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COMPLEMENT-MEDIATED AND CYTOKINE-DRIVEN INFLAMMATORY MECHANISMS IN SUBCLINICAL MYOCARDIAL INJURY IN PATIENTS WITH ARTERIAL HYPERTENSION

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Annotation: The article presents the results of a study of pro-inflammatory and complement-dependent mechanisms in patients with arterial hypertension (AH) and in those with combined pathology of AH and ischemic heart disease (IHD). A total of 78 patients were examined and divided into two groups: patients with isolated AH (Group I) and patients with AH complicated by IHD (Group II). The control group consisted of conditionally healthy individuals. The study included the analysis of pro-inflammatory cytokines (IL-6), C-reactive protein (CRP), and complement component C3a depending on the degree of subclinical myocardial injury assessed by high-sensitivity cardiac troponin (hs-cTn). It was found that an increase in hs-cTn levels is accompanied by a stepwise activation of inflammatory processes: IL-6 increased up to 4.9-fold, CRP up to 6.5-fold, and C3a up to 36.7-fold ($p<0.001$), reflecting pronounced activation of innate immunity and complement-dependent mechanisms. The highest levels of IL-6 and CRP were observed in patients with manifest IHD, whereas the peak activity of C3a was detected at the stage of pronounced subclinical myocardial injury.

Keywords: arterial hypertension, ischemic heart disease, subclinical myocardial injury, high-sensitivity troponin, immunoinflammation, cytokines, complement.

КОМПЛЕМЕНТ-ОПОСРЕДОВАННЫЕ И ЦИТОКИНОВЫЕ МЕХАНИЗМЫ ВОСПАЛЕНИЯ ПРИ СУБКЛИНИЧЕСКОМ ПОВРЕЖДЕНИИ МИОКАРДА У ПАЦИЕНТОВ С АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИЕЙ

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Аннотация: В статье представлены результаты исследования провоспалительных и комплемент-зависимых механизмов у пациентов с артериальной гипертензией (АГ) и при её сочетании с ишемической болезнью сердца (ИБС). Обследовано 78 пациентов, распределённых на две группы: пациенты с изолированной АГ (I группа) и пациенты с АГ, осложнённой ИБС (II группа). Контрольную группу составили условно здоровые лица. Проведён анализ уровней провоспалительных цитокинов (ИЛ-6), С-реактивного белка (СРБ) и компонента системы комплемента С3а в зависимости от степени субклинического повреждения миокарда, определяемого по уровню высокочувствительного сердечного тропонина (hs-cTn). Установлено, что повышение hs-cTn сопровождается последовательной активацией воспалительных процессов: уровень ИЛ-6 увеличивался до 4,9 раза, СРБ — до 6,5 раза, а С3а — до 36,7 раза ($p<0,001$), что отражает выраженную активацию

врождённого иммунитета и комплемент-зависимых механизмов. Максимальные значения ИЛ-6 и СРБ зарегистрированы при манифестной ИБС, тогда как пик активности С3а отмечался на стадии выраженного субклинического повреждения миокарда.

Ключевые слова: артериальная гипертензия, ишемическая болезнь сердца, субклиническое повреждение миокарда, высокочувствительный тропонин, иммуновоспаление, цитокины, комплемент.

АРТЕРИАЛ ГИПЕРТЕНЗИЯ БИЛАН ОҒРИГАН БЕМОРЛАРДА СУБКЛИНИК МИОКАРД ШИКАСТЛАНИШИДА КОМПЛЕМЕНТ ОРҚАЛИ ВОСИТАЧИЛАНГАН ВА ЦИТОКИНЛАРГА БОҒЛИҚ ЯЛЛИҒЛАНИШ МЕХАНИЗМЛАРИ

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Аннотация: Мақолада артериал гипертензия (АГ) билан касалланган беморлар ҳамда АГ ва ишемик юрак касаллиги (ИЮК) бирга кечиши ҳолатларида прояллиғланиш ва комплементга боғлиқ механизмлар тадқиқ қилинган. Жами 78 нафар бемор текширилиб, икки гуруҳга ажратилди: изолятсияланган АГ билан беморлар (I гуруҳ) ва АГ фонида ИЮК ривожланган беморлар (II гуруҳ). Назорат гуруҳини шартли соғлом шахслар ташкил этди. Тадқиқот доирасида субклиник миокард шикастланиш даражаси (юқори сезгир юрак тропонини — hs-cTn)га боғлиқ

ҳолда прояллиғланиш цитокинлари (ИЛ-6), С-реактив оқсил (СРБ) ва комплемент тизимининг С3а компоненти даражалари таҳлил қилинди. Аниқланишича, hs-cTn даражасининг ошиши яллиғланиш жараёнларининг босқичма-босқич фаоллашуви билан кузатилади: ИЛ-6 4,9 бараваргача, СРБ 6,5 бараваргача ва С3а 36,7 бараваргача ошди (p<0,001), бу эса туғма иммунитет ва комплементга боғлиқ механизмларнинг сезиларли фаоллашганини кўрсатади. ИЛ-6 ва СРБнинг энг юқори қийматлари манифест ИЮКда қайд этилган бўлса, С3а фаоллигининг энг юқори кўрсаткичлари субклиник миокард шикастланишининг яққол босқичида аниқланди.

Калит сўзлар: артериал гипертензия, ишемик юрак касаллиги, субклиник миокард шикастланиши, юқори сезгир тропонин, иммуноялиғланиш, цитокинлар, комплемент.

Relevance: Coronary heart disease (CHD) remains the leading cause of death worldwide, with hypertension considered a key risk factor. In recent years, increasing attention has been paid to the role of immune-inflammatory mechanisms in the pathogenesis of cardiovascular diseases.

Modern understanding of the development of coronary heart disease extends beyond hemodynamic disturbances to include complex interactions between innate and adaptive immunity, endothelial dysfunction, chronic inflammation, and myocardial remodeling processes. Biomarkers reflecting these processes, such as VEGF-A, TGFβ, interferons, proinflammatory cytokines, and complement components, are becoming increasingly important.

Of particular interest is the study of their relationship with subclinical myocardial damage, assessed by the level of high-sensitivity cardiac troponin (hs-cTn), as an early stage in the development of coronary heart disease.

Despite the accumulated data, the role of immune-inflammatory factors as predictors of the transition from subclinical myocardial damage to clinically manifest coronary heart

disease in patients with arterial hypertension remains insufficiently studied.

Purpose of the study. To assess the role of proinflammatory markers (IL-6, C-reactive protein) and the complement system component C3a in the progression of subclinical myocardial damage and the formation of coronary heart disease in patients with arterial hypertension.

Materials and methods of research. To conduct the study, a comprehensive clinical and laboratory examination was conducted on 78 patients undergoing inpatient and outpatient treatment at the Bukhara Regional Cardiology Dispensary. All study participants were carefully selected based on inclusion and exclusion criteria to ensure maximum data reliability and exclude the influence of comorbidities. Patients were divided into two main clinical groups based on their diagnosis:

Group I included 37 patients suffering from hypertension.

Group II consisted of 41 patients with a diagnosis of coronary heart disease that developed against the background of hypertension.

The control group consisted of 20 conditionally healthy individuals.

Research results: Complement component C3a was included in the analysis to assess innate immune activation associated with vascular wall inflammation and atherosclerotic plaque destabilization. Several studies have shown that complement activation, including C3a, contributes to an enhanced inflammatory response in vascular tissues, making it a significant marker in the pathogenesis of coronary heart disease, particularly in the setting of chronic inflammation and endothelial damage.

In the cohort of group I (patients with hypertension without clinical and instrumental signs of coronary heart disease), with a level of high-sensitivity cardiac troponin (hs-cTn) ≤ 2.0 ng/l (n=18), the concentration of IL-6 was 2.5±0.8 pg/ml, CRP - 1.2±0.4 mg/l, C3a - 4.82±1.27 pg/ml, taken as reference values reflecting the basal activity of systemic inflammation and complement under conditions of stable hypertension without subclinical myocardial stress.

Table 1.

Comparative analysis of the levels of proinflammatory markers in the studied patients

Indicator	Group I (n=25)			Group II (n=13)
	hs-cTn ≤ 2.0 ng/L (n=18)	hs-cTn 2.1–4.0 ng/l (n=3)	hs-cTn 4.1–4.9 ng/l (n=4)	
IL-6	2.5±0.8	4.2±1.1**	6.8±1.5***	12.3±3.2***
SRB	1.2±0.4	2.8±0.7**	4.5±1.0***	7.8±2.1***
C3a	4.82±1.27	49.8±3.98***	177.00±8.93***	119.86±26.8***

Note: confidence level*- r<0.05;**- r<0.01;***- r<0.001;

In the subgroup with hs-cTn 2.1–4.0 ng/l (n=3), an increase in IL-6 to 4.2±1.1 pg/ml (1.7-fold increase relative to the reference level, p<0.01), CRP to 2.8±0.7 mg/l (2.3-fold, p<0.01), C3a to 49.8±3.98 pg/ml (10.3-fold, p<0.001) was recorded, which indicates the initiation of proinflammatory cascades and complement activation in moderate subclinical myocardial damage. With hs-cTn 4.1–4.9 ng/l (n=4), IL-6 values reached 6.8±1.5 pg/ml (2.7-fold increase, p<0.001), CRP — 4.5±1.0 mg/l (3.8-fold increase, p<0.001), C3a — 177.00±8.93 pg/ml (36.7-fold increase, p<0.001), demonstrating a significant increase in the inflammatory response and complement-dependent mechanisms in severe subclinical myocardial dysfunction. In the cohort of group II (n=13), the concentration of IL-6 was 12.3±3.2 pg/ml (4.9-fold increase, p<0.001), CRP was 7.8±2.1 mg/l (6.5-fold increase, p<0.001), C3a was 119.86±26.8 pg/ml (24.9-fold increase, p<0.001), which indicates the maximum expression of these markers in manifest coronary artery disease.

An assessment of intragroup dynamics in Group 1 revealed a significant correlation between IL-6, CRP, and C3a concentrations and the progression of subclinical myocardial injury as determined by hs-cTn. At hs-cTn levels of 2.1–4.0 ng/L, IL-6 concentrations increased 1.7-fold (p<0.01) with a variation coefficient of 1.1 pg/mL, reflecting individual heterogeneity in the activation of proinflammatory pathways at the initial stages of myocardial stress, likely associated with increased IL-6 secretion by the monocyte-

macrophage pool in response to endothelial dysfunction. With hs-cTn 4.1–4.9 ng/L, the IL-6 level increased 2.7 times ($p<0.001$) with a variability of 1.5 pg/ml, indicating a more pronounced and stable activation of the cytokine response, including the possible participation of Th17 cells in the pathogenetic processes of atherogenesis.

The concentration of CRP with hs-cTn 2.1–4.0 ng/L increased by 2.3 times ($p<0.01$) with a variability of 0.7 mg/L, and with hs-cTn 4.1–4.9 ng/L – by 3.8 times ($p<0.001$) with a variability of 1.0 mg/L, which emphasizes the increasing induction of acute phase proteins by hepatocytes under the influence of IL-6 as a key mediator of systemic inflammation.

The C3a level at hs-cTn 2.1–4.0 ng/L increased 10.3-fold ($p<0.001$) with a variability of 3.98 pg/mL and peaked at 36.7-fold at hs-cTn 4.1–4.9 ng/L ($p<0.001$) with a variability of 8.93 pg/mL, demonstrating a significant increase in complement-mediated inflammation, likely via the alternative or classical pathway of activation associated with subclinical ischemia.

In the cohort of group II, a further escalation of markers was recorded, reaching maximum values in the chronic course of coronary artery disease. The concentration of IL-6 increased by 4.9 times relative to the reference level ($p < 0.001$) with a variation coefficient of 3.2 pg/ml, which may be due to the heterogeneity of the inflammatory phenotype and increased IL-6 production under conditions of chronic ischemia, including the contribution of Th17- and Th1-dependent pathways. The CRP level was 7.8 ± 2.1 mg/l, exceeding the baseline value by 6.5 times ($p < 0.001$) with a variability of 2.1 mg/l, reflecting a pronounced acute phase response correlating with the progression of the atherosclerotic process and plaque destabilization. The concentration of C3a reached 119.86±26.8 pg/ml, increasing 24.9 times relative to the baseline level ($p<0.001$), but was 1.5 times lower than the peak value with hs-cTn 4.1–4.9 ng/l ($p<0.01$), with high variability of 26.8 pg/ml, which may indicate a partial decrease in complement-mediated activity during the transition to the chronic phase of coronary heart disease.

Comparative analysis within group I showed that the escalation of hs-cTn from 2.1–4.0 ng/L to 4.1–4.9 ng/L was accompanied by an increase in IL-6 by 1.6 times ($p<0.05$),

CRP by 1.6 times ($p<0.05$), and C3a by 3.6 times ($p<0.001$), emphasizing the enhancement of inflammatory and complement-dependent mechanisms in the late stages of subclinical damage. With the transition from hs-cTn 4.1–4.9 ng/L to group II, IL-6 increased by 1.8 times ($p<0.05$), CRP by 1.7 times ($p<0.05$), while C3a decreased by 1.5 times ($p<0.01$), which may indicate a change in acute subclinical activation to chronic inflammation in manifest coronary artery disease. The most significant increase in C3a was recorded at hs-cTn 4.1–4.9 ng/l (36.7 times, $p<0.001$), while IL-6 and CRP reached a peak in group II (4.9 times and 6.5 times, respectively, $p<0.001$), emphasizing their differentiated dynamics depending on the stage of pathogenesis.

Thus, the established data indicate the decisive importance of IL-6, CRP and C3a in the immune regulation of the pathogenesis of coronary heart disease in patients with hypertension, reflecting the consistent increase in the innate inflammatory response, acute phase reaction and complement-mediated activation at the stages from subclinical myocardial damage to its manifest form.

Conclusions:

1. It has been established that the progression of subclinical myocardial damage in patients with arterial hypertension is accompanied by a significant increase in the levels of IL-6, C-reactive protein and complement component C3a, reflecting the activation of systemic inflammation and the innate immune response.

2. Maximum activation of complement-dependent mechanisms (C3a) is observed at the stage of severe subclinical myocardial damage, while the peak of pro-inflammatory markers (IL-6, CRP) is recorded in manifest coronary heart disease, which indicates the staging of immune-inflammatory processes.

3. Proinflammatory cytokines and components of the complement system can be considered as informative biomarkers of the progression of cardiovascular pathology and used for early stratification of the risk of developing coronary heart disease in patients with arterial hypertension.

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