complicated and uncomplicated course; ns – the difference is non-significant

Fibrinogen levels in the patients with a different course of CAD showed a noticeable increase with a more severe course of stable CAD – in patients with III FC angina pectoris. The levels of indicators were the highest in ACS patients (with UA and, especially, with AMI), although they did not acquire a significant difference compared to the patients with stable angina of III FC. The absence of such a difference gives no reason to consider the level of blood fibrinogen in patients with CAD as a criterion for destabilization of the atherosclerotic process (Fig. 1).

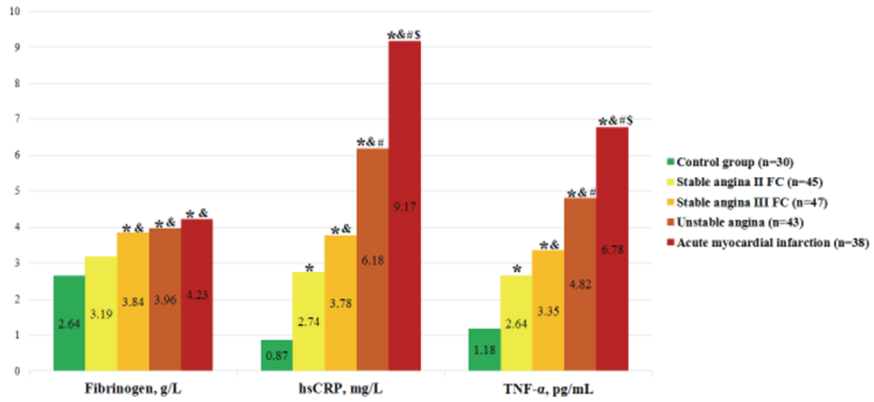

Fig. 1. Levels of inflammatory biomarkers in patients with various clinical variants of CAD

Notes: * – significantly compared to the control group (P<0.05); & – significantly compared to the stable angina II FC group (P<0.01); # – significantly compared to the stable angina III FC group (P<0.001); $ – significantly compared to the unstable angina group (P<0.001).

The analysis revealed an increase in the levels of hsCRP and TNF-α above the reference limits in all groups of subjects with CAD, but the greatest increase was observed in patients with an unstable course of the atherogenic process. The highest values of hsCRP and TNF-α were found in patients with AMI. They were significantly different not only from patients with stable forms of CAD but also from patients with UA (p<0.001).

Since the average values of hsCRP and TNF-α were the highest in patients with ACS and significantly differed from patients with stable angina, they can be attributed to the criteria of destabilization of the atherosclerotic process.

We set the limit values for indicators of destabilization of atherosclerosis and 3 main groups of patients were determined on this basis: without destabilization criteria (group A), with definite destabilization (group C), and with possible destabilization (group B). According to the analysis of indicators in the group of possible destabilization ("gray zone"), it was divided into 2 subgroups: with moderate (B-1) and high (B-2) probability of destabilization (Table 2).

Table 2

Limit values of indicators associated with destabilization of the process in patients with coronary artery disease

Indices	Without destabilization criteria	Possible CAD destabilization			Definite CAD destabilization
		Group together	Moderate destabilization probability	High destabilization probability	
hsCRP, mg/l	≤1.84	1.85-4.19	1.85-2.96	2.97-4.19	≥4.20
TNF-α, pg/l	≤1.99	2.00-3.44	2.00-2.43	2.44-3.44	≥3.45

The values of hsCRP ≥4.20 mg/l and TNF-α ≥3.45 ng/ml were the reason for including such patients in the group of patients with the destabilization of the disease even in the absence of clinical manifestations, which, in turn, determined the need for therapy intensification to reduce the destabilization process.

The values for hsCRP 1.85–4.19 mg/l and TNF-α 2.0–3.44 ng/ml corresponded to the "gray zone" (patients with possible destabilization of the process). In patients of subgroup B-2, the values of biomarkers approached the levels of patients with definite destabilization of the process, so it can be assumed that therapy intensification is also desirable for such patients.

It should be noted that there is no close correlation between the increase of destabilization biomarkers and different variants of the CAD course. An increase in the hsCRP level of more than 3.1 mg/l in patients with stable CAD indicates the definite or highly possible destabilization, while high levels (≥2.9 ng/ml) were observed more often in patients with the UA and AMI TNF-α indices.

The borderline criteria of definite destabilization or high degree of probable destabilization were predominant in patients with ACS. There were no significant differences between patients with UA and AMI. This may indicate that these criteria do not reflect the degree of myocardial damage, but they are predictors of such damage. The presence of criteria for definite and probable destabilization in some patients with stable CAD of III FC gives reason to assume that they have a moderate activation of the inflammatory process but without clinical manifestation of course instability, which determines the need for more careful monitoring of such patients.

Our data regarding the role of diagnostic markers of non-specific systemic inflammation in patients with CAD are consistent with the results of other authors. Thus, according to data from the Emerging Risk Factors Collaboration meta-analysis, hsCRP is an independent risk factor for cardiovascular diseases [7, 10]. Even its slight increase is associated with an increased risk of ACS development [6, 8].

According to Kleinbongard P. et al. the concentration of plasma TNF-α is associated with the degree of atherosclerosis progression, and the increase in TNF-α production is an early and central event in atherogenesis. It has been established that pro-inflammatory cytokines predominate in unstable atherosclerotic plaques, mainly the necrotizing cytokine TNF-α [9, 14].

Fedotova L.A. et al. noted that the level of fibrinogen in patients with angina pectoris increases before the occurrence of myocardial infarction, which is referred to as the deterioration of collateral circulation supply around the ischemia zone [2]. However, in our study, the level of fibrinogen in patients with ACS did not significantly differ from patients with stable angina of III FC. Therefore we did not consider it as a criterion for destabilization of the atherosclerotic process and did not calculate the limit values.

Since we revealed no significant relationship between the level of inflammatory biomarkers and the levels of troponins I and T during the first hours of MI we believe that they may be considered the criteria for destabilization of CAD rather than the markers of myocardial damage or necrosis.

Thus, an increase in the levels of hsCRP and TNF-α may indicate the destabilization of the atherosclerotic process and the occurrence of ACS. The reliability of the fibrinogen level as a criterion of destabilization is inferior to other abovementioned biomarkers.

Based on limit values for biomarkers of non-specific systemic inflammation in patients with CAD, groups with reliable and possible ("gray zone") destabilization and without destabilization were selected. It makes it possible to diagnose an exacerbation of CAD even in the absence of clinical manifestation of destabilization of the process.

Conclusions

1. Patients with coronary artery disease have an activation of nonspecific systemic inflammation with manifestation by an increase in plasma levels of hsCRP and TNF-α. The degree of changes in these markers is associated with the features of the course of the disease and its severity. The highest values are observed in patients with acute myocardial infarction.

2. An increase in the levels of hsCRP ≥4.20 mg/l and TNF-α ≥3.45 ng/ml in patients with CAD indicates the destabilization of the atherosclerotic process even in the absence of clinical manifestations, which determines the need to activate therapy in such patients.

Further research in this direction is required to improve the early diagnosis of exacerbation of CAD and optimize the therapy of patients to prevent damage and necrosis of the myocardium, thereby improving the prognosis of patients with CAD.

References

1. Antomonov MYu. Matematicheskaya obrabotka i analiz mediko-biologicheskikh dannykh. Kiĭv: Maliy druk; 2006. 558 s [in Russian]

2. Kovalenko VM, Kornatskyy VM, editors. Aktualni problemy zdorovya ta minimizatsiya yikh v umovakh zbroynoho konfliktu v Ukrayini: posibnyk. Kyiv: Derzhavna ustanova "Natsionalnyy naukovyy tsentr "Instytut kardiolohiyi imeni akademika M.D.Strazheska"; 2018. 518. [in Ukrainian]

3. Romanova VO, Kuzminova NV, Sierkova VK, Romanova LO, vynakhidnyky; Vinnytskyy natsionalnyy medychnyy universytet im. M.I.Pyrohova, patentovlasnyk. Sposib vyznachennya destabilizatsiyi perebihu zakhvoryuvannya u patsiyentiv z ishemichnoyu khvoroboyu sertsya. Patent Ukainy No. 127360. 2018 Lyp 25. [in Ukrainian]

4. Fedotova LA, Zorin VN, Plastun MYu. Gemostaz, fibrinoliz pri ishemicheskoy bolezni serdtsa i arterial'noy gipertenzii. Tavricheskiy mediko-biologicheskiy vestnik. 2013;4(64):183–186 [in Russian]
5. Cui Z, Zhao G, Liu X. Blood fibrinogen level as a biomarker of adverse outcomes in patients with coronary artery disease: A systematic review and meta-analysis. Medicine. 2022;101(33). DOI: 10.1097/md.0000000000030117
6. De Caterina R, D'Ugo E, Libby P. Inflammation and thrombosis – testing the hypothesis with anti- inflammatory drug trials. Thrombosis and Haemostasis. 2016;116(12):1012–21. DOI 10.1160/th16-03-0246
7. Ivanytskyi IV, Katerenchuk OI, Nekrasov KA, Ivanytska TA. Left ventricular noncompaction associated with genetic disturbance of folic acid metabolism. Kardiol Pol. 2019;77(12):1196–1197. DOI: 10.33963/KP.15024
8. Kuzminova N, Romanova V, Serkova V, Osovska N, Kniazkova I. Inflammation indicators and leptin level in patients with ischemic heart disease. Lekarsky Obzor. 2016;65(6):140–5.
9. Liberale L, Ministrini S, Carbone F, Camici GG, Montecucco F. Cytokines as therapeutic targets for cardio- and cerebrovascular diseases. Basic Research in Cardiology. 2021;116(1). DOI: 10.1007/s00395-021-00863-x
10. Omran F, Kyrou I, Osman F, Lim V, Randeva H, Chatha K. Cardiovascular biomarkers: Lessons of the past and prospects for the future. International Journal of Molecular Sciences. 2022;23(10):5680. DOI: 10.3390/ijms23105680
11. Ridker PM. Residual inflammatory risk: Addressing the obverse side of the Atherosclerosis Prevention Coin. European Heart Journal. 2016;37(22):1720–2. DOI 10.1093/eurheartj/ehw024
12. Schroder J, Mygind ND, Frestad D, Michelsen M, Suhrs HE, Bove KB, et al. Pro-inflammatory biomarkers in women with non-obstructive angina pectoris and coronary microvascular dysfunction. IJC Heart & Vasculature. 2019;24:100370. DOI: 10.1016/j.ijcha.2019.100370
13. Townsend N, Kazakiewicz D, Lucy Wright F, Timmis A, Huculeci R, Torbica A, et al. Epidemiology of Cardiovascular Disease in Europe. Nature Reviews Cardiology. 2021;19(2):133–43. DOI: 10.1038/s41569-021-00607-3
14. Urschel K, Cicha I. TNF-A in the cardiovascular system: From physiology to therapy. International Journal of Interferon, Cytokine and Mediator Research. 2015;7:9–25. DOI: 10.2147/ijicmr.s64894
15. Wolf D, Ley K. Immunity and inflammation in atherosclerosis. Circulation Research. 2019;124(2):315–27. DOI: 10.1161/circresaha.118.313591

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CHANGES IN THE FREQUENCY OF EEG WAVES IN THE CEREBRAL CORTEX OF SANGUINE STUDENTS

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The study is devoted to the change of the oscillation of alpha-, beta-, delta- and theta-waves in the forehead and occipital part of the brain during the exam process in V-year students, depending on the temperament of the nervous system. Before starting the study, temperament types of the students' nervous system, their individual and situational anxiety levels were studied. The amplitude of alpha-, beta, delta- and theta-waves in the foreheads of students of different temperament types was determined and recorded using an electroencephalograph device in all 3 groups: on normal days, before the exam and after the exam. It was determined that there is a noticeable difference in the electrical activity of the brain of students in the V course at all stages.

Key words: EEG waves, amplitude, emotional stress, situational and individual excitement, sanguine type of temperament.

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ЗМІНИ ЧАСТОТИ ХВИЛЬ ЕЕГ У КОРІ ГОЛОВНОГО МОЗКУ У СТУДЕНТІВ САНГВІНІКІВ

Дослідження присвячено зміні коливань альфа-, бета-, дельта- і тета-хвиль у лобно-потиличній частині головного мозку під час екзаменаційного процесу у студентів V курсу в залежності від темпераменту нервової системи. Перед початком дослідження були вивчені типи темпераменту нервової системи студентів, рівень їх індивідуальної та ситуативної тривожності. Амплітуду альфа-, бета-, дельта- і тета-хвиль на лобі студентів різних типів темпераменту визначали та реєстрували за допомогою електроенцефалографа у всіх 3 групах: у звичайні дні, перед іспитом і після іспиту. Визначено помітну різницю в електричній активності мозку студентів V курсу на всіх етапах.

Ключові слова: хвилі ЕЕГ, амплітуда, емоційне напруження, ситуативне та індивідуальне збудження, сангвінічний тип темпераменту.

In modern times, higher education institutions play an important role in the training of professional specialists and in the formation of a completely healthy person [2]. The education of students in higher educational institutions is represented by several important characteristics, and it highly depends on the majors chosen by students, their living conditions, age, gender, nutrition and unhealthy habits and so on [2, 6]. The task of teaching staff in higher education today, based on the targets set, is to select from their