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V.O. Romanova, N.V. Kuzminova, A.V. Ivankova, S.E. Lozinsky, I.I. Kniazkova[1],
O.L. Poberezhets, Yu.L. Shkarovskyi
National Pirogov Memorial Medical University, Vinnytsya
[1]Kharkiv National Medical University, Kharkiv

CRITERIA FOR DESTABILIZATION OF THE DISEASE COURSE IN PATIENTS WITH CORONARY HEART DISEASE

e-mail: kuzminova5517@gmail.com

173 patients with various coronary heart disease course variants were examined to identify possible pathogenetically based criteria for destabilization of the disease course. It was established that patients with an unstable course of coronary heart disease were characterized by both more pronounced inflammatory reaction and impairment of vascular endothelial function. Inflammatory activation was 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. The same differences were observed about endothelial dysfunction that was evidenced by a significant increase in its biochemical markers (ET-1, sVCAM, and PAPP-A). Therefore, such markers can be considered as criteria for destabilizing of the atherosclerotic process.

Key words: coronary heart disease, nonspecific systemic inflammation, endothelial dysfunction, hyperleptinemia, dyslipidemia.

В.О. Романова, Н.В. Кузьмінова, А.В. Іванкова, С.Е. Лозинський, І.І. Князькова, О.Л. Побережець, Ю.Л. Шкарівський

КРИТЕРІЇ ДЕСТАБІЛІЗАЦІЇ ПЕРЕБІГУ ЗАХВОРЮВАННЯ У ХВОРИХ НА ІШЕМІЧНУ ХВОРОБУ СЕРЦЯ

З метою виявлення можливих патогенетично обгрунтованих критеріїв дестабілізації перебігу захворювання у хворих на ішемічну хворобу серця обстежено 173 пацієнти з різними варіантами перебігу захворювання. Встановлено, що пацієнти з нестабільним перебігом ішемічної хвороби серця характеризувалися як більш виразною запальною реакцією, так і більшим порушенням функцій судинного ендотелію. Про активацію запалення свідчило 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. Такі ж відмінності спостерігалися щодо ендотеліальної дисфункції, про що свідчило значне підвищення її біохімічних маркерів (ЕТ-1, sVCAM і PAPP-A). Тому вказані маркери можна розцінювати в якості критеріїв дестабілізації атеросклеротичного процесу.

Ключові слова: ішемічна хвороба серця, неспецифічне системне запалення, ендотеліальна дисфункція, гіперлептинемія, дисліпідемія.

The study is a fragment of the research project "Metabolic risk factors, cardiovascular remodeling and functional state of the kidneys in patients with cardiovascular disease. Possibilities of pharmacological correction", state registration No. 0119U101849.

Cardiovascular disease (CVD), primarily coronary heart disease (CHD), has been the leading cause of death worldwide for decades. According to the WHO, in 2021, CVD caused 20.5 million deaths – a third of all deaths in the world, which is almost twice higher than the cardiovascular mortality recorded in 1990 [9, 12].

The prognosis of a patient with coronary heart disease is largely determined by the destabilization of the process, which is clinically manifested by acute coronary syndrome (ACS). The methods used to diagnose ACS are based on the detection of foci of necrosis or transient myocardial dysfunction. However, it is equally important to search for markers that would allow predicting the development of ACS or diagnosing it in a patient before the onset of irreversible changes in the myocardium.

The pathophysiology of coronary heart disease is based on the discrepancy between the myocardial oxygen demand and its supply, which is most often caused by a deterioration in myocardial blood supply due to coronary atherosclerosis.

Atherosclerosis (from the Greek words "athere" – gruel, "sclerosis" – hard) is a chronic disease with a wave-like course characterized by lipid deposition in the arterial wall, inflammation, and connective tissue proliferation with the formation of fibrous plaques, which narrow the lumen of the affected arteries and lead to circulatory disorders.

As early as the nineteenth century, Rudolf Virchow described inflammation as an active driving factor in plaque formation. Still, the importance of these findings was only appreciated more than a century later. Since then, modern immunology has developed significantly, paving the way for a deeper understanding of how the immune system works, including in atherosclerosis [4].

In addition, one of the important links in the pathogenesis of atherosclerosis is endothelial dysfunction, which is understood as an imbalance between the production of vasodilating, angioprotective, and antiproliferative factors on the one hand and vasoconstrictive, prothrombotic, and proliferative factors on the other. Since the interaction of blood lipoproteins with the vascular endothelium determines the development and progression of atherosclerosis, numerous studies in recent years have been aimed at developing methods to evaluate and improve endothelial function [1, 14].

Obesity is an independent cardiovascular risk factor, the effect of which on the development and progression of atherosclerosis is associated with the paracrine function of white adipose tissue – the synthesis of adipocytokines [5, 7].

Given that atherosclerosis is a multifactorial disease, a comprehensive study of markers of various pathogenic links is needed to determine the risk of progression of the atherosclerotic process and destabilization of the course of coronary heart disease.

The purpose of the study was to identify possible pathogenetically based criteria for destabilization of the disease course in patients with coronary heart disease.

Materials and methods. The study included 173 patients with coronary heart disease (mean age: 57.24±5.12 years) who were treated in the cardiology department of the Vinnytsia Regional M.I. Pirogov Memorial Clinical Hospital and the department of myocardial infarction of the Vinnytsia Regional Clinical Treatment and Diagnostic Center for Cardiovascular Pathology. After the examination, the patients were divided into 2 main clinical groups – 92 patients with stable CHD (45 – II and 47 – II I functional classes, respectively) and 81 patients with ACS (subsequently, 43 patients were diagnosed with unstable (progressive) angina, and 38 patients with acute myocardial infarction (AMI)).

The control group included 30 practically healthy individuals of the appropriate age and gender.

Blood sampling from the cubital vein for clinical and biochemical examination was performed on the first day of admission to the hospital (in case of ACS – in the first 2 hours). In 82 patients (47.4 %), CHD was combined with hypertension.

The diagnosis of stable coronary heart disease and variants of acute coronary syndrome was made following the 2012, 2013, and 2015 European Society of Cardiology Guidelines and Orders of the Ministry of Health of Ukraine No. 455 of July 02, 2014, No. 164 of March 03, 2016 and No. 152 of March 02, 2016.

The study did not include people over 75 years of age with chronic heart failure of NYHA functional classes III-IV, malignant neoplasms, secondary arterial hypertension, acute inflammatory or exacerbation of chronic diseases at the time of the examination, obesity of II-III degrees, liver and kidney diseases with impaired function, diseases causing secondary dyslipidemia (diabetes mellitus, hypothyroidism, nephrotic syndrome, cholestasis).

Laboratory examination of patients included: general blood and urine tests, blood lipid profile, blood glucose, blood electrolyte composition (namely, K^+ and Na^+), urea and creatinine levels, total protein, fibrinogen, prothrombin index or INR, total bilirubin and its fraction, alanine and aspartate aminotransferase activity.

The endocrine function of adipose tissue was assessed by blood leptin levels (determined by enzyme-linked immunosorbent assay using the Leptin ELISA kit, DRG Diagnostics, Germany) and calculation of leptin resistance.

Markers of endothelial dysfunction and nonspecific systemic inflammation in the serum of patients with coronary heart disease were determined by enzyme-linked immunosorbent assay using special reagent kits (ELISA kits "Endotelin-1" and “hsCRP ELISA” manufactured by DRG, USA; “sVCAM” by Bender Medsystems, Austria; highly sensitive PAPP-A by Diagnostics Systems Laboratories, USA; TNF-a ELISA test kit by Diaclone, France).

Excel-2010 spreadsheets and StatSoft Statistica v. 6.0 and 10.0 statistical processing software were used to create the database and analyze the results. The reliability of the differences was determined using the Student's and Mann- Whitney's t-test.

Results of the study and their discussion. Comparison of biomarkers of inflammation and endothelial dysfunction in groups of patients with stable and unstable courses of coronary heart disease (Table 1) showed significant differences in the values of indicators with a high degree of reliability for the levels of hsCRP, TNF-a, PAPP-A, sVCAM ($p<0.001$), which gives reason to associate their increase with destabilization of the process. The degree of differences in the level of ET-1 and leptin was somewhat smaller but also significant ($p<0.01$). When comparing the lipid spectrum in patients with different disease courses, no significant difference was observed, except for HDL cholesterol, which was slightly but significantly higher in patients with stable CHD than in patients with ACS ($p<0.05$).

Table 1

Biochemical parameters in patients with different courses of coronary heart disease

Index	Control group (n=30)	Stable course (n=92)	Unstable course (n=81)	p
Blood fibrinogen, g/L	2.64±0.28	3.52±0.18*	4.09±0.22*	<0.05
hsCRP, mg/L	0.87±0.04	3.27±0.16*	7.58±0.21*	<0.0001
TNF-a, pg/mL	1.18±0.07	3.00±0.17*	5.74±0.14*	<0.0001
PAPP-A, mIU/L	3.12±0.42	4.44±0.27*	16.15±0.24*	<0.0001
ET-1, ng/mL	4.01±0.36	8.84±0.28*	11.08±0.37*	<0.01
sVCAM, ng/mL	626.0±34.1	1195.3±31.44*	1724.3±41.20*	<0.0001
Leptin, ng/mL	10.32±1.12	18.26±0.95*	23.89±1.12*	<0.01
Leptin resistance, units	6.26±0.28	10.15±0.57*	11.59±0.76*	ns
Total cholesterol, mmol/L	5.08±0.41	5.99±0.13*	6.01±0.17*	ns
TG, mmol/L	1.65±0.07	1.80±0.05	1.90±0.07*	ns
LDL cholesterol, mmol/L	2.96±0.31	4.05±0.12*	4.07±0.14*	ns
LDL cholesterol, mmol/L	0.75±0.04	0.80±0.03	0.85±0.04*	ns
HDL cholesterol, mmol/L	1.37±0.07	1.14±0.02*	1.07±0.02*	<0.05
Atherogenicity index, units	2.71±0.22	4.25±0.21*	4.62±0.19*	ns

Notes: p is the significance of the difference between the groups with complicated and uncomplicated courses; ns – difference is not significant (p>0.05)

Mathematical analysis of the indices using β-coefficients for statistical characterization of individual independent predictors allowed us to identify the main criteria of destabilization (Table 2). To assess the informativeness of these markers, their sensitivity and specificity were calculated. The table includes the most informative indicators for which the p-coefficient was greater than 0.50 units.

Table 2

Clinical, instrumental, and laboratory predictors of coronary heart disease destabilization

Markers of process instability	ß	Sensitivity	Specificity
TNF-a ≥2.44 pg/mL	0.75	86 %	76 %
hsCRP ≥2.97 mg/L	0.73	84 %	72 %
PAPP-A ≥7.15 mIU/L	0.70	87 %	74 %
sVCAM ≥1170.0 ng/mL	0.70	79 %	72 %
ET-1 ≥7.88 ng/mL	0.68	77 %	71 %
Leptin ≥17.25 ng/mL	0.64	67 %	61 %
LDL cholesterol ≥3.75 mmol/L	0.51	58 %	49 %
HDL cholesterol ≤1.35 mmol/L	0.59	64 %	53 %

The coefficient of determination (RI) of the predictors was 0.75, and the adequacy of the analysis by the F-criterion was 143.5, p<0.0001.

Our findings on the diagnostic significance of markers of nonspecific systemic inflammation and endothelial dysfunction in patients with coronary heart disease are in line with the results of studies by other authors.

According to a meta-analysis by the Emerging Risk Factors Collaboration, hsCRP is an independent risk factor for cardiovascular events in both healthy individuals and patients with established disease [4]. Even a slight increase in CRP, which can be determined only by a highly sensitive method, has been associated with an increased risk of ACS in clinical practice [3, 7].

According to Ridker P.M. et al., the concentration of plasma TNF-a after myocardial infarction is a strong predictor of recurrent events [15]. According to a meta-analysis of 28 randomized clinical trials, a decrease in TNF-a concentration under the influence of TNF-a inhibitor therapy in patients with rheumatoid arthritis was associated with a 41 % reduction in the risk of myocardial infarction and a 43 % reduction in stroke in such patients [8].

According to Davenport AP et al, the content of ET-1 in unstable atherosclerotic plaques is significantly higher than in stable ones [2], so an increase in its concentration in blood plasma may indicate destabilization of the atherosclerotic process. In addition, in patients with stable coronary heart disease, plasma levels of ET-1 correlate with the severity of angina symptoms, and in patients with AMI – with the severity of the pathological process and prognosis [2, 6].

The earliest stage of inflammation characteristic of atherosclerosis is the adhesion of monocytes to activated endothelial cells due to overexpression of vascular adhesion molecules (including sVCAM) on their surface. In the prospective AtheroGene study, the level of sVCAM-1 was recognized as a strong independent predictor of future fatal cardiovascular events. In the study by Mulvihill N.T. et al., increased

concentration of sVCAM-1 was positively correlated with an increased risk of major cardiovascular events during 6 months of follow-up [13].

According to the study by Parveen N. et al [10], an increase in plasma PAPP-A levels in patients with suspected ACS is an important tool for diagnostic and therapeutic stratification when cardiac troponin and MB-CK levels are not elevated and ECG changes are inconclusive.

Numerous in vitro studies have demonstrated the ability of leptin to cause oxidative stress in endothelial cells. In addition, leptin can stimulate the proliferation and migration of vascular smooth muscle cells and calcification of endothelial cells, which may contribute to the onset and exacerbation of the atherosclerotic process [11]. The possibility that leptin levels may be related to cardiovascular disease has been shown not only in animal experiments but also in clinical studies, where a correlation between leptin levels and inflammation was found [7, 11] in patients with coronary heart disease.

Given that the concentration of the studied markers was higher in patients with unstable disease, we compared them with the content of troponins I and T, determined in the first hours of MI. Since we did not find a significant relationship between the studied markers and troponins, these indicators were considered as criteria for the destabilization of CHD, rather than myocardial damage.

Conclusion

Patients with coronary heart disease have activation of nonspecific systemic inflammation and vascular endothelial dysfunction, as evidenced by increased serum levels of fibrinogen, hsCRP, TNF-a, PAPP-A, leptin, ET-1, and sVCAM. Moreover, the levels of these biomarkers are significantly higher in patients with unstable disease not only compared to healthy individuals but also to patients with a stable course. Determination of diagnostic criteria such as hsCRP, TNF-a, PAPP-A, sVCAM, and, to a lesser extent, ET-1, and leptin levels makes it possible to diagnose destabilization of the atherosclerotic process, which can help improve the diagnosis, prognosis, and optimization of treatment of patients with coronary heart disease.

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