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ВЗАИМОСВЯЗЬ ИММУНОЛОГИЧЕСКИХ НАРУШЕНИЙ, ГИПОКСИИ И ВОСПАЛЕНИЯ ПРИ АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИИ И МЕТАБОЛИЧЕСКОМ СИНДРОМЕ

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Резюме. Целью нашей работы явилась оценка взаимосвязи иммунных нарушений, гипоксии и воспаления при артериальной гипертензии (АГ) в условиях метаболических нарушений. Клиническое исследование включало 117 пациентов, рандомизированных на группы согласно протоколу исследования, в возрасте от 30 до 62 лет, обратившихся за амбулаторной помощью или проходивших периодические медицинские осмотры на базе ГБУЗ РМ «Республиканская клиническая больница № 5» г. Саранска. Группа контроля включала 25 практически здоровых лиц, не имеющих признаков метаболического синдрома (МС) и повышения артериального давления. Группа сравнения состояла из 47 пациентов с АГ I-II степени с поражением органов мишеней, но не имевших ассоциированных клинических состояний согласно проведенным обследованиям. Основная группа включала 45 пациентов с достигнутой I-II степенью АГ при обращении на фоне гипотензивной терапии с поражением органов мишеней и признаками МС с случайным сочетанием его компонентов, но без ассоциированных клинических состояний. Пациенты основной группы и группы сравнения получали гипотензивную терапию согласно стандартам и клиническим рекомендациям по ведению пациентов с АГ, состоящую из комбинации одного из блокаторов ренинангиотензинальдостероновой системы, диуретика и/или дигидропидинового блокатора кальциевых каналов. В плазме крови испытуемых оценивали цитокиновый профиль, показатели гипоксии и неспецифического воспаления. Проведенные исследования показали, что у пациентов с АГ, не имеющих метаболические нарушения и при сочетании АГ с метаболическим синдромом, отмечается сдвиг цитокинового профиля в сторону повышения про- и противовоспалительного звена, что указывает на формирование дисбаланса в иммунорегуляторной системе. Наблюдалось развитие гипоксических изменений в сыворотке крови, что подтверждалось ростом содержания молочной и пировиноградной кислот в данных группах больных. В условиях формирования данной патологии гипоксия выступает в качестве модулятора иммунного и неспецифического воспаления. Повышение показателей неспецифического вялотекущего воспаления коррелирует с развитием необратимых изменений в органах, ассоциированных с АГ, прогрессированием атеросклероза и ускорением кардиометаболического континуума. В совокупности эти нарушения определяют патогенетические механизмы повреждения, возникающие при сочетании АГ и МС, и являются взаимоотягощающим фактором наряду с активацией ренинангиотензинальдостероновой системы.

Ключевые слова: артериальная гипертензия, метаболический синдром, патогенез, цитокиновый дисбаланс, гипоксия, неспецифическое воспаление, сердечно-сосудистые события

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RELATIONSHIP BETWEEN IMMUNOLOGICAL ALTERATIONS, HYPOXIA AND INFLAMMATION IN ARTERIAL HYPERTENSION COMBINED WITH METABOLIC SYNDROME

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Abstract. Our study was aimed at assessing a relationship between immune system alterations, hypoxia and inflammation in arterial hypertension (AH) coupled to metabolic disturbances. A total of 117 patients were enrolled into clinical study, having been randomized into groups in accordance with study protocol, aged 30 to 62 years. They sought care in outpatient setting or underwent periodic health examination at the Republican Clinical Hospital №5, Saransk, Mordovia, Russia. A control group contained 25 apparently healthy subjects lacking signs of metabolic syndrome (MS) and elevated arterial pressure. A comparison group contained 47 patients with AH grade I-II featured with damaged target organs, but lacking associated relevant clinical manifestations, as based on the assay data. The main group contained 45 patients receiving antihypertensive therapy with overt AH grade I-II verified upon medical consultation coupled to damaged target organs and MS signs with its randomly combined components, but lacking associated clinical manifestations. The patients from main and comparison groups received antihypertensive therapy in accordance with approved guidelines and clinical recommendations for management of AH patients consisting of one of renin-angiotensin-aldosterone system blockers, diuretic and/or dihydropyridine calcium channel blocker. Cytokine profile, level of hypoxia and non-specific inflammation were measured in blood serum. The data obtained demonstrated that AH patients with/without metabolic syndrome were noted to display cytokine profile shifted towards elevated pro- and anti-inflammatory immune arm pointing at imbalanced immune regulation. Hypoxic changes were also found in blood serum that was confirmed by elevated level of lactic and pyruvic acid in these groups. Moreover, development of such pathology was coupled to hypoxia which served as a modulator of immune-related and non-specific inflammation. Rise of non-specific low-grade inflammation correlates developing irreversible AH-associated changes in organs, progression of atherosclerosis and accelerated cardio-metabolic continuum. Altogether, such alterations underlie pathogenetic mechanisms of tissue damage emerging upon AH and MS being mutually aggravating factor along with activated renin-angiotensin-aldosterone system.

Keywords: arterial hypertension, metabolic syndrome, pathogenesis, cytokine imbalance, hypoxia, non-specific inflammation, cardiovascular events

Introduction

Arterial hypertension (AH) defined as a chronic disease featured with elevated blood pressure without identifying overt causes has moved far beyond global pandemic. Its epidemiology does not depend neither on social status being found at similar rate in high-, middle- and low-income countries, nor on sex identity reaching up to 47 and 40% in males and females under 60, respectively, equalized, however, after age over 60 affecting more than 60% of subjects [1, 2]. Sedentary lifestyle and obesity related to diverse metabolic disorders are the most valuable risk factors for cardiovascular events in aging human population [3, 4, 5].

Current population-wide studies starkly demonstrate significant relationship between immune imbalance markers and inflammatory parameters in patients with elevated blood pressure and metabolic disorders. Changes in cytokine network showed significant positive correlation with increased vascular stiffness and lowered elasticity in AH patients underlying pathogenetic role for cytokinemia. In particular, pro-inflammatory cytokines (tumor necrosis factor (TNF), interleukin-1 (IL-1), IL-6, IL-8) are able to induce development of endothelial dysfunction. TNF in chronic diseases may also contribute to developing insulin resistance and dyslipidemia, whereas IL-6 acting via TNF and IL-1 elicits endothelial dysfunction being a potential triggering agent for acute coronary events [6, 7, 8].

Previously, it was shown that level of fibrinogen, C-reactive protein (CRP) and neopterin was increased in inflammatory events, which serve as sensitive markers for inflammation and necrosis. Their rise in the serum higher than reference values correlates with increased risk of complications in cardiovascular diseases [9, 10].

Hypoxia developing in AH patients under pathological conditions due to metabolic syndrome (MS) contributes to activated lipid peroxidation (LPO) and production of copious amount of pro-inflammatory cytokines involved in developing adaptation to hypoxia [11, 12].

Elevated serum level of AH-coupled pro-inflammatory markers, hypoxia-related components, cytokine imbalance in combination with MS evidence

about significance of such homeostatic arms in disease pathogenesis.

Currently available publications lack data on relation between hypoxia, parameters of immune imbalance and altered components of non-specific inflammation in AH patients with metabolic disorders.

Our study was aimed at examining a relationship between immunological disturbances, hypoxia and inflammation in combination with arterial hypertension and metabolic syndrome.

Materials and methods

Clinical study was conducted in the outpatient-polyclinic unit of the State Budgetary Healthcare Institution Republic of Mordovia Republican Clinical Hospital No. 5, City of Saransk, Russia. There were enrolled 117 patients randomized into groups in accordance with study protocol. Control group contained 25 apparently healthy subjects (15 males and 10 females aged 30 to 45 years) lacking signs of metabolic syndrome and elevated blood pressure (BP).

A comparison group contained 47 patients (26 males and 21 females, aged 32 to 58 years) with AH grade I-II featured with damaged target organs, but lacking associated clinical manifestations based on surveillance data. The main group contained 45 patients (19 males and 26 females, aged 37 to 62 years) receiving antihypertensive therapy with overt AH grade I-II verified upon medical consultation and coupled to damaged target organs and MS signs with its randomly combined components, but lacking associated clinical manifestations. Patients from main and comparison groups received antihypertensive therapy in accordance with approved guidelines and clinical recommendations for management of AH patients consisting of one of renin-angiotensin-aldosterone system (RAAS) blockers, diuretic and/or dihydropyridine calcium channel blocker.

Serum cytokine profile was assessed by using ELISA Microplate Analyser (Personal Lab, Italy) with ELISA reagent kits (Vector-Best, Novosibirsk, Russia; BIOHIT, Helsinki, Finland; DRG, Germany).

Intensity of serum hypoxia was measured by level of pyruvic acid (Pyr) during the reaction in 2,4-dinitrophenylhydrazine assay (Kushmanova O.D., Ivchenko G.M., 1983) and lactic acid (LA) in the reaction with paraoxydiphenyl (Menshov V.V., 1987).

Automatic biochemical analyzer ABX Pentra 400 (France) was used to measure glucose, total cholesterol (TCH), triglycerides (TG), low- and high-density lipoproteins (LDL and HDL), uric acid (LA) in the serum after an overnight fast to check for metabolic syndrome.

Serum pro-inflammatory changes were assessed by measuring level of high-sensitivity C-reactive protein (CRP, Protein Complex LLC, St. Petersburg). Fibrinogen concentration was measured by Clauss chronometric method on coagulation analyzer (Tehnologia Standart, Barnaul, Russia). Neopterin concentration was measured by ELISA (Concile GmbH, USA).

Cytokine profile, hypoxia level, and concentration of pro-inflammatory markers were measured upon initial medical consultation, and the data obtained from 25 control volunteers were considered as parameter normal range.

Statistical processing of study data was performed by using routine statistics software Microsoft Office XP and Excel by calculating arithmetic mean (M), error of mean (m), as well as significance value by using Student's t-test (significance is set at $p < 0.05$). An inter-parameter relationship was assessed by measuring a correlation coefficient r.

Results and discussion

Initially, serum cytokine profile was assessed in patients from the three groups by using ELISA. It was found that both pro-inflammatory and anti-inflammatory cytokine level was elevated in the main and comparison groups, whereas in control group they were within the reference range.

Next, hypoxia level was measured. It was shown that lactate level was higher than the reference range solely in the main group, whereas pyruvate level was increased both in the main and comparison groups *vs* control group being within the normal range.

After that, intensity of non-specific inflammation was assessed. In particular, neopterin level did not exceed reference range in any group, whereas it tended to rise in the main and comparison groups. CRP and neopterin levels were higher than normal range in the main group.

According to the neuro-humoral theory, RAAS blockade lowers cardiovascular risk by 23% suggesting about importance of additional mechanisms in development of cardiovascular events. Uncovering etiopathogenesis as well as blockade of additional mechanisms particularly immune-related cues results in overall decrease in sudden vascular events.

Examining patients from comparison group (group II) and main group (group III) revealed elevated pro-inflammatory cytokines such as IL-1β, IL-6, IL-8, and TNFα). Cytokine profile in various groups is shown in Table 1. Level of IL-1β in group II was significantly elevated by 237% ($p < 0.001$) compared to control (group I), whereas IL-6 – by 120% ($p < 0.001$), IL-8 – by 42% ($p < 0.01$), and TNFα – by 22% ($p < 0.05$).

Most prominently rise in cytokine level was shown in AH + MS patients *vs* control group (group III *vs* I). In particular, amount of IL-1β was significantly increased by 349% ($p < 0.001$), IL-6 – by 162% ($p < 0.001$), IL-8 – by 191% ($p < 0.001$), and TNFα – by 59% ($p < 0.001$) compared to control group.

Comparing cytokine profile in group III (main group) *vs* group II (AH patients), they were significantly

TABLE 1. LEVEL OF SERUM CYTOKINES IN VARIOUS PATIENT GROUPS (M±m)

Parameters	Reference range	Groups	Study data	p-value
IL-1β, pg/ml	< 5	I	3.21±0.18	D I-II < 0.001 D I-III < 0.001 D II-III < 0.05
		II	10.70±1.3	
		III	14.43±1.21	
IL-6, pg/ml	< 7	I	4.60±0.38	D I-II < 0.001 D I-III < 0.001 D II-III>0.05
		II	10.15±1.4	
		III	12.07±0.65	
IL-8, pg/ml	< 62	I	17.4±1.13	D I-II < 0.01 D I-III < 0.001 D II-III < 0.001
		II	24.8±1.91	
		III	50.7±1.8	
IL-10, pg/ml	< 9.1	I	8.5±0.66	D I-II < 0.001 D I-III < 0.001 D II-III < 0.01
		II	15.1±0.18	
		III	18.2±0.83	
TNFα, pg/ml	0-8.21	I	6.76±0.28	D I-II < 0.05 D I-III < 0.001 D II-III < 0.005
		II	8.27±0.50	
		III	10.81±0.31	

Note. I, control group; II, comparison group; III, main group. D I-II, significant differences in group I vs II; D I-III, significant differences in group I vs III; D II-III, significant differences in group II vs III.

TABLE 2. SERUM HYPOXIA PARAMETERS AND INFLAMMATION MARKERS IN PATIENT GROUPS (M±m)

Parameters	Reference range	Groups	Study data	p-value
Lactate, mmol/g protein	0.5-2.2	I	1.79±0.07	D I-II > 0.05 D I-III < 0.005 D II-III < 0.01
		II	1.93±0.06	
		III	2.27±0.09	
Pyruvate, mmol/g protein	0.08-0.16	I	0.11±0.01	D I-II < 0.005 D I-III < 0.001 D II-III < 0.01
		II	0.17±0.01	
		III	0.22±0.01	
Neopterin, nmol/l	< 10	I	2.68±0.03	D I-II < 0.005 D I-III < 0.001 D II-III < 0.01
		II	3.95±0.31	
		III	5.23±0.28	
C-reactive protein, mg/l	< 5	I	0.16±0.01	D I-II < 0.01 D I-III < 0.001 D II-III < 0.001
		II	1.52±0.06	
		III	5.16±0.31	
Fibrinogen, g/l	2.00-4.00	I	2.41±0.01	D I-II > 0.05 D I-III < 0.001 D II-III < 0.005
		II	2.68±0.34	
		III	4.6±0.07	

Note. I, control group; II, comparison group; III, main group. D I-II, significant differences in group I vs II; D I-III, significant differences in group I vs III; D II-III, significant differences in group II vs III.

elevated: IL-1β – by 34% ($p < 0.05$), IL-8 – by 104% ($p < 0.001$), TNFα – by 30% ($p < 0.005$). However, no significant changes in IL-6 level were found.

Moreover, we found a significant increase in concentration of anti-inflammatory cytokine IL-10 in group II *vs* control group by 75% ($p < 0.001$) and in group III – by 114% ($p < 0.001$), respectively. Comparing parameters in group I *vs* II, revealed that they differed by 20% ($p < 0.01$), which might suggest their production in response to hypoxia. Sharply elevated level of anti-inflammatory cytokine IL-10 points at development of compensatory anti-inflammatory defense to chronic hypoxia emerging upon AH progression, especially in case of metabolic disorders.

Cytokines (IL-1β, IL-6, IL-8, TNFα) belong to primary broad-range humoral pro-inflammatory cytokines which trigger production of the secondary

messenger of low-grade inflammation such fibrinogen, C-reactive protein, and neopterin (Table 2). It was shown that in group II (AH patients) *vs* group I (control) serum samples was significantly higher by 8.5-fold ($p < 0.01$) and neopterin – by 47% ($p < 0.005$). No significant changes in fibrinogen level in these groups were found. Most prominently, parameters of non-specific inflammation were increased in AH + MS patients (group III). In particular, CRP level was elevated by 31.2-fold ($p < 0.001$), neopterin – by 95% ($p < 0.001$), and fibrinogen – by 90% ($p < 0.001$) compared to healthy volunteers. Comparing AH (group II) *vs* AH + MS patients (group III) also revealed significantly increased parameters in the latter group: CRP – by 239% ($p < 0.001$), fibrinogen – by 71% ($p < 0.005$), neopterin – by 32% ($p < 0.01$). Although neopterin level did not exceed the reference range in AH (group II) *vs* AH + MS (group III), it was significantly increased as compared to that one found in healthy volunteers and taken as arbitrary normal interval for patients lacking MS and elevated BP. It was found that neopterin level higher than reference range was observed in viral infections. Upon that, in case it was increased within the reference range it might evidence about subclinical low-grade inflammation in AH + MS patients.

Thus, a biochemical profile observed by us evidences about cascade immune reactions in AH + MS patients resulting in accelerated development of cardiometabolic continuum, which likely become augmented in hypoxia due to end-products able to modulate pro-inflammatory immune response. The level of hypoxia-related parameters is shown in Table 2. In particular, serum samples were found to contain hypoxia-related marker lactate elevated by 26% ($p < 0.005$) in AH + MS patients (group III) *vs* healthy volunteers (group I) as well as by 17% ($p < 0.01$) in group III compared to AH patients lacking metabolic disturbances. Pyruvate level was elevated by 54% ($p < 0.005$) in AH patients (group II) and by 100% ($p < 0.001$) in AH + MS patients (group III) compared to healthy volunteers (group I) that was also significantly higher in AH patients exhibiting metabolic disturbances compared to group II.

Conclusion

Thus, our study revealed that immune imbalance, chronic hypoxia and inflammation play a pivotal role in structure of AH pathogenesis particularly in case of metabolic disturbances. Elevated amount of pro- and anti-inflammatory cytokines in hypoxia suggests about developing imbalance in immune regulation, proving that hypoxia serves as a predictor of chronic inflammation. Such pathogenetic mechanisms undoubtedly exert mutually aggravating effects upon disease progression, which is further confirmed by revealed correlation between parameters related to immune disturbances and elevated parameters of non-specific inflammation. Moreover, we were able to uncover a positive correlation between parameters related to hypoxia and non-specific inflammation, as well as immune disturbances and hypoxia. It is of special importance by giving deeper insights into understanding pathogenetic mechanisms behind AH progression during metabolic disturbances as well as development of various cardiovascular events.

Differences in cytokine profile, non-specific inflammation in hypoxia evidence about severity of homeostatic disturbances in AH patients and more profound changes in AH + MS patients that correlate with intensity of damage in target organs and development of vascular catastrophe. A combined influence on arms of AH progression along with RAAS blockade may retard irreversible processes in organs and tissues related to AH.

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