THE DEPENDENCE OF IMMUNE-INFLAMMATORY REACTIONS ON THE RISK LEVEL OF A HIGH SENSITIVITY C-REACTIVE PROTEINS IN PATIENTS WITH UNSTABLE ANGINA

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Abstract: *in this article has shown the range of changes of pro-inflammatory cytokines (IL-6, TNF-α, IL-18), depending on the risk level of hsCRP in patients with unstable angina (according to the recommendations of the American Heart Association at hsCRP less than 1 mg / l the risk of vascular complications is low, at hsCRP from 1 to 3 mg / l - average when hsCRP more than 3 mg / l the risk is high). The study of chronic inflammatory process correlates with a higher risk level of hsCRP. Production of proinflammatory cytokines increased depending on the risk level of hsCRP, with the largest values observed in the high-risk group hsCRP and had a truthful manner (p <0,05). Despite the multifactorial changes we detected their pointedness in the pathogenesis of chronic inflammation in unstable angina, which proves that the systemic inflammatory process.*
Keywords: *cytokines, unstable angina, C-reactive protein, inflammatory.*

ЗАВИСИМОСТЬ ИММУНОВОСПАЛИТЕЛЬНЫХ РЕАКЦИЙ ОТ УРОВНЯ РИСКА ВЫСОКОЧУВСТВИТЕЛЬНОГО С-РЕАКТИВНОГО БЕЛКА У БОЛЬНЫХ НЕСТАБИЛЬНОЙ СТЕНОКАРДИЕЙ

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Аннотация: *в данной статье показан диапазон изменений провоспалительных цитокинов (ИЛ-6, ФНО-α, ИЛ-18) в зависимости от уровня риска вчСРБ у больных нестабильной стенокардией (согласно рекомендациям Американской ассоциации кардиологов, при hsСРБ менее 1 мг/л - риск сосудистых осложнений низкий, при hsСРБ от 1 до 3 мг/л – средний, при hsСРБ более 3 мг/л – высокий). По результатам исследования хронический воспалительный процесс коррелирует с повышением уровня риска вчСРБ. Продукция провоспалительных цитокинов повышалась в зависимости от уровня риска вчСРБ, причем наибольшие их значения отмечались в группе высокого риска вчСРБ, и имела достоверный характер (p<0,05). Несмотря на многофакторность изменений, нами выявлена их однонаправленность в патогенезе хронического воспалительного процесса при нестабильной стенокардии, что доказывает системность процесса воспаления.*
Ключевые слова: *цитокины, нестабильная стенокардия, С-реактивный белок, воспаление.*

Cardiovascular diseases firmly hold first place among causes of death in the developed world for 50 years [5]. Atherosclerosis of the coronary arteries is the pathological basis of coronary heart disease [2]. Moreover, the destabilization of atherosclerotic plaques is determined by the high activity of chronic inflammation in the pathogenesis of that is high the role of high-sensitivity C-reactive protein (hsCRP) and other mediators of inflammation [9]. The Inflammatory theory of atherogenesis confirmed by increasing of concentration of inflammatory CRP-response protein markers, neopterin, interleukin-6 (IL-6), fibrinogen, and others in the blood of patients with CHD. [9] Fibrinogen is the most sensitive of hemostatic factors, which in addition to participating in the aggregation process and formation of fibrin, is also involved in inflammatory processes [11]. Several prospective studies have demonstrated the value of IL-6 as a predictor of clinical manifestations of atherosclerotic vascular lesions in healthy individuals without any signs of cardiovascular disease [12]. CRP - a multifunctional protein of the acute phase, which plays an important role in inflammation, defense against foreign agents and autoimmune processes. In the serum of patients with coronary artery disease CRP characterizes the intensity of inflammation in atherosclerotic plaque and does not reflect the severity of coronary artery stenosis [10].

Nowadays it is a topical issue to examine and identify the prognostic significance of inflammatory mediators in the course of the disease, especially in unstable angina, which is accompanied by the destabilization of atherosclerotic plaques.

The aim of the research

To investigate the range of changes of proinflammatory cytokines, depending on the risk level of hsCRP in patients with unstable angina.

Materials and methods

The study involved 36 patients with unstable (progressive), angina (USC) II-III FC according to Braunwald E. et al. (1989) [1], aged from 34 to 74 years (mean age was 56.88 ± 1.70 years). 66.7% of them were men (24 people) and women - 33.3% (12 people). The Prescription of CHD in patients at the time of inclusion in the study averaged 6,91 ± 0,61 years. The CHD on the background of arterial hypertension (AH) was observed in 83% of patients, in 38.8% of cases it was combined with diabetes mellitus type 2. The indications of myocardial infarction (MI) were in 47% of patients.

When interpreting the results of the hsCRP determination we followed the recommendations of the American Heart Association, according to which the risk of vascular complications (acute myocardial infarction, stroke) at the hsCRP less than 1 mg / l is low, when the hsCRP from 1 to 3 mg / l – the risk is average, when the hsCRP more than 3 mg / l – the risk is high. If the level of hsCRP is more than 10 mg / l, the measurement is repeated and carried out examination to identify of infectious and inflammatory diseases in patients [7, 9, 10]. Depending on the risk level of hsCRP three groups of patients were formed: A – a low-risk group, including 6 patients, B – an average risk group - 10 patients and group C – a high risk one, consisting of 18 patients with unstable angina. In two patients the CRP level was greater than 10 mg / l, so that they were excluded from the study.

The patients with complex disorders of rhythm and conduction of the heart; chronic heart failure FC III-IV (NYHA); acute myocardial infarction; resting heart rate <60 beats per minute before treatment; renal and hepatic failure; thyroid dysfunction, diabetes mellitus type 2 in the stage of severe decompensation requiring insulin treatment; oncological and immunological diseases were excluded from the study.

The Immunological studies were performed in the laboratory of immunopathology and immunopharmacology of Institute of Immunology, Academy of Sciences of Republic of Uzbekistan. The cytokines IL-6 and TNF-α were determined in blood serum with ELISA method using kits produced by "Vector-Best" ltd. (Novosibirsk, Russia) with the usage of enzyme immunoassay analyzer «Stat Fax- 2100" (USA). The high-sensitivity C-reactive protein (hs-CRP) was determined with the help of the biochemical autoanalyzer «Randox» (United Kingdom).

Statistical processing of the results was carried out with the use of software applications for statistical processing of data Statistica® version 6.0. The significance of differences between treatment groups was evaluated by Student's t test. The correlation analysis was held with the calculation of the Spearman's coefficient. The differences of compared values recognized statistically significant at p<0,05.

Results and discussion

We studied a clinical (hsCRP, fibrinogen) and immunological (IL-6, IL-18 and TNF-a) significances of inflammation mediators in patients with unstable angina. According to our study, the content of hsCRP in a total group of patients with unstable angina ranged from 0.5 mg / l to 11.85 mg / l (median 5 mg / l) and averaged 6.2 ± 0.94 mg / l. During the comparison of hsCRP in dependence from its risk levels obtained significant results (p <0,001), which are presented in the table and coincide with other studies [10, 12]. The Increasing of hsCRP risk level and intensity of the inflammatory process are combined with an increased risk of coronary complicatios. According to a meta-analysis [6] hsCRP is a predictor of poor outcome in patients with acute coronary syndrome.

Table 1. The indicators of inflammatory mediators relative to hsCRP risk levels in patients with unstable angina (M ± SD)

Indicators	**A**	**B**	**C**	**A и B**	**A и C**	**B и C**
hsCRP, mg / l	0,93±0,22	2,62±0,23	7,51±0,49	p<0,001	p<0,001	p<0,001
Fibrinogen g / l	2,93±0,31	2,64±0,1	3,26±0,17	-	-	p<0,01
IL-6 pg / ml	8,93±0,83	17,89±6,45	37,88±11,31	-	p<0,05	-
TNF-α, pg / ml	7,07±0,72	16,46±8,09	16,36±4,49	-	p<0,05	-

IL-18 pg / ml	139,15±20,02	148,86±16,31	167,38±15,87	-	-	-

According to the results of our study the indicator of fibrinogen when comparing of examined groups of the low and high-risk tended to increase, and when comparing the groups B and C also had authentic character of the increase (p <0,01). Also, at the correlation analysis have been identified direct relationship between hsCRP and fibrinogen at high risk (r = 0,37; p <0,05).

The range of values of IL-6 in the total group of patients ranged from 6.8 pg / ml to 142.7 pg / ml and averaged 28.71 ± 6.96 pg / ml. The content of IL-6 and hsCRP according to distribution of risk level tended to increase in the group from low-risk to high risk that exceed 4 times and had a valid character (p <0,05).

The analysis of the proinflammatory cytokine TNF-α has allowed to note its gradual increase depending on the increase in the risk levels of hsCRP that exceed the same indicator in group C in 2 times than in group A (p <0,05), it should be noted that, in the group C its values were similar to the group B. The results of correlation analysis showed a strong direct relationship between hsCRP and TNF-α in the low-risk group (r = 0,86; p <0,0001), which testifies to their proximity and in line with the research of many authors [2, 5, 10].

The content of IL-18 in patients with unstable angina ranged from 67 pg / ml to 309.3 pg / ml, the median was 102.6 pg / ml. wih the Higher of group of the hsCRP risk level was noted the increasing of the cytokine IL-18, but had no significant nature due to the large spread of the deviation interval. The highest level of IL-18 in limits of 113,4-309,3 pg / ml accounted for the high-risk of hsCRP group. Consequently, in the unstable angina group with an average risk level of hs CRP was observed the presence of a strong direct relationship between hsCRP and IL-18 (r = 0,54; p <0,05), which indicates the indissoluble complicity markers of inflammation in the pathogenesis of angina.

Also, at the correlation analysis revealed a strong direct relationship between TNF-α and IL-6 in the medium-risk group (r = 0,37; p <0,0001), and in the high-risk group a strong relationship between IL-6 and IL-18 (r = 0,34; p <0,05), TNF-α a and IL-18 (r = 0,46; p <0,01), IL-6 and TNF-α (r = 0,76; p < 0.0001). Despite the multifactorial changes we detected their pointedness in the pathogenesis of chronic inflammation in unstable angina, which proves the systemic inflammatory process. Our results are consistent with the data of authors that CRP, IL-6, TNF-α, IL-18 can exert a systemic effect and induce inflammatory activity in vascular regions located at a distance from the unstable plaque, which leads to increased risk of atherothrombotic complications not only in the coronary vein, and in the carotid artery and other basins. At present, the activity of subclinical inflammation is assessed as a key pathophysiological response, inducing the development and progression of major diseases of the cardiovascular system [3, 4, 8].

CONCLUSIONS

1. Patients with unstable angina is clinically characterized by different levels of risk depending on the hsCRP values. And inflammation is correlated with an increase in the hsCRP risk level.
2. The correlation analysis revealed a direct relationship of hsCRP and fibrinogen at high risk, indicating a one-way or the participation of both factors in the development of the inflammatory process.
3. The content of IL-6, depending on the risk values tended to incresing and its value was the highest in the high-risk group. This indicates the activation of IL-6, which is the cytokine intermediate steps by which we can predict the course and outcome of desease.
4. TNF-α also tended to increase depending on the risk level of hsCRP. It should be noted that TNF-α is a cytokine concentrations elevated, damaging effect in this connection it may be a prognostic factor, as well as IL-6, destabilization of atherosclerotic plaque.
5. The production of IL-18 was increased depending on increase hsCRP. The maximum value of IL-18 was observed in the group of high-risk patients with hsCRP, that indicating the pleiotropic and synergies with other proinflammatory cytokines.
6. A direct correlation between the studied cytokines, which in varying degrees of risk are participating in the pathogenesis of inflammation in unstable angina and may be bright diagnostic and prognostic markers of disease severity and its complications.

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