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L.A. Vozniuk, I.O. Doroshkevych, O.O. Klekot, O.V. Kyrychenko
National Pirogov Memorial Medical University, Vinnytsia

VALUE OF ENDOTHELIUM DYSFUNCTION AND INFLAMMATORY MARKERS LEVEL FOR PREDICTING RISK ASSESSMENT IN UNFAVORABLE COURSE OF ISCHEMIC HEART DISEASE

E-mail: laravoznyuk@gmail.com

Study of the coronary artery disease course suggests that along with proatherogenic changes in the blood lipid composition in patients with coronary artery disease, an increase in the C-reactive protein (CRP) concentration and proinflammatory cytokines (TNF- α) was observed in comparison with the control group. Characterized by the patterns of the correlations existing between the degree of increase in the level of CRP and ESR, particularly in patients with ACS ($r = 0.48$, $p < 0.01$). The degree of increase in von Willebrand factor was revealed in the group of patients with fatal and nonfatal myocardial infarction, which was significantly higher than in the group of patients with uncomplicated CHD. An increase in the CRP level was not inferior in frequency to dyslipidemia and was observed in the majority of CHD patients (65.3%). Correlations between the severity of extracranial artery remodeling and the content of TNF- α ($r = 0.30$, < 0.05) and a less pronounced connection with the concentration of interleukins (IL-6) ($r = 0.25$, $p < 0.05$) were determined.

Key words: coronary heart disease, proinflammatory cytokines, PSA, von Willebrand factor, cholesterol.

The present study is a fragment of the research project "Organ-protective activity and metabolic correctors safety in the treatment of comorbid pathological conditions" (state registration No. 0114U000195).

High level of cholesterol (particularly low density lipoproteins (LDL) cholesterol in blood plasma is the most important atherosclerosis risk factor and therefore it is no wonder that atherosclerosis is seen primarily as a process associated with the accumulation of lipids in the vessel wall [1,9]. Cardiovascular diseases are still remaining the leading cause of death in most of the developed countries, despite changes in lifestyle and the use of modern pharmacological treatment approaches aimed at lowering the cholesterol level in blood plasma [3,5,8]. According to the present-day concepts, atherosclerosis can be considered as a series of cellular and molecular disorders that are sequentially developing, which all totaled can be described as an inflammatory disease [11]. The commonality of inflammation and atherosclerosis is quite natural, since both syndromes form the same connective tissue cells [1,6-7]. In both syndromes, in the arteries intima smooth muscle cells proliferate, lipid spots (streaks) are formed, and the content of cholesterol (CH) esters is increased in cells and in the extracellular matrix [14-15]. Increased level of inflammatory markers circulating in the blood may indicate a risk of cardiovascular disease (CVD) developing in both the general population and patients with ischemic heart disease (IHD) [2-4]. Systemic inflammation in atherosclerosis naturally manifests itself in patients even without clinical signs of IHD and correlates with the most important factors [10,15]. It is believed that the presence of the inflammatory component is important in the process of a stable atherosclerotic plaque transition into an unstable condition characterized by its rupture and formation of a thrombus [2,12]. One of the most studied inflammation markers is C-reactive protein, which has a high degree of correlation with morphological signs of inflammation in the vessel wall [6, 9-10]. Modern studies have proved that an increase in the formation of proteins and cytokines with local accumulation of inflammatory cells, which is semeiotic for the acute phase in patients with acute coronary syndrome, is the unstable angina [5,10-11].

One of the of our study's objectives was to determine the prognostic significance of the increased inflammatory markers level in the blood when assessing the risk of developing IHD.

Materials and methods. The total of 117 patients with coronary heart disease aged 30-70 years undergoing the inpatient treatment in the cardiology department of the Vinnitsa Regional Clinical Hospital named after M.I. Pirogov during the period from December 2014 to May 2017. The control group included 20 practically healthy persons, matched by age and gender. Of the total number of patients, 63 men aged 30-70 years – the mean age 58.3 ± 1.5 - and 54 women aged 30-70 years - mean age 57.3 ± 2.2 . A significant proportion of the examined persons were of the employable age. The mean age of all the examined patients was 56.52 ± 4.47 years. After verifying the diagnosis by a number of clinical and instrumental research methods, it was found that 84 patients had a combination of IHD with II-III degree hypertensive disease (HD) (71.8%). The diagnosis of IHD was set in accordance with the Recommendations of the European Society of Cardiology (2006). The list of diagnostic studies included: estimation of the angina syndrome,

confirmed by the documented AMI, ECG at rest and that with daily monitoring, veloergometry in the absence of contraindications, EchoCG on therapeutic grounds.

Criteria for exclusion from the study were: patients with diseases that cause secondary dyslipidemia, disorders of the blood lipid profile, the age over 70 and in the presence of decompensated kidney, liver disorders and heart failure.

Clinical laboratory methods (general blood and urine tests, functional liver and kidney tests) were copied from the disease history. Biochemical methods of research included the blood lipid profile, the Willebrand factor activity, the levels of CRP, TNF- α ; the analyses were performed in the biochemical laboratory of the Ukrainian Scientific Research Institute of Medical Rehabilitation and Resort Therapy. The index of atherogenicity was determined. The body weight assessment was carried out, the body mass index (BMI) (the Kettle index) was calculated using the formula:

$$\text{BMI} = \text{body weight (kg)} / \text{height (m}^2\text{)}.$$

All patients, as well as the control group persons, were exposed to daily ECG monitoring in real life conditions using an outpatient ECG monitoring system to assess the myocardial ischemia extent. The morphofunctional status of the heart determined by ultrasound methods was estimated using the MyLab 25 diagnostic ultrasound system (manufactured by "ESAOTE", USA). To confirm the extracranial vessels atherosclerosis, the morphofunctional status of the vessels was studied by means of duplex scanning and color Doppler blood flow mapping. General, internal and external carotid arteries (CA) were examined. The artery patency, vascular geometry, the intima-media CA complex condition, the presence of changes, their severity and structure, and the linear and volumetric blood flow velocity in the general CA (GCA) were assessed.

To create the database and to analyze the obtained data, the Exell-2000 spreadsheets and the Statistica 6.0 statistical processing software for personal computer were used. Methods of parametric and nonparametric variation statistics were used. The reliability of the differences was determined using the Student's and Mann-Whitney's t-criterion. The hypothesis on the equality of mean values of parameters in the studied groups at a given accuracy of 0.95 was checked, and on the basis of this the conclusion was drawn about the respective indicator's significance. To determine the independent predictors of the cardiovascular system structural remodeling with GC and AH resistance, a multivariant analysis using multiple stepwise regression ("Multiple Regression" module of StatSoft "Statistica v. 6.0" software) was performed prior to treatment.

Results of the study and their discussion. To assess the overall mortality and frequency of the serious cardiovascular diseases development and their complications, careful observation of all participants during 2.5-3 years was carried out. 3 patients were excluded from the study due to changes in residence after 24, 36 and 45 days from the beginning of the observation. The analysis included 114 persons, the completeness of the observation was 97.4%.

Depending on the nature of the disease course, the patients examined were divided into 2 groups. The main group consisted of 26 patients, in 22 of which, as from the date of inclusion into the study until its completion, the nonfatal myocardial infarction (MI) or unstable angina, requiring hospitalization, were registered in 4 cases: death from IHD. The reference group comprised 88 patients with coronary artery disease of the corresponding age and gender, which until the end of the study were alive, did not have MI, and / or were not hospitalized due to deterioration of their condition associated with the IHD progression.

To calculate the relative risk (RR) of the IHD development complications, age, smoking, body mass index (BMI), glucose, total cholesterol and LP fractions cholesterol, triglycerides and inflammatory markers BSR, CRP, and Willebrand factor levels in the blood were taken into account. After that, it was studied how much an additional determining of the inflammation markers level raised the predictive value of detecting the traditional risk factors for IHD development. The comparison between the groups was made using regression analysis ("Statistika" software, version 6.0). The odds ratio was sequentially adjusted for the following variables: age, gender, blood pressure, total cholesterol level, triglyceride level, body mass index (BMI), presence or absence of diabetes mellitus and inflammatory markers concentration. It was studied whether successive addition of inflammatory response markers increased the predictive value of the main traditional coronary risk factors. The odds ratio is presented with 95 percent confidence intervals.

Statistically significant differences in the frequency of detection and severity of some known risk factors for the IHD development were detected between the main and the reference groups (table 1). Thus, in the main group, the increase in glucose content, the decrease in CH-LPDH content, the atherogenicity index growth, arterial hypertension, growth of the body mass index (BMI); however, the incidence of smoking and hypercholesterolemia did not differ significantly in the both groups of the examined patients. Significant differences in the ESR, CRP and Willebrand factor level were outlined.

When comparing the CRP level with the Willebrand factor and the ESR level, the correlation coefficient was 0.38 and 0.24 respectively, while the comparison of ESR and the Willebrand factor resulted 0.22 ($p < 0.05$ for all comparisons). The higher CRP level was statistically significant due to smoking, increased BMI and triglycerides levels in the blood ($p < 0.01$ for all factors); higher ESR values were due to the older age, decreased hemoglobin, elevated levels of uric acid in blood serum, smoking ($p < 0.01$ for all factors); and a higher level of Willebrand factor was associated with age and smoking ($p < 0.01$ for both factors).

In assessing the risk of cardiac death, fatal and non-fatal MI in patients with coronary artery disease in the main and control groups with CRP levels exceeding the reference values (0.78-2.0 mg / l), the odds ratio (OR) was 1.92 at 95 % CI (1.68-2.18), and after the correction for smoking, other known risk factors and the socioeconomic status, the standardized OR was somewhat lower - 1.65 at 95% CI (1.45-1.85). This suggests that the high CRP level during hospitalization (> 3.0 mg / l) indicated an unfavorable prognosis, mainly in patients with unstable angina pectoris.

Table 1

Frequency of unfavorable IHD course risk factors

Risk factors	Main group (n=26)		Reference group (n=88)		P
	n	%	n	%	
Smoking	15	75	48	71.6	>0.05
BMI ≥ 0.30	12	60	27	40.3	<0.05
↑blood glucose level	9	45	14	20.9	<0.05
↑ AP	14	70	38	56.7	<0.05
↑ TCH level	11	55	33	49.2	>0.05
↑TG level	8	40	25	37.3	>0.05
↓CH-HDL level	14	70	35	52.2	<0.05
↑ AI	16	80	36	53.7	<0.05
↑ ESR	7	35	13	19.4	<0.05
↑ CRP level	15	75	19	28.3	<0.05
↑Willebrand factor level	9	45	16	23.9	<0.05

When comparing the participants of the main and control groups with the ESR levels, the corresponding upper and lower quartile values (> 10 and < 4 mm per hour of measurement), the standardized OR of the unfavorable IHD course was 1.30 at 95% CI from 1.13 to 1.51, and when comparing patients with the Willebrand factor levels, corresponding to the upper and lower quartiles, the OR values were 1.5 (at 95% from 1.1 to 2.0).

The performed comparison of the risk factors' effect on the IHD course with a sequential increase of their number (table 2) revealed an additional increase of the unfavorable disease course relative risk when the inflammatory response markers were included in the prognosis.

Table 2

Additional effect of inflammation markers on the risk of unfavorable IHD course

Inflammation markers	Odds ratio		
	Age, gender	Age, gender + traditional IHD risk factors	Age, gender + traditional IHD risk factors +increased inflammation markers level
CRP (norm)	1.92 (1.68-2.18)	1.45 (1.25-1.69)	1.42 (1.18-1.62)
ESR (norm)	1.64(1.44-1.87)	1.31 (1.13-1.51)	1.18 (1.0-1.38)
Willebrand factor norm)	1,23 (1,09)	1.12 (0.98-1.29)	1.09 (0.98-1.26)

The presence of such known risk factors as smoking, hyperlipidemia, arterial hypertension, and increased BMI did not have a statistically significant effect on the correlation between the CRP level and the risk of an unfavorable IHD course, suggesting that CRP content increase in the blood serum of IHD patients is an independent predictor of a possible aggravation of the process and development of cardiovascular events.

The study of the CRP level in the dynamics (after a month, 3 months and every 6 months in the process of further observations) showed that despite the stabilization and reversal of clinical symptoms, the inflammatory process is often maintained, as evidenced by the increased CRP concentration in the blood serum of 22 patients (25.3%) 3 months after discharge from the hospital. Attention is drawn to the fact that in the group of patients with further adverse results, the frequency of increase in CRP level was significantly higher (75% vs. 28.3% in the group with favorable prognosis, $p < 0.05$).

The persistent increase of CRP concentration after an unstable angina episode was associated with re-hospitalization for relapse of the disease and / or severe complications development. The prognostic significance of increasing Willebrand factor content in patients with coronary heart disease was somewhat less than the significance of the CRP level. Attention is drawn to the fact that in the group of patients with fatal and non-fatal myocardial infarction, the degree of Willebrand factor increase was significantly higher than in the group of patients with uncomplicated coronary artery disease.

The performed studies indicate that along with the proatherogenic changes in the blood lipid profile in IHD patients, an increase in the CRP and proinflammatory cytokines (TNF- α) concentration was observed in comparison with the control group's standards. The study of the level of CRP in the dynamics showed that, despite the stabilization and reversal of clinical symptoms, the inflammatory process is quite often preserved, as evidenced by the increased CRP concentration in the blood serum 3 months after discharge from the hospital in 25.3% of patients. In the group of patients with further adverse effects, the CRP and proinflammatory cytokines increase frequency was significantly higher (75% vs. 28.3% in the favorable prognosis group, $p < 0.05$) [3].

The frequency of the CRP level increase was higher than the frequency of lipid blood levels increase [4]. The persistent increase of CRP concentration after an unstable angina episode was associated with re-hospitalization for relapse of the disease and / or the development of severe complications.

In the group of patients with fatal and non-fatal myocardial infarction, the degree of the Willebrand factor increase was significantly higher than in the group of patients with uncomplicated IHD [8, 14].

Conclusion

Taking into account the diversity of IHD forms in the examined patients, a comparison was made between changes in the biochemical parameters under study, depending on the IHD variant. When comparing the CRP concentration in the blood of patients with different IHD variants, quite convincing differences were obtained. Its highest level was observed at the activation of the process, that is, in patients with acute coronary syndrome. A sufficiently significant increase in CRP levels was also observed in patients with angina pectoris, and there was no significant difference between the CRP levels in patients with II and III functional angina classes.

The CRP values in patients with no clinical manifestations of myocardial ischemia were the lowest. It can be thought that these patients have a more stable course of the disease without significantly exacerbation of the atherosclerotic process. The correlation between the degree of CRP increase and ESR, particularly in patients with ACS ($r = 0.48$, $p < 0.01$) [4,6].

Attention is drawn to the fact that in the group of ACS patients the ESR increase was observed when compared with the data in the control group. In patients with stable angina pectoris, mean values of ESR were close to the upper limit of normal values, but higher than those in the control group.

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Реферати

**ЗНАЧЕННЯ ДИСФУНКЦІЇ ЕНДОТЕЛІЯ
ТА РІВНЯ МАРКЕРІВ ЗАПАЛЕННЯ
ДЛЯ ПРОГНОЗУВАННЯ ОЦІНКИ РИЗИКУ
НЕСПРИЯТЛИВОГО ПЕРЕБІГУ ІШЕМІЧНОЇ
ХВОРОБИ СЕРЦЯ**

Вознюк Л.А., Дорошкевич І.О., Клекот О.О.,
Кириченко О.В.

Проведені дослідження перебігу ІХС свідчать про те, що поряд з проатерогенними змінами ліпідного складу крові хворих на ІХС спостерігалось збільшення концентрації С-реактивного протеїну (СРП) та прозапальних цитокинів (ФНП-α) в порівнянні з нормативами контрольної групи. Охарактеризовано закономірності наявності кореляційних зв'язків між ступенем збільшення рівня СРБ і ШОЕ, особливо у хворих з ГКС ($r = 0,48, p < 0,01$). Виявлено ступінь збільшення фактору Виллебранда в групі пацієнтів з фатальним і нефатальним інфарктом міокарда, який був значно більшим, ніж в групі пацієнтів із ІХС з неускладненим перебігом. Збільшення рівня СРП не поступалося по частоті ДЛП і спостерігалось у більшості хворих ІХС (65,3%). Визначились кореляційні зв'язки між вираженістю ремоделювання екстракраніальних артерій і вмістом ФНП-α ($r = 0,30, < 0,05$) і менш виражений зв'язок з концентрацією ІЛ-6 ($r = 0,25, p < 0,05$).

Ключові слова: ішемічна хвороба серця, прозапальні цитокини, СРП, фактор Виллебранда, холестерин.

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**ЗНАЧЕНИЕ ДИСФУНКЦИИ ЭНДОТЕЛИЯ
И УРОВНЯ МАРКЕРОВ ВОСПАЛЕНИЯ
ДЛЯ ПРОГНОЗИРОВАНИЯ ОЦЕНКИ РИСКА
НЕБЛАГОПРИЯТНОГО ТЕЧЕНИЯ
ИШЕМИЧЕСКОЙ БОЛЕЗНИ СЕРДЦА**

Вознюк Л.А., Дорошкевич И.А., Клекот А.А.,
Кириченко О.В.

Проведенное исследование течения ИБС свидетельствует о том, что вместе с проатерогенными изменениями липидного состава крови больных ИБС наблюдалось увеличение концентрации С-реактивного протеина (СРП) и провоспалительных цитокинов (ФНП-α) в сравнении с нормативами контрольной группы. Охарактеризованы закономерности наличия корреляционных связей между степенью увеличения уровня СРП и СОЭ, особенно у больных с ОКС ($r = 0,48, p < 0,01$). Выведена степень увеличения фактора Виллебранда в группе пациентов с фатальным и нефатальным инфарктом миокарда, который был значительно больше, чем в группе пациентов с ИБС с неосложненным течением. Увеличение уровня СРП не уступало по частоте ДЛП и наблюдалось у большинства больных ИБС (65,3%). Определялись корреляционные связи между выраженностью ремоделювания экстракраниальных артерий и содержанием ФНП-α ($r = 0,30, < 0,05$) и менее выраженная связь с концентрацией ИЛ-6 ($r = 0,25, p < 0,05$).

Ключевые слова: ишемическая болезнь сердца, провоспалительные цитокины, СРП, фактор Виллебранда, холестерин.

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А.О. Волосовець, І.С. Зозуля

Національна медична академія післядипломної освіти імені П. І. Шупика, Київ

**ДОСЛІДЖЕННЯ ВПЛИВУ ВНУТРІШНІХ ФАКТОРІВ РИЗИКУ
НА ЧАС ВИНИКНЕННЯ ІШЕМІЧНОГО ІНСУЛЬТУ**

E-mail: healermaster@gmail.com

Метою дослідження було визначити вплив внутрішніх модифікованих факторів ризику на час виникнення ішемічного інсульту. Проведено клініко-неврологічне та нейровізуалізаційне обстеження 300 хворих, які перенесли гострий ішемічний інсульт (чоловіків – 196, жінок - 104) віком від 42 до 84 років (середній вік – $65,2 \pm 8,7$ року). Фактор артеріальної гіпертензії спостерігався серед всіх груп пацієнтів. Фактор миготливої аритмії мав чітку асоціацію з денним та вечірнім періодом (1 і 2 групи), що абсолютно збігається з особливостями виникнення кардіоеMBOLІЧНОГО підтипу ішемічного інсульту. Фактор атеросклерозу складав велике значення для всіх груп. В той же час фактор цукрового діабету демонстрував значне підвищення саме для пацієнтів 3-ї групи (82,9 %), що підтверджує зв'язок глікемічних метаболічних порушень з вегетативною регуляцією судин в нічний період. Предиктор надмірної ваги продемонстрував вагому присутність у всіх пацієнтів, але чітку тенденцію превалювання саме в 2-й та 3-й групах. Рівень холестерину, який виявляли серед пацієнтів з інсультом, мав дещо іншу тенденцію – в 1-й групі спостерігався незначний рівень гіперхолестеринемії ($5,4 \pm 0,5$ ммоль/л); для 2-ї групи більш властивим був високий рівень гіперхолестеринемії ($7,3 \pm 0,7$ ммоль/л); в 3-й групі, не зважаючи на відносно превалювання надмірної ваги, мав місце помірний рівень гіперхолестеринемії ($5,8 \pm 0,5$ ммоль/л). Внутрішні фактори ризику відіграють важливу роль у виникненні церебральної ішемії, але демонструють виражену неспецифічність у виявленні впливу на час виникнення патології.

Ключові слова: інсульт, час виникнення, внутрішні фактори ризику.

Робота є фрагментом «Клініко-патогенетична характеристика та фактори ризику гострого ішемічного інсульту залежно від часу виникнення: особливості діагностики, лікування та прогнозу», номер державної реєстрації 0114U006316.

На сьогоднішній день проблема гострого ішемічного інсульту залишається однією із найбільш важливих в сучасній медичній науці. Це обумовлено тим, що дана патологія є одною із найбільш поширених причин смертності та порушення працездатності людей як в Україні, так і в усьому світі. Оскільки лікування ішемічного інсульту залишається дороговартісним і часто недостатньо ефективним, світові організації по боротьбі з інсультом роблять наголос на профілактиці даного захворювання [2].

В основі профілактики ішемічного інсульту важливу роль відіграє чітке визначення та уніфікація факторів ризику церебральної ішемії [1]. Дослідники всього світу рекомендують в