Antihypertensive Pharmacotherapy in Correcting the Indicators of Innate Immunity in Patients with Essential Arterial Hypertension

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Abstract

Introduction: The study of indicators of innate immunity in patients with arterial hypertension in clinical trials makes it necessary to correct them in order to reduce vascular inflammation in arterial hypertension to prevent damage to target organs and development of cardiovascular complications. The aim of the study was to assess the effectiveness of antihypertensive therapy to correct indicators of innate immunity in patients with essential arterial hypertension.

Materials and methods: Patients with essential arterial hypertension (EAH) (II stage, 3rd degree) were divided into 3 groups: the 1st group included the patients with hypertrophy of the left ventricular myocardium; the 2nd group included the patients with atherosclerotic vascular lesions; the 3rd group included the patients with chronic kidney disease. As an initial antihypertensive pharmacotherapy, all the patients with essential arterial hypertension were prescribed perindopril (5–10 mg/day) and amlodipine (5–10 mg/day).

Results and discussion: Changes in innate immunity indices in patients with essential arterial hypertension (II stage, 3rd degree) are differentiated depending on the affected target organ. The antihypertensive pharmacotherapy with perindopril and amlodipine in patients with essential arterial hypertension has various corrective effects on impaired innate immunity, depending on the nature of target organ damage. Regardless of target organ damage, no antihypertensive therapy with perindopril and amlodipine does not affect the reduced functional and increased metabolic activities of peripheral blood neutrophils.

Conclusion: The results obtained dictate the need for further clinical studies of other classes of antihypertensive drugs and their combinations in the correction of innate immunity indices in order to effectively prevent the progression of target organ damage.
Introduction

The identification of points of application, with the help of which it is possible to modulate the inflammation accompanying arterial hypertension will probably establish new pharmacotherapeutic goals for us to treat not only arterial hypertension, but also other cardiovascular diseases and their complications (Timasheva 2019; Zemskov et al. 2019). Considering that the innate immune system is responsible for the initiation of most inflammatory reactions and causally contributes to the progression of cardiovascular pathology, a number of experiments have been made to study the indicators of innate immunity in arterial hypertension (Chamarthi et al. 2011; Hashmat et al. 2016; Wenzel 2019).

For example, IL-6 is one of a few cytokines for which an independent association with the development and/or progression of arterial hypertension has been demonstrated; it is an independent risk factor for hypertension in apparently healthy people (Bautista et al. 2005). IL-6 may also serve as a biomarker for high blood pressure, as it has been shown to be significantly increased in hypertensive patients compared with normal blood pressure controls (Chamarthi et al. 2011). In experimental studies in mice, IL-6 suppression neutralized an increase in blood pressure in response to angiotensin II infusion and decreased the progression of chronic kidney disease, as measured by albuminuria (Lee et al. 2006). Interestingly, this nephroprotection was associated with a decrease in the number of monocytes infiltrating the kidney and a decrease in the number of renal macrophages (Hashmat et al. 2016). This indicates that intervention at the IL-6 application points can be an effective way to suppress target organ damage in hypertension by blocking the activation of myelomonocytic cells.

IL-12 is secreted by activated monocytes and macrophages, usually when exposed to IFN-γ. In addition, it can also be active in a membrane-bound form (Fan et al. 1996; Gavrilyuk et al. 2016). Under the conditions of an angiotensin II-induced model of arterial hypertension, it was found that IFN-γ stimulates monocytes to produce IL-12, which, in turn, enhances the formation of IFN-γ by NK-cells (Kossmann et al. 2013). This mutual activation depends on a transcription factor expressed in T cells, which are essential not only for the transcription of IFN-γ in lymphoid cells, such as T cells and NK-cells, but also for the production of IL-12 by myelomonocytes (Soderquest et al. 2011).

Currently, there are no clinical studies that would comprehensively study the state of innate immunity in patients with essential arterial hypertension; there is no information on the representativeness of other cytokines (IL-8, IL-10, IL-1Ra, IL-6) or the activity of the complement system in arterial hypertension either, and most importantly, on the activity of neutrophils, which are an activator of inflammation in the tissue of target organs (Timasheva 2019).

Based on the literature data obtained, it can be assumed that the study of innate immunity indices in patients with arterial hypertension in clinical trials may lead us to the need for their correction in order to reduce vascular inflammation in arterial hypertension to prevent damage to target organs and the development of complications of the cardiovascular system (Gertsev et al. 2017; Dzekh et al. 2018), and initially it is necessary to establish the effectiveness of antihypertensive pharmacotherapy in the correction of innate immunity indices in patients with essential arterial hypertension.

The aim of the study was to assess the effectiveness of antihypertensive therapy in the correction of impairments in innate immunity indices in patients with essential arterial hypertension and subclinical damage to target organs.

Material and methods

Under constant supervision, on the basis of the Therapeutic Department of the Kursk City Clinical Emergency...
Hospital over the period from 2013 to 2017, there were 105 patients with essential arterial hypertension (EAH) (II stage, 3rd degree) aged 35 to 60 years (43.1 ± 6.2 years, 49 men and 56 women). The clinical diagnosis was based on the results of anamnesis, assessment of lifestyles and risk factors for cardiovascular diseases (CVD), clinical, laboratory and instrumental research methods. Clinical observations were approved by the Regional Ethics Committee of Kursk State Medical University (Protocol №2, 09.02.2018).

All the patients with EAH were divided into 3 independent groups, randomized by sex, age, duration of history, BP, heart rate, bad habits, and CVD risk factors (Table 1):

- the first group (33 patients) included patients with EAH with left ventricular myocardial hypertrophy (LVHM) (echocardiographic study – left ventricular myocardial mass index more than 115 g/m², and/or electrocardiographic study – Sokolov-Lyon index more than 35 mm; Cornell index over 20 mm for men and over 28 mm for men) (Table 1);
- the second group (37 patients) included patients with EAH with atherosclerotic vascular lesions (asymptomatic atherosclerosis, i.e. without associated clinical conditions and clinical manifestations) in the form of a thickening of the carotid artery wall and/or an increase of more than 10 m s⁻¹ in the pulse wave velocity with ultrasound study and a decrease in the ankle-brachial systolic pressure index less than 0.9 (Table 1);
- the third group (35 patients) included patients with stage 3 chronic kidney disease (CKD) with microalbuminuria (30–300 mg/L) and/or blood creatinine clearance of 30–60 ml/min/1.73 m² (MDRD formula) (Table 1).

The control group consisted of 24 healthy individuals at the time of examination (41.5 ± 5.4 years).

The phagocytic activity of peripheral blood neutrophils was assessed by the phagocytic index and phagocytic number, and the oxygen-dependent activity of neutrophils was assessed on a PD 303 Apel (Japan) spectrophotometer by the nitro blue tetrazolium reduction reaction (NBT-test) before and after stimulation with zymosan.

The concentration of cytokines (TNFα, IL-8, IL-6, IL-10, IL-1Ra) and components of the complement system (C1, C4, C5, C3, Factor H and C3-inhibitor) in the blood serum was assessed upon admission to hospital and 1 month after the start of the antihypertensive therapy (sets made by Vector-Best, Russia).

As a starting systematic antihypertensive pharmacotherapy, all the patients with EAH were prescribed a two-component pharmacotherapy with perindopril (5–10 mg/day) and amlodipine (5–10 mg/day).

For the analysis and comparison of qualitative indicators, the χ²-test was used, and for quantitative ones – Student’s t-test after determining that the quantitative features belonged to the normal distribution (Shapiro-Wilk test). The level of statistical significance was set at p < 0.05.

### Table 1. Clinical Profile of the Examined Groups of Patients with Essential Arterial Hypertension

| Parameters                                      | 1st group with LVHM (N = 33) | 2nd group with asymptomatic atherosclerosis (N = 37) | 3rd group with chronic kidney disease (N = 35) |
|-------------------------------------------------|------------------------------|-----------------------------------------------------|-----------------------------------------------|
| Male, n/%                                       | 15/45.5                     | 17/46.0                                             | 17/48.6                                       |
| Age (years), M ± m                              | 45.8 ± 1.9                  | 44.7 ± 2.0                                          | 46.2 ± 1.9                                    |
| Anamnesis (years), M ± m                        | 6.4 ± 2.2                   | 6.0 ± 2.3                                           | 6.3 ± 1.9                                     |
| SBP (mm Hg), M ± m                              | 189.7 ± 5.3                 | 189.8 ± 6.4                                         | 188.5 ± 5.1                                   |
| DBP (mm Hg), M ± m                              | 114.5 ± 2.2                 | 113.8 ± 2.4                                         | 115.1 ± 2.7                                   |
| Heart rate (beats/min), M ± m                   | 79.2 ± 6.5                  | 78.2 ± 7.8                                          | 79.2 ± 7.2                                    |
| Smoking, n/%                                    | 16/8.5                      | 24/64.9                                             | 18/51.4                                       |
| Dyslipidemia (Total cholesterol over 4.9 mmol/L and/or cholesterol low density lipoprotein over 3.0 mmol/L), n/% | 9/27.3                      | 23/62.2                                             | 7/20.0                                        |
| Glucose concentration 5.6–6.9 mmol/L, n/%       | 5/15.2                      | 8/21.6                                              | 5/14.3                                        |
| Impaired glucose tolerance, n/%                 | 11/33.3                     | 10/27.0                                             | 12/34.3                                       |
| Body mass index ≥ 30 kg/m², n/%                 | 30/90.9                     | 31/83.8                                             | 28/80.0                                       |
| Waist circumference: ≥ 102 cm for men; ≥ 88 cm for women, n/% | 25/75.8                     | 30/81.1                                             | 29/82.9                                       |
| Family history of cardiovascular disease, n/%   | 25/70.6                     | 34/91.9                                             | 27/77.1                                       |
| LVHM according to electrocardiography, n/%      | 25/70.6                     | 32/86.5                                             | 28/80.0                                       |
| LVHM according to echocardiography, n/%         | 33/100                      | 37/100                                              | 35/100                                        |
| Thickening of the wall of the carotid arteries, n/% | –                          | 33/89.2*                                            | –                                              |
| Pulse wave speed > 10 m/s, n/%                  | –                           | 33/89.2*                                            | –                                              |
| Ankle-brachial systolic pressure index < 0.9, n/% | –                           | 34/91.9*                                            | –                                              |
| Chronic kidney disease, n/%                     | –                           | –                                                   | 35/100*                                       |

Note: SBP – systolic blood pressure; DBP – diastolic blood pressure; LVHM – left ventricular myocardial hypertrophy; a, b - significant differences in the mean (p < 0.05); a – in relation to the indicators of the 1st group of patients, b – in relation to the indicators of the 2nd group of patients.

### Results and discussion

Cardiovascular diseases are the leading cause of death and a decline in the quality of life, as evidenced (Demchenko et al. 2020). Clinical trials have identified chronic inflammatory diseases as a risk for cardiovascular diseases, and recent studies have identified the contribution of various inflammatory cells to vascular oxidative stress and inflammation. Atherosclerosis and cardiovascular diseases are closely related to inflammation, probably due to the close interaction of inflammation with oxidative stress, with innate immunity being responsible for this (Chuong et al. 2019).

Monocytes play an important role in the inflammatory process in hypertension. Their molecular and cellular actions are multifaceted and can be potentially used for pharmacotherapy of essential arterial hypertension (Gorshunova et al. 2018). The promising targets are...
cytokines, such as IL-1β, IL-6, IL-12, or IFN-γ, which are either secreted by myelomonocytic cells or affect them; transmission of signaling chemokines, such as mysterious MCP-1/CCR2 axis to block monocyte recruitment and adhesion and infiltration into the vasculature, and phagocytic-type NADPH oxidase or antioxidant enzymes that interfere with the formation of reactive oxygen species in myelomonocytic cells. In general, reducing the inflammatory response in blood vessels caused in the body by inflammatory myelomonocytic cells may help reduce the incidence of complications of cardiovascular diseases triggered by hypertension (Radaeva and Simbirtsev 2018; Steven et al. 2019).

In patients with EAC and LVMH, compared with the comparison group, the oxygen-dependent activity of neutrophils is activated (by 75% higher value of the NBT-test before stimulation and by 30% higher after stimulation with zymosan), whereas their phagocytic activity decreases (the phagocytic index is reduced by 18%) (Table 2). In patients with EAH and asymptomatic atherosclerosis in blood, the value of the NBT-test before stimulation increases to a lesser extent (by 41%), and in patients with EAH and CKD, compared with the 1st and 2nd groups of patients, the phagocytic index remains at the level of the control group and the NBT-test indicator increases before stimulation to a lesser extent (Table 2).

In the patients with EAH of the 1st group (LVMH) in blood serum, there were increased concentrations of TNFα (2 times), IL-6 (by 37%), IL-8 (2.3 times), IL-10 (6.4 times), IL-1Ra (3 times), C3 (by 57%), C4 (by 28%), C5 (by 20%), and C5a (by 45%), while the concentration of the C5a-component of the complement system decreased (by 27%) (Table 2).

In the patients with EAH of the 2nd group (asymptomatic atherosclerosis), there was a greater increase in the levels of TNFα, IL-10, IL-1Ra, C3, C4, and C5 in blood serum.

In the patients with EAH of the 3rd group, compared with the 1st and 2nd groups, there are increased concentrations of IL-10 (13.6 times higher than in the control group) and the C5a-component of the complement system (2.7 times higher than in the group comparison), while in contrast to the 2nd group of patients with EAH, the concentration of factor H is higher (by 45% from the level of the comparison group). At the same time, in this group of patients with EAH, the concentrations of C3 and C4 in the blood serum remain at the level of the control group (Table 2).

Changes in innate immunity indices in patients with essential arterial hypertension are differentiated depending on the affected target organ: heart (left ventricular myocardial hypertrophy), vessels (asymptomatic atherosclerosis), and kidneys (chronic kidney disease). The largest changes in the functional and metabolic activities of peripheral blood

**Table 2. Indices of Innate Immunity in Patients with Essential Arterial Hypertension on the Background of Antihypertensive Pharmacotherapy (M ± m)**

| Characteristic before/after antihypertensive therapy | Control group (N = 24) | Patients with essential arterial hypertension | 1st group with LVMH (N = 33) | 2nd group with asymptomatic atherosclerosis (N = 37) | 3rd group with chronic kidney disease (N = 35) |
|------------------------------------------------------|------------------------|---------------------------------------------|-------------------------------|-----------------------------------------------|-----------------------------------------------|
| Phagocytic index, %                                   | 81.5 ± 4.1             | 67.2 ± 4.2*                                | 75.6 ± 6.6*/                  | 84.6 ± 6.4*/                                  |
| Phagocytic number, n                                  | 7.8 ± 0.5              | 7.6 ± 0.6*                                 | 7.5 ± 0.6/                   | 7.8 ± 6.5/                                   |
| NBT-test before stimulation, %                        | 7.2 ± 0.5              | 12.6 ± 1.1**                              | 10.2 ± 1.1*/                 | 8.5 ± 0.6*/                                  |
| NBT-test after stimulation, %                         | 7.2 ± 0.5              | 11.9 ± 1.2                                 | 10.5 ± 1.1                   | 8.2 ± 0.7                                    |
| TNFα, pg/ml                                           | 3.4 ± 0.2              | 51.4 ± 0.4                                 | 9.0 ± 1.0                    | 6.1 ± 0.6                                    |
| IL-8, pg/ml                                           | 4.6 ± 0.3              | 10.6 ± 0.9**                               | 8.9 ± 0.8*                   | 5.2 ± 0.4**                                  |
| IL-6, pg/ml                                           | 5.7 ± 0.4              | 9.1 ± 1.0                                  | 7.1 ± 0.6*                   | 5.1 ± 0.5                                    |
| IL-10, pg/ml                                          | 0.9 ± 0.1              | 6.8 ± 0.5*                                 | 6.5 ± 0.6*                   | 12.3 ± 0.9**                                 |
| IL-1Ra, pg/ml                                         | 220.1 ± 22.5           | 652.3 ± 81.1**                             | 1002.3 ± 126.4**             | 746.3 ± 65.1**                               |
| C3, pg/ml                                            | 116.2 ± 8.1            | 87.4 ± 8.1*                                | 98.3 ± 6.1*                  | 91.8 ± 8.1*                                  |
| C3α, ng/ml                                           | 65.0 ± 5.3             | 102.1 ± 8.7**                              | 136.6 ± 12.8**               | 56.6 ± 4.5**                                 |
| C3α, ng/ml                                           | 46.3 ± 3.7             | 98.3 ± 6.1*                                | 140.2 ± 13.7                 | 75.7 ± 5.1                                   |
| C3α, ng/ml                                           | 42.9 ± 4.1             | 47.6 ± 4.1*                                | 48.6 ± 3.9                   | 41.2 ± 3.9*                                  |
| Factor H, ng/ml                                       | 220.2 ± 18.7           | 275.2 ± 26.7**                             | 152.3 ± 13.6**               | 321.1 ± 25.1**                               |
| C5a-inhibitor, ng/ml                                  | 28.8 ± 2.1             | 30.1 ± 2.7*                                | 26.3 ± 2.2*                  | 25.4 ± 2.1*                                  |

*Note: NBT-test – nitro blue tetrazolium reduction test; TNFα – tumor necrosis factor alpha; IL-1Ra – receptor antagonist IL-1; LVMH – left ventricular myocardial hypertrophy; *a, *b, *c – significant differences between the means (p < 0.05); a – in relation to the indicators of the control group, b – in relation to the indicators of the 1st group of patients, c – in relation to the indicators of the 2nd group of patients; *a – the indicators were corrected in relation to the indicators of the control group; ** – indicators were normalized in relation to indicators of the control group.
neutrophils, the concentrations of cytokines and the activity of the complement system are observed in the group of patients with EAH and LVMH, whereas the smallest disturbances in the studied parameters of innate immunity take place in patients with EAH and CKD.

Prescription of perindopril and amlodipine to patients of the 1st group of patients with EAH (LVMH) reduces serum concentrations of TNF, IL-6, IL-1Ra, C5a, and C3c-components of the complement system compared to their levels before admission to hospital, but not to the level of the control group (Table 2).

Against the background of antihypertensive therapy with perindopril and amlodipine in patients of the 2nd group of patients with EAH (asymptomatic atherosclerosis), the concentration of C5a completely normalizes, and the concentrations of IL-8, IL-6, IL-10, and IL-1Ra decrease, while the level of factor H increases, but not to the level of the control group (Table 2).

In patients with EAH of the 3rd group (CKD), the administration of perindopril and amlodipine made it possible to reduce the concentrations of IL-10, C5a, and IL-1Ra in the blood serum not to the level of the control group and even further to increase the level of the C5a-component of the complement system (Table 2).

Antihypertensive pharmacotherapy with perindopril and amlodipine in patients with essential arterial hypertension has various corrective effects in relation to impaired indicators of innate immunity (cytokine link and activity of the complement system), depending on the nature of a target organ damage. Regardless of the damage to target organs (vessels, heart, or kidneys), antihypertensive therapy with perindopril and amlodipine does not affect the reduced functional and increased metabolic activities of peripheral blood neutrophils, which are the primary link in the innate immune response and initiate damage to target organs.

Evaluating the effectiveness of antihypertensive pharmacotherapy with perindopril and amlodipine in the correction of innate immunity indices in patients with essential arterial hypertension, depending on the affected target organ, the following was established:

Antihypertensive therapy in patients with EAH of the 1st and 3rd groups does not affect the number of altered indices of innate immunity, correcting (i.e. changing the level of the index towards the values of the control group), respectively, 33.3% and 20.0% of the studied indices, and in patients with EAH of the 2nd group it allowed to normalize (i.e. change the level of the index to the values of the control group) 6.6% of the indices (one studied index) and correct, but not to the level of the control group, 40.0% of the studied indices (Table 3). At the same time in the 1st group of patients with EAH after antihypertensive therapy, 80.0% of the studied parameters remained altered (i.e. different from the values of the control group), in the 2nd group – 66.7% of the parameters, and in the 3rd group – 53.3% of indices (Table 3).

**Conclusion**

Antihypertensive drugs of various classes and their combinations are currently causing doctors to effectively and safely lower blood pressure in patients with essential arterial hypertension. Nevertheless, there are variants of the course of arterial hypertension that do not correspond to the treatment being carried out, accompanied by cardiovascular complications against the background of progressive damage to target organs.

The obtained results of the study reveal the need and feasibility of further clinical studies of other classes of antihypertensive drugs and their combinations in the correction of not only blood pressure, but also innate immunity indicators in order to further prevent damage to target organs and the development of cardiovascular diseases and their complications.

In future clinical studies, it is necessary to fully clarify the role of indicators of not only congenital, but also acquired (adaptive) immunity in arterial hypertension in humans. When considering immunocorrective pharmacological agents for the treatment of patients with EAH, the risk of off-target immunosuppressive effects should be weighed against the risk of catastrophic cardiovascular complications resulting from persistent and/or recurrent arterial hypertension.

**Conflict of interests**

The authors declare no conflict of interests.

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