11. Shaposhnyk OA, Prykhodko NP, Savchenko LV, Shevchenko TI, Sorokina SI, Yakymyshyna LI. Clinical and diagnostic aspects of managing patients with valvular heart disease World of Medicine and Biology. 2022; 2(80): 178–183. doi: 10.26724/2079-8334-2022-2-80-178-183

12. Sundqvist MG, Sahlén A, Ding ZP, Ugander M. Diastolic function and its association with diabetes, hypertension and age in an outpatient population with normal stress echocardiography findings. Cardiovasc Ultrasound. 2020; 18(1): 46. doi: 10.1186/s12947-020-00228-9

13. Tzanavari T, Giannogonas P, Karalis KP. TNF-alpha and Obesity. Curr Dir Autoimmun. 2010; 11: 145–156. doi: 10.1159/000289203.

14. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M. ESC National Cardiac Societies; ESC Scientific Document Group. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2021; 42(34): 3227–3337. doi: 10.1093/eurheartj/ehab484.

15. Worley E, Rana B, Williams L, Robinson S. Left ventricular diastolic dysfunction: identifying presence by left atrial function. Echo Res Pract. 2018; 5: 97–104. doi: 10.1530/ERP-18-0013

Стаття надійшла 30.10.2022 р.

T.V. Bohdan, V.V. Bogdan, V.O. Sobol, I.V. Biliachenko, Yu.O. Moshkovska, Yu.V. Tyravska
Bogomolets National Medical University, Kyiv

RELATIONSHIP BETWEEN IMMUNOLOGICAL STATUS AND ISCHEMIA, ECTOPIC MYOCARDIAL ACTIVITY IN PATIENTS WITH ANGINA PECTORIS

e-mail: vik.o.sobol@gmail.com

The purpose of the study was to improve the diagnosis of stable angina and unstable angina by determining the correlations between the development of myocardial ischemia and cardiac arrhythmias with disorders of cellular and humoral immunity in patients with coronary artery disease. Using the obtained results, further optimize the treatment of patients with stable and unstable angina pectoris. It was determined that in the stable angina pectoris the development of painful myocardial ischemia depends on the level of CD4+ subpopulation (T-helpers) and circulating immune complexes, the development of painless myocardial ischemia depends on the level of CD4+ and CD8+ subpopulations (T-suppressors). Coronary artery disease destabilization and group ventricular extrasystoles are associated with elevated CD4+ subpopulations, CD8+ subpopulations and circulating immune complexes levels. Pathogenetic links between coronary circulatory disorders and ectopic myocardial activity with the development of imbalance of cellular and humoral immunity in patients with stable and unstable angina pectoris confirm the theory of immune inflammation as one of the pathogenetic links in the development of coronary artery disease and encourage studies and development of new drugs in antianginal therapy algorithms.

Key words: stable angina pectoris, unstable angina pectoris, painful ischemia, painless ischemia, extrasystole, immunity.

Т.В. Богдан, В.В. Богдан, В.О. Соболь, І.В. Біляченко,
Ю.О. Мошковська, Ю.В. Тиравська

ЗВ’ЯЗОК ІМУНОЛОГІЧНОГО СТАТУСУ З ІШЕМІЄЮ ТА ЕКТОПІЧНОЮ АКТИВНІСТЮ МІОКАРДА У ХВОРИХ НА СТЕНОКАРДІЮ

Метою роботи було удосконалити діагностику стабільної стенокардії та нестабільної стенокардії на підставі визначення кореляційних зв’язків між розвитком ішемії міокарда і порушень серцевого ритму з порушеннями клітинного і гуморального імунітету у хворих на ішемічну хворобу серця. Визначено, що при стабільному перебігу ішемічної хвороби серця розвиток больової ішемії міокарда залежить від рівня субпопуляції CD4+ (Т-хелпери) та циркулюючих імунних комплексів, розвиток безбольової ішемії міокарда – від рівня субпопуляції CD4+ та CD8+ (Т-супресори). Дестабілізація коронарного кровообігу та виникнення групової шлуночкової екстрасистолії пов’язані з підвищеним рівнем субпопуляції CD4+, субпопуляції CD8+ та рівнем імунних комплексів. Патогенетичні зв’язки порушення коронарного кровообігу і ектопічної активності міокарда з розвитком дисбалансу клітинного та гуморального імунітету у хворих на стабільну та нестабільну стенокардію підтверджують теорію імунного запалення, як однієї з патогенетичних ланок розвитку ішемічної хвороби серця і спонукають до пошуку та розробки нових лікарських засобів, які б входили у алгоритми антиангінальної терапії.

Ключові слова: стабільна стенокардія, нестабільна стенокардія, больова ішемія, безбольова ішемія, екстрасистолія, імунітет.

Coronary artery disease (CAD), manifested by severe clinical course, high disability and mortality among the population, has become widespread over the last decade [4]. This creates important medical and social problems and encourages clinicians to further study the causes, pathogenetic mechanisms, improve diagnosis, implementation of effective treatment algorithms and prevention of this disease [13]. Moreover,

profound differential diagnosis with plethora disorders including congenital heart disease should be provided in patients with CAD suspicion [12].

There are many known risk factors [3] and pathogenetic links in the development of CAD (dyslipidemia, impaired rheological properties of blood, endothelial dysfunction and immune inflammation, gut microbiome, the presence of bacterial and viral infections, matrix metalloproteinases with inhibitors, aminoacid imbalance of blood plasma) [2, 10, 11].

The efficacy of CAD treatment and prevention of fatal complications depends on the timely diagnosis of the disease. In this aspect, painless myocardial ischemia (PLMI) deserves attention. If groups of people at risk of PLMI have already been identified, the mechanisms of development have not been definitively studied. The presence of PLMI increases the risk of sudden death by 5–6 times, arrhythmias – by 2 times, the development of congestive heart failure – by 1.5 times [6].

To prevent the development of adverse cardiac events, it is necessary to diagnose the patient with the presence of PLMI. However, unlike painful myocardial ischemia (PMI), the absence of pain does not encourage the patient to seek medical help and examination in a timely manner. PLMI can be documented only by means of instrumental diagnostic methods [8].

A priority field of modern research in cardiology is also the study of possible pathogenetic links in the development of atherosclerosis (AS) and CAD. The results of research in recent decades leave no doubt about the legitimacy of the hypothesis that the humoral and cellular immunity play crucial role in the pathogenesis of AS, CAD and acute forms of its clinical course [9].

Since PLMI is a prognostically important form of CAD and is common, and impaired immune status is one of the pathogenetic mechanisms of AS and myocardial ischemia, it is advisable to analyze the possible relationship between PMI, PLMI, myocardial ectopic activity and the immunity (humoral and cellular) in patients with stable angina pectoris (SAP) and unstable angina pectoris (UAP). The obtained pathogenetically substantiated results of the study will further optimize the diagnosis and treatment of patients with CAD.

The purpose of the study was to improve the diagnosis of SAP and UAP by determining the correlations between the development of myocardial ischemia and cardiac arrhythmias with imbalance of cellular and humoral immunity in patients with CAD, which will further optimize the treatment of patients with this pathology.

Materials and methods. We examined 123 patients with CAD aged 56 to 76 years (the mean age of 62.0±8.6 years), which were divided into two groups: group I – 62 patients with SAP (30 patients with SAP functional class (FC) II, 32 patients – with SAP FC III), group II – 61 patients with UAP (20 patients – new-onset angina pectoris, 42 patients – progressive angina pectoris) aged 51 to 73 years (the mean age of 66.3±4.7 years).

All groups of patients were statistically homogeneous and comparable. The control group (CG) consisted of 34 clinically healthy individuals aged 55 to 67 years (mean age – 62.0±5.6 years).

Studies of the population and subpopulation of lymphocytes were performed by monoclonal antibodies on the enzyme-linked immunosorbent assay RT 2100C Microplate Reader Layton's (Stormoff, Germany). Diagnostics for the determination of T-lymphocytes, T-helpers and T-suppressors are fixed particles – erythrocytes or latex coated with monoclonal antibodies against CD3+ (T-lymphocytes), CD4+ (T-helpers), CD8+ (T-suppressors) antigens.

Determination of class G, A, M immunoglobulins (Ig) in blood serum was performed by the Mancini method (1965). Monospecific human IgG, IgA, IgM serum is used to quantify class IgG, IgA, IgM in blood serum. The content of circulating immune complexes (CIC) in the serum of patients was determined by precipitation with polyethylene glycol with a molecular weight of 6000 (Serva), followed by measurement of the optical density of the studied samples with a SF46 spectrophotometer with a wavelength of 450 nm.

To record cardiac arrhythmias and ischemic myocardial changes, all subjects underwent 24-hours Holter monitoring (HM) ECG in the first 1–2 days of stay in the clinic. For this purpose, the Holter monitoring system "Cardiosens K" manufactured by HAI-MEDICA (Kharkiv, Ukraine) was used. According to HM ECG data, the following indices were determined: arrhythmia (single supraventricular extrasystoles (SSE), paired supraventricular extrasystoles (PSE), group supraventricular extrasystoles (GSE), single ventricular extrasystoles (SVE), paired ventricular extrasystoles (PVE), group ventricular extrasystoles (GVE)); the number of episodes of ischemia during the day, the mean heart rate of the ischemic episode (beats/min.), the mean duration of one episode of ischemia (min.), the total duration of ischemia per day (min.). The comparative analysis of these indices for PMI and PLMI was conducted.

Statistical processing of the study results was performed in "MS Exel XP" and SPSS-17 for Window. Student's parametric criterion was used to assess intergroup differences. The difference at $p<0.05$ was considered statistically significant. The results are given as M±m. The percentile method was used to establish standards for individual biochemical parameters. To establish the correlation, the Pearson correlation coefficient (r) was determined and a linear regression analysis was performed to determine the standardized coefficient β.

Results of the study and their discussion. Analysis of the results of HM ECG showed that episodes of displacement of the ST segment of the ischemic type were registered in 45 of 62 patients with SAP (72 %). 17 of 62 patients (28 %) did not have such changes. Only PMI was registered in 24 patients out of 62 (37 %), a combination of PMI and PLMI – in 23 (38 %), isolated PMI – in 6 (11 %).

With the increase of FC, the number of patients with exclusively painless changes in the ST segment decreased: 9 out of 30 patients (31.5 %) with SAP FC II and 6 out of 32 patients (21.8 %) with SAP FC III. The combination of PMI and PLMI was less frequent – in 8 out of 30 patients (27.4 %) with SAP FC II and more often in patients with SAP FC III – 21 out of 32 (68.5 %). Exclusively PMI in patients was observed rarely: the frequency of its detection in patients with SAP FC II and III – 4 out of 30 (13.6 %) and 3 out of 32 (10.2 %), respectively. The number of patients without myocardial ischemia episodes during HM ECG is higher in the group SAP FC II – 7 out of 30 (25.8 %) compared to the group SAP FC III – 4 out of 32 (12.7 %) (Table 1).

Table1

Comparative characteristics of myocardial ischemia episodes and arrhythmias according to 24-hour HM ECG in patients with SAP and UAP (M±m)

Index	SAP	UAP	p*
Myocardial ischemia type			
PLMI number of episodes	2.5±0.2	7.1±0.6	0.01
PMI number of episodes	2.4±0.2	2.7±0.3	0.05
p**	0.05	0.01	
PLMI total duration, min.	35.8±6.5	141.4±17.2	0.01
PMI total duration, min.	30.2±4.1	49.8±7.9	0.01
p**	0.05	0.01	
Arrhythmias			
SVE, n	122.5±22.6	131.5±21.2	0.01
PVE, n	4.9±1.8	5.5±1.3	0.05
GVE, n	7.8±2.6	29.1±19	0.01
SSE, n	121.6±27.3	69.1±10.7	0.01
PSE, n	5.7±0.8	4.9±1.5	0.05
GSE, n	4.9±1.5	4.4±1.1	0.05
SVE, n	122.5±22.6	131.5±21.2	0.01

Notes: p* – probability while comparison SAP and UAP groups, p** – probability while comparison indices between groups of patients with PMI and PLMI.

According to the results of HM ECG, out of 61 patients with UAP in 54 (89.4 %) episodes of ST-segment displacement by ischemic type were registered. Among them, 20 out of 61 patients (38.2 %) were diagnosed exclusively with PLMI, in 34 of 61 (61.8 %) – a combination of PMI with PLMI. The number of episodes of PLMI during the day and their total duration compared to similar indices for PMI indicates their significant advantage in PLMI.

In patients with emergencies compared to patients with SAP there was a significantly higher daily number of episodes and the duration of PLMI by 64.8 % and 60.6 %, respectively, and the total duration of PMI by 39.4 %.

Patients with SAP have a high frequency of heart rhythm disorders. SVE was registered in 47 of 62 patients (76.5 %), PVE – in 7 of 62 (12 %), GVE – in 5 of 62 (8.4 %), SSE – in 51 of 62 (83.6 %), PSE – in 9 out of 62 (14 %), GSE – in 8 out of 62 (13.8 %) (Table 1).

Assessment of electrical instability of the myocardium, according to HM ECG, indicates a high frequency of heart rhythm disorders in patients with emergencies – in 57 out of 61 (94.2 %). According to the results of HM ECG, SVE was registered in 52 out of 61 patients (85.4 %), PVE – in 15 out of 61 (24.8 %), GVE – in 7 out of 61 (11.5 %), SSE – in 43 out of 61 (71 %), PSE – in 8 out of 61 (13.5 %), GSE – in 7 out of 61 (11.5 %).

In patients with emergencies, compared with patients with SAP, there was a significantly higher daily amount of SSE by 43.2 %, SVE – by 6.9 %, GVE – by 73.2 %.

Analyzing the immune status in patients with SAP and UAP, it should be noted that in patients with UAP, in contrast to patients with SAP, abnormalities were found in the values of most indices of cellular and humoral immunity (Table 2).

Table 2

Indices of immunological reactivity of patients with stable and unstable angina pectoris (M ± m)

Index	Control group n = 21	Stable angina n=40	Unstable angina n=65
Lymphocytes, %	30.16±1.54	31.08±1.31≠	15.70±0.94*#
CD3+, %	48.7±2.9	35.90±0.48*	37.19±1.17*
CD4+, %	32.57±2.06	28.32±0.94*	36.70±1.71*#
CD8+, %	22.35±0.68	22.82±1.27	12.70±0.73*#
CD22+, %	20.37±1.70	22.23±1.56	25.10±1.73*
CD4/CD8	1.61±0.03	1.28±0.07	3.10±0.15*#
IgA, g/L	2.45±0.09	2.15±0.15	2.40±0.06
IgM, g/L	1.09±0.07	1.16±0.09	1.18±0.03
IgG, g/L	11.84±0.78	12.53±0.47	14.00±0.56*
CIC, c.u.	1.39±0.08	2.28±0.05*	6.10±0.69*#

Notes: * – significant difference in relation to the CG; # – significant difference between groups of patients.

In patients with SAP compared to CG there was a significantly lower level of CD3+ by 24.6 % (p<0.01), CD4+ – by 13.1 % (p<0.01) and a significantly higher level of CIC at 1.6 times (p<0.05).

In patients with UAP compared to CG, the following changes were detected: the population of lymphocytes was significantly lower by 47.6 % (p<0.01), the level of CD3+ – by 27.2 % (p<0.01); the level of CD8+ – by 38.3 % (p<0.01), the level of CD4+ significantly higher by 15.1 % (p<0.05), the level of CD22+ – by 22.7 % (p<0.01), the ratio CD4/CD8 is significantly higher – 1.9 times (p<0.01), IgG level – 1.2 (p<0.01), CIC level – 4.3 times (p<0.01). When comparing the immunological reactivity of patients with SAP and UAP revealed changes in the following indices: the level of the population of lymphocytes in patients with UAP significantly lower than in patients with SAP by 47.8 % (p<0.01), the level of CD8+ by 44.4 % (p<0.01); the level of CD4+ is significantly higher by 21.5 % (p<0.05); the CD4/CD8 ratio is 1.9 times (p<0.01), the CIC level is 2.7 times (p<0.01).

It was registered the significantly lower values of the population lymphocytes, CD8+ and significantly higher levels of CD4+ and CIC in patients with UAP compared to patients with SAP. A correlation analysis between these indices and indices of HM ECG. In patients with stable angina statistically significant direct mild correlation were registered between PLIM and CD4+ (r=0,28, p<0.05), CD8+ (r=0.23, p<0.05), PIM and CD4+ (r=0,52, p<0.05), CIC (r=0.42, p<0.05), as well as in patients with unstable angina direct mild correlation were registered between PLIM and CD4+ (r=0.43, p<0.05), CD8+ (r=0.51, p<0.05), CIC (r=0.53, p<0.05). In addition, in patients with unstable angina mild direct corellations were registered between GSE and CD4+ (r=0.35, p<0.05), CD8+ (r=0.38, p<0.05), CIC (r=0.27, p<0.05) unlike in patients with stable angina.

In UAP, coronary circulatory disorders lead to the development of resorption changes in myocardial tissue, which in turn is accompanied by an immune response: a decrease in the relative content of lymphocytes in the peripheral blood, an increase in B-lymphocytes (CD22+). The increase in CD4+ can be explained as a compensatory response (stimulation of B-lymphocytes to antibody synthesis), and a decrease in CD8+ indicates a decrease in the suppressive activity of T-lymphocytes, which is also a protective reaction (disruption of B-lymphocytes in antibody synthesis) [9]. In SAP, in the absence of marked death and resorption of muscle tissue, circulating anticardiac autoantibodies are either not detected at all or are registered in small quantities [7]. The content of these antibodies increases in emergencies, regardless of whether the attack was stopped, or there was a tendency to transition to myocardial infarction, and most pronounced – against the background of myocardial infarction, which is probably less due to pathogenetic features of coronary insufficiency, and most importantly thus, these processes reflect the severity of heart disease [9].

Thus, according to HM ECG, in patients with emergencies PLMI was registered in most cases and is predominant in the structure of MI with a significant predominance of the number and duration of episodes of PLMI compared to PMI. In contrast to patients with emergencies, in patients with SAP on similar indices no significant difference was found. Thus, this profile of ischemic reaction allows us to regard it as an objective criterion for destabilization of coronary circulation [7]. In addition, there is a significantly larger number of GVE are prognostically significant for the adverse course of CAD [5].

Correlation analysis showed that destabilization of coronary circulation is accompanied by tension of the cellular and humoral part of the immune system and increased ectopic activity of the ventricles. This

is confirmed by the fact that in patients with emergencies revealed a direct correlation between the occurrence of GVE on the level of subpopulations of CD4+ and CD8+ and the level of the CIC [1].

Pathogenetic links between coronary circulatory disorders and ectopic myocardial activity with the development of imbalance of cellular and humoral immunity in patients with stable and unstable angina pectoris confirm the theory of immune inflammation as one of the pathogenetic links in the development of coronary heart disease and encourage research and development of new drugs in antianginal therapy algorithms.

Conclusions

1. In patients with UAP compared with patients with SAP is manifested by a greater daily number of episodes and the total duration of PLMI, respectively, by 64.8 % and 60.6 % and the total daily duration of PMI by 39.4 %. In patients with emergencies, compared with patients with SAP, there was a higher daily amount of SSE by 43.2 %, SVE – by 6.9 %, GVE – by 73.2 %.

2. In patients with CAD there is a violation of cellular and humoral immunity. When destabilizing the coronary circulation compared to the stable course of the disease decreases the relative content of the population of the population lymphocytes by 47.8 %, the level of the subpopulation CD8+ – by 44.4 %; the level of CD4+ subpopulation is significantly higher by 21.5 %, the CD4/CD8 ratio is 1.9 times, the CIC level is 2.7 times higher.

3. With a SAP, the development of PMI depends on the level of the CD4+ subpopulation and the CIC, the development of PLMI – on the level of the CD4+ and CD8+ subpopulations.

4. CAD destabilization and GVE are associated with elevated CD4+ subpopulations, CD8+ subpopulations and CIC levels.

References

1. Lyzohub VH, Zavalska TV, Stakhurska LA, Khalied Akhmad Khalil Abu Sara, Pliskevych DA, Dunaievskyi VI, Hrubnyk BP. Rol porushen humoralnoho imunitetu v rozvytku aterosklerozu i hostroho koronarnoho syndromu. Lik. Sprava. 2012;5: 63–72. [in Ukrainian]

2. Arvanitis M, Lowenstein CJ. Dyslipidemia. Ann Intern Med. 2023 Jun;176(6): 81–96. https://doi.org/10.7326/aitc202306200

3. Devkota S, Dhungana RR, Pandey AR, Poudel CM, Shrestha H, Bhattarai A. Risk Factors of Coronary Artery Disease: A Hospital-Based Study. J Nepal Health Res Counc. 2022 Nov 3;20(2):487–493. https://doi.org/10.33314/jnhrc.v20i02.4240

4. Duggan JP, Peters AS, Trachiotis GD, Antevil JL. Epidemiology of Coronary Artery Disease. Surg Clin North Am. 2022 Jun;102(3):499–516. https://doi.org/10.1016/j.suc.2022.01.007.

5. Durmaz E, Ikitimur B, Kilickiran Avci B, Atıcı A, Yurtseven E, Tokdil H, Ebren C, Polat F, Karaca O, Karadag B, Ongen Z. The clinical significance of premature atrial contractions: How frequent should they become predictive of new-onset atrial fibrillation. Ann Noninvasive Electrocardiol. 2020 May;25(3): e12718. https://doi.org/10.1111/anec.12718

6. Fearon WF. The prognostic importance of silent ischemia. Int J Cardiol. 2019 Sep 15; 291:27–28. https://doi.org/10.1016/j.ijcard.2019.05.050

7. Feng X, Zhang Y, Du M, Li S, Ding J, Wang J, Wang Y, Liu P. Identification of diagnostic biomarkers and therapeutic targets in peripheral immune landscape from coronary artery disease. J Transl Med. 2022 Sep 5;20(1):399. https://doi.org/10.1186/s12967-022-03614-1

8. Gallino A. The dilemma of detecting silent myocardial ischemia. Int J Cardiol. 2017 Oct 1; 244:86. https://doi.org/10.1016/j.ijcard.2017.06.049

9. Laera N, Malerba P, Vacanti G, Nardin S, Pagnesi M, Nardin M. Impact of Immunity on Coronary Artery Disease: An Updated Pathogenic Interplay and Potential Therapeutic Strategies. Life (Basel). 2023 Oct 27;13(11):2128. https://doi.org/10.3390/life13112128

10. Larsen JB, Hvas AM. Fibrin clot properties in coronary artery disease: new determinants and prognostic markers. Pol Arch Intern Med. 2021 Nov 30;131(11):16113 https://doi.org/10.20452/pamw.16113

11. Medina-Leyte DJ, Zepeda-García O, Domínguez-Pérez M, González-Garrido A, Villarreal-Molina T, Jacobo-Albavera L. Endothelial Dysfunction, Inflammation and Coronary Artery Disease: Potential Biomarkers and Promising Therapeutical Approaches. Int J Mol Sci. 2021 Apr 8;22(8):3850. https://doi.org/10.3390/ijms22083850

12. Shevchenko TI, Shaposhnyk OA, Sorokina SI, Kudrya IP, Efremenko VM. Features of management of patient with late diagnosted congenital heart disease. W Med Biology. 2019;1(67):111–116. https://doi.org/10.26724/2079-8334-2019-1-67-111

13. Yazdani AN, Pletsch M, Chorbajian A, Zitser D, Rai V, Agrawal DK. Biomarkers to monitor the prognosis, disease severity, and treatment efficacy in coronary artery disease. Expert Rev Cardiovasc Ther. 2023 Jul-Dec;21(10):675–692. https://doi.org/10.1080/14779072.2023.2264779