ISSN: 3060-4737 Volume 3, Issue 3 IF(Impact Factor) 10.98 / 2025

UDC: 616.45-006-089.197.6-072.1

IMMUNOINFLAMMATORY FACTORS AS PREDICTORS OF ISCHEMIC HEART DISEASE DEVELOPMENT IN PATIENTS WITH ARTERIAL HYPERTENSION

Khamdamov B.Z., Sharipov J.R.

Bukhara state medical institute, Uzbekistan, Bukhara, Gijduvan St. e-mail: info@bsmi.uz

Annotation. The article presents the results of a study on clinical, laboratory, and immunoinflammatory characteristics 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 assessment of high-sensitivity cardiac troponin (hs-cTn) levels, as well as key immunoinflammatory markers, including VEGF A, TGFβ, interferons (IFN-α, IFN-γ), pro-inflammatory cytokines (IL-6), C-reactive protein (CRP), and complement component C3a.

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

ИММУНОВОСПАЛИТЕЛЬНЫЕ ФАКТОРЫ КАК ПРЕДИКТОРЫ ФОРМИРОВАНИЯ ИШЕМИЧЕСКОЙ БОЛЕЗНИ СЕРДЦА У ПАЦИЕНТОВ С АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИЕЙ

Хамдамов Б.З., Шарипов Ж.Р.

Бухарский государственный медицинский институт Узбекистан. г. Бухара. Гиждуванская ул. 23. e-mail: info@bsmi.uz

Аннотация. В статье представлены результаты исследования клинико-лабораторных и иммуновоспалительных особенностей у пациентов с артериальной гипертензией (АГ) и при сочетании АГ 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

ISSN: 3060-4737 Volume 3, Issue 3 IF(Impact Factor) 10.98 / 2025

анализ уровней высокочувствительного сердечного тропонина (hs-cTn), а также ключевых иммуновоспалительных маркеров, включая VEGF A, TGFβ, интерфероны (ИФНα, ИФНγ), провоспалительные цитокины (ИЛ-6), С-реактивный белок (СРБ) и компонент комплемента С3а.

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

АРТЕРИАЛ ГИПЕРТЕНЗИЯ БИЛАН ОҒРИГАН БЕМОРЛАРДА ИШЕМИК ЮРАК КАСАЛЛИГИ ШАКЛЛАНИШИНИНГ ПРЕДИКТОРЛАРИ СИФАТИДА ИММУНОЯЛЛИҒЛАНИШ ОМИЛЛАРИ

Хамдамов Б.З., Шарипов Ж.Р.

Бухоро давлат тиббиёт институти. Ўзбекистон. Бухоро ш., Ғиждувон кўчаси, 23. e-mail*;* *info@bsmi.uz*

Аннотация. Мақолада артериал гипертензия (АГ) билан касалланган беморлар ҳамда АГ ва ишемик юрак касаллиги (ИЮК) бирга кечиши ҳолатларида клиник-лаборатор ва иммуноялллиғланиш хусусиятлари 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 юқори сезгир юрак тропонини (hs-cTn) даражаси, шунингдек асосий иммуноялллиғланиш маркерлари — VEGF A, TGFβ, интерферонлар (ИФНα, ИФНγ), яллиғланиш цитокинлари (ИЛ-6), С-реактив оқсил (СРБ) ва комплемент тизимининг С3а компоненти таҳлил қилинди.

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

Relevance: Cardiovascular diseases continue to occupy a leading position in morbidity and mortality, remaining one of the key medical and social problems of our time. Arterial hypertension is considered one of the leading modifiable risk factors for the development of coronary heart disease, contributing to the development of structural and functional changes in the myocardium and vascular wall.

In recent years, particular attention has been paid to the concept of subclinical

ISSN: 3060-4737 Volume 3, Issue 3 IF(Impact Factor) 10.98 / 2025

myocardial injury, in which morphofunctional changes precede the clinical manifestation of coronary artery disease. In this context, high-sensitivity cardiac troponin (hs-cTn), which allows for the detection of minimal damage to cardiomyocytes, is of significant interest.

Despite the widespread use of hs-cTn in the diagnosis of acute coronary syndrome, its role in assessing chronic forms of cardiovascular disease, particularly in patients with hypertension, requires further clarification. The hs-cTn threshold values reflecting the transition from subclinical myocardial injury to manifest coronary artery disease remain poorly defined.

In this regard, the study of the prognostic potential of hs-cTn in patients with hypertension is of significant scientific and practical interest.

Purpose of the study. To determine immunoinflammatory predictors associated with the transition of subclinical myocardial damage to clinically manifest coronary heart disease in patients with arterial hypertension based on the analysis of hs-cTn levels and immunological markers.

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: When comparing the duration of the disease between the two groups of patients, it was revealed that 27.0% of patients with isolated hypertension (group I) had a disease duration of 3-5 years, while in the group of patients with a combination of hypertension and coronary heart disease (group II), this indicator was reduced by 12.4% and amounted to 14.6%, which indicates that, To assess the role of immunological factors in the pathogenesis of coronary heart disease in patients with hypertension, this study analyzed the levels of a number of key biomarkers reflecting the activity of innate and adaptive immunity, as well as the processes of inflammation, reparation and regulation of the immune response. The studied parameters included VEGF A, TGFβ, IFNα and IFNγ, IL-6, CRP and complement component C3a. The choice of these markers is due to their established role in inflammatory and ischemic processes underlying the progression of hypertension and the development of coronary

ISSN: 3060-4737 Volume 3, Issue 3 IF(Impact Factor) 10.98 / 2025

heart disease, as well as their potential association with subclinical myocardial damage, endothelial dysfunction and atherosclerosis.

The measurement of VEGF A was motivated by its key role in the regulation of angiogenesis and vascular permeability, which is of primary importance in the context of myocardial ischemia associated with hypertension and coronary heart disease. Ferrara et al. (2013) found that VEGF A, synthesized by macrophages in response to hypoxic conditions, stimulates neoangiogenesis, promoting compensatory restoration of blood supply.

TGFβ was included in the study due to its multifunctional role in modulating inflammation and fibrosis, which is critical in left ventricular hypertrophy and chronic myocardial ischemia. Bujak and Frangogiannis (2017) demonstrated that elevated TGFβ concentrations correlate with myocardial remodeling in patients with hypertension, positioning it as a potential biomarker of coronary heart disease progression.

Table 1.

Comparative analysis of regulatory factors 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)	
VEGF A	23.3±1.57	88.1±7.19**	120.31±6.22***	144.84±28.9***
TGFβ	22.6±1.09	84.6±7.72**	155.01±5.36***	143.91±28.7***

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

In group I, with a hs-cTn level of ≤ 2.0 ng/l (n=18), the concentration of VEGF A was 23.3±1.57 pg/ml, and TGFβ was 22.6±1.09 pg/ml, taken as baseline values characterizing minimal activity of angiogenesis and fibrosis in conditions of stable hypertension without subclinical changes in the myocardium. In the subgroup with hs-cTn 2.1–4.0 ng/l (n=3), the VEGF A level increased to 88.1±7.19 pg/ml (3.8 times higher than baseline, p<0.01), and TGFβ to 87.1±7.72 pg/ml (3.9 times, p<0.01), indicating activation of angiogenesis and fibrogenic processes in moderate subclinical damage. With hs-cTn 4.1–4.9 ng/L (n=4), VEGF A values reached 120.31±6.22 pg/ml (5.2-fold, ***p<0.001), and TGFβ — 155.01±5.36 pg/ml (6.9-fold, p<0.001), demonstrating a significant increase in these processes in severe subclinical damage. In group II (AG+CHD, n=13), the VEGF A concentration was 144.84±28.9 pg/ml (6.2-fold increase, p<0.001), and TGFβ — 143.91±28.7 pg/ml (6.4-fold, p<0.001), reflecting the maximum expression of these factors in manifest CHD.

ISSN: 3060-4737 Volume 3, Issue 3 IF(Impact Factor) 10.98 / 2025

Comparison of VEGF A and TGFβ levels revealed their pronounced dependence on the degree of myocardial damage both within Group I and upon transition to Group II. In Group I, with an increase in hs-cTn from ≤ 2.0 ng/L to 2.1–4.0 ng/L, VEGF A increased by 3.8 times ($p<0.01$), with a variability of 7.19 pg/ml, indicating individual differences in the activation of angiogenesis in the early stages of the subclinical process, and to hs-cTn 4.1–4.9 ng/L — by 5.2 times ($p<0.001$), with a smaller spread (6.22 pg/ml), reflecting a more stable response to significant damage.

For TGFβ, the increase was 3.9 times at hs-cTn 2.1–4.0 ng/L ($p<0.01$), with noticeable variability (7.72 pg/ml), and 6.9 times at hs-cTn 4.1–4.9 ng/L ($p<0.001$), with less variability (5.36 pg/ml), emphasizing the progressive increase in fibrosis. In group II, VEGF A exceeded the baseline level by 6.2 times ($p<0.001$), with high variability (28.9 pg/ml), probably due to the heterogeneity of the course of coronary heart disease, and TGFβ — by 6.4 times ($p<0.001$), with variability of 28.7 pg/ml, which may be associated with differences in the degree of tissue remodeling.

The following differences were established between the subgroups of group I and group II: in group II, VEGF A (144.84±28.9 pg/ml) was 6.2 times higher than the baseline level ($p<0.001$), 1.6 times higher than with hs-cTn 2.1–4.0 ng/l ($p<0.05$), and 1.2 times higher than with hs-cTn 4.1–4.9 ng/l, without statistical significance of the latter difference. The TGFβ level in group II (143.91±28.7 pg/ml) was 6.4 times higher than the baseline value ($p<0.001$), 1.7 times higher than with hs-cTn 2.1–4.0 ng/l ($p<0.05$), and 0.93 times lower than with hs-cTn 4.1–4.9 ng/l, also without significance. Within group I, VEGF A with hs-cTn 4.1–4.9 ng/l was 1.4 times higher than with hs-cTn 2.1–4.0 ng/l ($p<0.05$), and TGFβ was 1.8 times higher ($p<0.01$), which confirms more intense activation of these factors in the late stages of subclinical damage. The transition from hs-cTn 4.1–4.9 ng/l to group II increased VEGF A by 1.2 times, and TGFβ decreased by 0.93 times, which may indicate stabilization of processes in manifest coronary artery disease.

Thus, the obtained data indicate a significant role for VEGF A and TGFβ in the pathogenesis of coronary heart disease in patients with hypertension, reflecting a progressive increase in angiogenesis and fibrosis mediated by immune processes, including the production of these factors by macrophages under conditions of inflammation and ischemia. The highest expression at hs-cTn levels of 4.1–4.9 ng/L and in Group II emphasizes their potential as markers of subclinical changes and coronary heart disease progression.

IFNα and IFNγ were assessed to analyze the activity of innate and adaptive immunity, respectively. IFNα, produced by plasmacytoid dendritic cells as part of the nonspecific immune response, serves as an indicator of the early anti-inflammatory

ISSN: 3060-4737 Volume 3, Issue 3 IF(Impact Factor) 10.98 / 2025

response, and its decrease is associated with depletion of the innate immune potential in chronic pathologies, including cardiovascular diseases.

IFNγ, secreted predominantly by Th1, enhances inflammatory processes in atherosclerotic plaques by activating macrophages and producing proinflammatory cytokines, which highlights its importance in the adaptive immune response and the progression of CAD, as noted by Libby (2017) in the context of atherogenesis.

In group I, with a hs-cTn level of ≤ 2.0 ng/l (n=18), the concentration of IFNα was 37.2±6.17 pg/ml, and IFNγ was 18.8±1.23 pg/ml, taken as baseline values characterizing the initial activity of innate and adaptive immunity under conditions of stable hypertension without subclinical myocardial damage.

Table 2.

Comparative analysis of interferon levels 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)	
IFNα	37.2±6.17	64.2±4.65**	113.56±3.52***	54.3±2.63**
IFNγ	18.8±1.23	26.6±1.42**	37.4±1.01***	37.3±2.19***

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), the IFNα level increased to 64.2±4.65 pg/ml (1.7 times higher than baseline, p<0.01), and IFNγ to 26.6±1.42 pg/ml (1.4 times, p<0.01), indicating initial activation of the immune response with moderate subclinical damage.

With hs-cTn 4.1–4.9 ng/L (n=4), IFNα values reached 113.56±3.52 pg/mL (3.1 times higher than baseline, p<0.001), and IFNγ — 37.4±1.01 pg/mL (2.0 times, p<0.001), demonstrating a significant increase in interferon production in severe subclinical damage. In group II (AG+CHD, n=13), the IFNα concentration was 54.3±2.63 pg/mL (1.5 times higher than baseline, p<0.01), and IFNγ — 37.3±2.19 pg/mL (2.0 times, p<0.001), indicating different dynamics of these factors in manifest CHD.

Comparison of IFNα and IFNγ levels within Group I revealed a significant dependence on the degree of subclinical myocardial damage assessed by hs-cTn. With hs-cTn 2.1–4.0 ng/L, the IFNα concentration increased by 1.7 times relative to the baseline level (p<0.01), with a variability of 4.65 pg/ml, reflecting individual differences in the activation of innate immunity at the early stages of the pathological

ISSN: 3060-4737 Volume 3, Issue 3 IF(Impact Factor) 10.98 / 2025

process. To hs-cTn 4.1–4.9 ng/L, it increased by 3.1 times ($p<0.001$), with less variability (3.52 pg/ml), indicating a more uniform and intense immune system response, likely associated with increased interferon production by plasmacytoid dendritic cells in response to subclinical ischemia. For IFNγ, the increase was 1.4-fold at hs-cTn 2.1–4.0 ng/L ($p<0.01$), with a variability of 1.42 pg/mL, and 2.0-fold at hs-cTn 4.1–4.9 ng/L ($p<0.001$), with minimal variation (1.01 pg/mL), highlighting the consistent enhancement of the Th1-mediated adaptive immune response with progression of myocardial injury.

Upon transitioning to Group II, interferon dynamics became more variable. IFNα levels in Group II were 1.5 times higher than baseline ($p<0.01$), but were 2.1 times lower than the peak value with hs-cTn levels of 4.1–4.9 ng/L ($p<0.001$), with a variability of 2.63 pg/mL. This may indicate exhaustion of the innate immune response in chronic inflammation and overt coronary artery disease.

At the same time, the concentration of IFNγ in group II reached 37.3±2.19 pg/ml, which is 2.0 times higher than the baseline level ($p<0.001$) and almost identical to the value with hs-cTn 4.1–4.9 ng/l (37.4±1.01 pg/ml), maintaining low variability (2.19 pg/ml), which reflects the consistently high activity of Th1 cells in manifest coronary artery disease. Comparison of the subgroups of group I with group II showed that IFNα in group II was 1.5 times lower than with hs-cTn 4.1–4.9 ng/l ($p<0.01$), but 1.2 times higher than with hs-cTn 2.1–4.0 ng/l, without the significance of the latter difference. The IFNγ level in group II was 1.4 times higher than the value with hs-cTn 2.1–4.0 ng/l ($p<0.05$) and remained virtually unchanged compared to hs-cTn 4.1–4.9 ng/l (1.0 times).

Within group I, the transition from hs-cTn 2.1–4.0 ng/L to hs-cTn 4.1–4.9 ng/L increased IFNα by 1.8 times ($p<0.01$) and IFNγ by 1.4 times ($p<0.05$), which emphasizes more intense activation of innate and adaptive immunity in the late stages of subclinical damage. From hs-cTn 4.1–4.9 ng/L to group II, IFNα decreased by 2.1 times ($p<0.001$), and IFNγ remained stable (by 1.0 times), which may indicate a transition from acute immune activation to chronic inflammation in manifest coronary artery disease. The most pronounced increase in IFNα was observed at hs-cTn 4.1–4.9 ng/L (3.1 times, $p<0.001$), and IFNγ reached its maximum at hs-cTn 4.1–4.9 ng/L and in group II (2.0 times, $p<0.001$), emphasizing the different roles of these interferons in immune processes.

Thus, the results of the study reveal the differentiated dynamics of IFNα and IFNγ in the development of coronary heart disease in patients with hypertension, demonstrating a pronounced activation of the innate immune response (IFNα) at subclinical stages with subsequent weakening in manifest coronary heart disease and a

ISSN: 3060-4737 Volume 3, Issue 3 IF(Impact Factor) 10.98 / 2025

stable increase in adaptive immunity (IFNγ) associated with chronic inflammation and the atherosclerotic process.

Conclusions:

1. It has been established that an increase in the levels of VEGF A and TGFβ is closely associated with the degree of subclinical myocardial damage and the progression of coronary heart disease in patients with arterial hypertension, reflecting the stepwise activation of angiogenesis and fibrotic processes, reaching a maximum in manifest coronary heart disease.

2. The dynamics of interferons are multidirectional: in the early stages of subclinical myocardial damage, a pronounced activation of the innate immune response (IFNα) is observed, whereas in manifest coronary heart disease, its relative decrease is observed against the background of persistently increased activity of the adaptive immunity (IFNγ), which indicates a transition from an acute immune response to chronic inflammation.

3. The progression of myocardial damage is accompanied by a consistent escalation of systemic inflammation and activation of complement-dependent mechanisms (IL-6, CRP, C3a), which confirms the key role of immune-inflammatory processes in the pathogenesis of coronary heart disease and justifies their use as risk stratification markers in patients with arterial hypertension.

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