Immunological aspects of acute coronary syndrome

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Abstract

Coronary Trigger Syndrome (Acute) - violation of the integrity of the atherosclerotic plaque with subsequent thrombus formation. An important role in this process is played by immuno-inflammatory reactions that promote the activation of macrophages and the destruction of the atheroma capsule [1,2,6]. It is believed that inflammation contributes to the deposition of oxidized low density lipoproteins (LDL) in the vascular wall and plays a significant role in the destabilization of atherosclerotic plaque and the development of atherothrombotic complications [3,7]. Among the wide range of immunological markers used to assess the activity of the inflammatory process, the most studied is C-reactive protein (CRP), which belongs to the family of proteins of the acute phase of inflammation [4, 5]. It is also known that proinflammatory cytokines support local inflammation in atherosclerotic plaque by activating endothelial cells and inducing the expression of adhesion molecules and prothrombotic activity of the endothelium [23]. Meanwhile, there are only a few works on the assessment of the relationship of immuno-inflammatory reactions with hemodynamic parameters in patients with different clinical course of coronary artery disease [7,8]. The role of immune-inflammatory reactions in the progression of coronary artery disease and the formation of ACS remains unclear. The aim of the study was to determine the role of immune-inflammatory reactions in the development of unstable angina pectoris (NS) and acute myocardial infarction (AMI) in patients with coronary artery disease.

Keywords: acute coronary syndrome, unstable angina pectoris, myocardial infarction, immune-inflammatory reactions, cytokines.

Material and methods The study included 176 men (mean age 52.4 ± 3.8 years) with various forms of coronary artery disease. National Rational Pharmacotherapy in Cardiology 2007, № 5 15 93 patients with ACS were followed, 60 of them with NS and 33 with AMI. The comparison group consisted of 83 patients with stable angina pectoris II-IV functional class. The diagnosis of ischemic heart disease was established on the basis of clinical and instrumental data. Attention was drawn to the typicality of anginal syndrome, the specificity of ECG changes at rest, during daily monitoring and during exercise on a bicycle ergometer (VEM); recorded the data of echocardiography (ECHOKG). Patients with grade II arterial hypertension, congestive heart failure, complex heart rhythm disturbances, decompensated diabetes mellitus, severe liver, kidney, lung, and blood diseases were not included in the study. Patients with active inflammatory processes, oncological and immunopathological diseases were excluded from the study. Patients with HC according to the classification [9] were divided into 2 groups: 32 people with HC I class and 28 with HC II III class.The criteria for inclusion of NS patients in the study were clinical manifestations of NS upon admission to the intensive care unit in the

form of rest angina (duration more than 10, but less than 30 minutes); exertional angina (with a load that has not previously caused angina pectoris); increased frequency of seizures in combination with transient changes in the ECG in the form of depression of the ST segment (more than 0.1 mV) and / or inversion of the T wave in two or more leads without the appearance of new Q waves on the ECG. AMI was diagnosed in 33 patients based on WHO criteria in the presence of two of the following three signs: anginal pain> 30 min and / or ST segment elevation> 0.2 mV in two chest leads, or ST segment elevation> 0.1 mV in standard leads, or the development of acute blockade of the left bundle branch; the appearance of pathological Q waves on the ECG and / or an increase in the level (MV - AK) of creatine phosphokinase (CPK) (2 times from the norm), troponins T and J. Basic therapy for stable angina pectoris included antiplatelet agents, β-blockers.

Basic therapy for stable angina pectoris included antiplatelet agents, β-blockers, calcium antagonists, nitrates, statins, angiotensin-converting enzyme inhibitors; in NS, additional anticoagulants were prescribed, in AMI, thrombolytic therapy was carried out in 26.6% of cases. The control group included 25 healthy male volunteers (mean age 49.9 ± 6.2 years) who underwent VEM (to exclude latent coronary insufficiency), echocardiography (to exclude myocardial damage), duplex scanning of the carotid arteries (to exclude atherosclerosis non-coronary localization), study of blood lipids. Patients with stable angina pectoris underwent VEM to verify IHD and determine exercise tolerance; to record episodes of myocardial ischemia, daily ECG monitoring was performed. The study of intracardiac hemodynamics was performed using echocardiography with the assessment of linear and volumetric parameters, myocardial mass index and parameters of left ventricular remodeling according to the method recommended by the American Society of Echocardiographers. To characterize immunoinflammatory reactions, the level of CRP, proinflammatory (IL1β, IL-6, TNF-α) and anti-inflammatory (IL-4, IL10) cytokines in blood serum was studied by the method of enzyme immunoassay using test systems of OOO Proteinovy contour (St. Petersburg). Statistical data processing was carried out using Microsoft Excel 7.0 and Statistica for Windows 6.0 programs. Data are presented as M ± m. Correlation analysis of quantitative values was carried out with the calculation of the Pearson correlation coefficient.Differences were considered significant at the p level

Results

The CRP level in patients with NS of both classes I and II-III was significantly increased compared with healthy men and patients with stable angina pectoris (Table 1.).

CRP and proinflammatory cytokine levels in patients with acute coronary syndrome

Indicator (M±m)	Control group	Stable stenocardia	Unstable stenocardia		Miocard infarct
	№25	№83	I-class (№ 32)	II and III group (№28)	№33
CRP pg/l	1,9±0,2	3,8±0,6	5,9±0,4	8,84±0,62	16,9±4,1

IL 1β pg/l	34,3±2,1	47,4±2,7	54,0±2,5	80,3±0,9	115,3±10,2
IL-6 pg/l	40,5±3	56,4±3,9	70,8±5,3	110,01±8,2	157,3±12,9
TNF-α pg/l	20,9±1,2	32,9±4,1	53,4±4,9	85,7±7,1	112,2±8,7
IL-4 pg/l	124,5±5,3	129,1±8,5	94,8±8,6	65,1±3,2	53,1±7,2
IL-10 pg/l	16,1±0,4	16,9±2,0	12,01±2,04	8,0±0,34	7,5±0,42

The reliability of the result p> 0.05

When comparing CRP concentrations in patients with different course of NS, the highest rates were observed in NS II-III classes. The maximum CRP values were recorded in AMI, their values significantly exceeded not only the parameters in the control groups (7 times) and stable angina pectoris (3.8 times), but also significantly differed from the data in patients with both I and II NS. -III classes. IL-6 indices in patients with NS classes I and II-III were 1.7 and 2.5 times higher than in the control group. An increase in the level of IL-6 was recorded in NS classes II-III and exceeded the same indicator in patients with stable and progressive angina pectoris. An extremely high level of IL-6 was found in AMI: its values were 3.6 and 2.6 times higher than the parameters in healthy individuals and patients with stable angina pectoris, and also significantly differed from those of NS classes I and II-III. Correlation analysis carried out in patients with NS and AMI revealed the expected close relationships between the content of IL-6 and the level of CRP (r = 0.56;) in healthy individuals and patients with stable angina pectoris, and also significantly differed from the values in patients with NS I and II-III classes. Correlation analysis revealed a relationship between the level of IL-1β and CRP (r = 0.38;) of cytokines in patients with ACS, accompanied by overexpression of IL-6, IL-1β and TNF-α, was associated with the severity of IHD and was the most significant with HC II-III classes and AMI.

Discussion

In recent years, immunoinflammatory reactions have been of great importance in destabilizing the course of ischemic heart disease, while activation of the cytokine system with the induction of intercellular adhesion molecules and chemokines, proteins of the acute phase of inflammation, plays a significant role [9,22]. A number of studies have established an increase in the concentration of CRP in patients with NS compared with patients with stable angina pectoris [10]. This fact was confirmed in our work. In works [11, 12], it was shown that overproduction of CRP in NS is associated with the risk of rapid progression of coronary atherosclerosis (according to angiography data). At the same time, there is evidence that an increase in CRP synthesis is not associated with the activation of inflammation, but rather reflects a “hyperimmune” response to a minimal proinflammatory stimulus [10,13]. Earlier it was shown that cardiac muscle necrosis is a powerful stimulus for the synthesis of CRP, the level of which correlates with the dynamics of MV CPK and the prevalence of AMI [5]. In our study, the highest CRP rates were also recorded in AMI. Literature data and the results of our own research indicate an undoubted relationship between an increase in the level of CRP and the progression of IHD, especially since CRP is found in atherosclerotic plaque in the aorta [4], the intima of the coronary arteries and

in the heart muscle in AMI [4, 14] . Known pro-inflammatory effect of CRP associated with the induction of the expression of adhesion molecules: ICAM-1, VCAM-1 and E-selectin on the membrane of endothelial cells (in vitro) [15]. It is believed that CRP can participate in the formation of "foamy" cells by enhancing the uptake of LDL by macrophages [4].The pathogenetic effect of CRP is realized in combination with other mediators of inflammation, especially with IL-6, which is the main inducer of CRP synthesis. It is known that IL-6 plays a fundamental role in the development of inflammation, its overproduction is of great importance in a number of inflammatory processes, including atherosclerosis [16]. IL-6 production is controlled by IL-1, IFN-γ and TNF-α. We have established that IL-6 is overexpressed in ACS, its maximum values have been determined in HC II-III classes and AMI. The results obtained are consistent with the literature data, which show that the complicated course of NS is associated with a significant increase in the level of IL-6, CRP and troponin T, and the content of IL-6 increases faster than the indicators of troponin T and CRP [4,17]. There is information in the literature that cells that form atheroma are able to induce the production of TNF-α and IL-1β, while endotheliocytes, smooth muscle cells, macrophages secrete IL-1β, and TNF-α is produced by smooth muscle cells, macrophages and T-lymphocytes [3 ,7.18]. We have shown that the course of ACS with the development of NS and AMI was accompanied by overproduction of IL-1β, which developed against the background of increased synthesis of CRP and IL-6. IL-1β and TNF-α are proinflammatory cytokines with partially overlapping additive activity, which at low (physiological) concentrations play an important role in the regulation of the immune response and tissue homeostasis, and at high concentrations have numerous systemic and local effects. Many of these effects can play a significant role in the development of myocardial pathology [19].In our work, TNFα overexpression was established in patients with ACS, its levels of IL-1β, IL-6 and CRP were revealed. It should be assumed that the simultaneous determination of TNF-α, IL-6, IL-1β and CRP will provide a more complete picture of the severity of the course and prognosis in patients with ACS. The data obtained, indicating an increased production of proinflammatory cytokines associated with the severity of ACS, emphasize the important role of overexpression of TNF-α, IL-1β, IL-6, and CRP in the formation of the clinical course and progression of IHD.

The results of the study are consistent with experimental data indicating an increased expression of inflammatory mediators not only in the blood plasma, but also in the myocardium when its function is impaired [4, 20]. The experiment established the ability of pro-inflammatory cytokines, in particular TNF-α, to induce myocardial remodeling with a progressive decrease in its contractility [21]. IL-4 and IL-10 are anti-inflammatory cytokines that suppress the cellular immune response [19,22]. IL-10 acts as a factor suppressing the activity of macrophages, inhibits the secretion of proinflammatory cytokines (IL-1, IL-6, IL-8, IL-12, TNFα), reduces the expression of adhesion molecules (ICAM-1) and stimulates fibrinolysis [23].

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heart disease. At the same time, an imbalance in the system of the regulatory cytokine network is clearly seen in NS and AMI. When the levels of IL-4 and IL-10 fall, non-specific factors of the immunoregulatory system, belonging to the family of cytokines, can lead to the activation of potentially autoreactive T-lymphocytes, inducing excessive production of pro-inflammatory cytokines that perform destructive functions in relation to the myocardium as a target organ and source autoantigenic determination [5]. Consequently, in the mechanisms of atherosclerotic plaque activation, which results in the destabilization of the course of IHD, factors regulating the production of pro- and anti-inflammatory cytokines are of great importance: an imbalance in the cytokine network leads to the activation of immune-inflammatory reactions.

Conclusion

The destabilization of the course of ischemic heart disease is characterized by inhibition of the activity of anti-inflammatory cytokines against the background of overexpression of IL-1β, IL-6 and TNF-α, increased synthesis of CRP. The severity of immune-inflammatory reactions is associated with the severity of ACS. In NS, a significant increase in the level of IL-1β, IL-6 and TNF-α was noted against the background of a decrease in the content of anti-inflammatory cytokines. Maximum levels of proinflammatory cytokines and low concentrations of IL-4 and IL-10 were found in AMI. Thus, an important role in the progression of ischemic heart disease and the formation of ACS belongs to the activation of immune-inflammatory reactions.

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