



CHARACTERISTIC OF CELL IMMUNITY IN ARTERIAL HYPERTENSION

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Abstract

The article discusses issues related to cardiovascular diseases, in particular, arterial hypertension and the characteristics of cellular immunity in arterial hypertension (AH). It is known that the presence of cardiovascular risk factors, such as hypertension, diabetes, hypercholesterolemia, smoking, disrupts the structural and functional state of endothelial cells. The author confirms that endothelial dysfunction, which persists for a long time against the background of sluggish inflammation, is accompanied by a decrease in the elasticity of the aorta and large arteries and an increase in the pulse wave velocity in patients with essential hypertension (HD). Analysis of personal data showed that men with hypertension are characterized by a deficiency of the initial content of T-lymphocytes with CD3 + and CD5 + receptors, which is significantly lower than the generally accepted physiological norms. In order to study the state of immunity in combination with indicators of the carbohydrate and lipid spectrum, the author carried out a comparative assessment of indicators depending on the degree of hypertension.

Keywords: vasoconstructions, endothelial, dysfunction, aorta, receptors, leukocytes, lipid spectrum, physiological norms.

Introduction

For several years scientists have been discussing the role of nonspecific inflammation and cell proliferation in the development of many cardiovascular diseases, in particular hypertension [Krivoshey I.V., 2013; Shavrin A.P., et al., 2006] Nonspecific inflammation is a significant component of arterial vascular lesions. At the same time, the results of clinical and experimental studies on the study of the relationship between the indicators of HB and AH are few and contradictory [Shavrin A.P., et al., 2006].

Endothelial dysfunction is characterized by the predominance of vasoconstriction, adhesion of leukocytes, and readiness for thrombus formation. The presence of cardiovascular risk factors, such as hypertension, diabetes, hypercholesterolemia, smoking, disrupts the structural and functional state of endothelial cells. Endothelial





dysfunction that persists for a long time against the background of sluggish inflammation is accompanied by a decrease in the elasticity of the aorta and large arteries and an increase in the pulse wave velocity in patients with hypertension [Golovach I.Yu., 2013; Zakirova A.N., et al., 2013]. Analysis of personal data showed that men with hypertension are characterized by a deficiency of the initial content of T-lymphocytes with CD3 + and CD5 + receptors, which is significantly lower than the generally accepted physiological norms, and a decrease in the concentration of T-cells was observed in $90.90 \pm 3.06\%$ and $100.00 \pm 3.20\%$ of people, respectively [Morozova O.S., et al., 2014].

Discussion and Conclusion

Deficiency of phagocytic protection (decrease in phagocytic number) was established in patients with hypertension which was observed in $53.33 \pm 2.11\%$ of people. Phagocytic defense is the main one, since phagocytosis initiates the development of a protective immune response of the body, providing the level of its activity and duration [Morozova O.S., et al., 20148]. In 55% of hypertensive patients with moderate and high risk, elevated concentrations of CRP and IL-6 are found in the blood, as well as a close relationship of these indicators with the level of blood pressure, which indicates the existence of HB in hypertension [Dmitriev V.A. et al., 2007; Zakirova A.N., et al., 2013]. Damage to target organs is a natural stage in the course of uncontrolled EAH, which leads to the development of cardiovascular complications (myocardial infarction, stroke, heart and renal failure) [Gavrilyuk E.V. et al., 2008; Mansimova O.V., et al., 2010].

The vascular endothelium regulates vascular tone, releasing vasoconstrictor and vasodilating mediators, which control not only vascular tone, but also the structure and permeability of the vascular wall, local processes of hemostasis, fibrinolysis and inflammation. With endothelial dysfunction, the balance of production of these biologically active substances is disturbed, as a result of which endothelium-dependent vascular relaxation decreases. The endothelin family belongs to one of the most powerful vasoconstrictor substances. At physiological concentrations, endothelin (ET) acts on endothelial receptors, causing the release of relaxation factors; at higher concentrations, it activates receptors on smooth muscle cells, stimulating persistent vasoconstriction, primarily at the level of microcirculation. At the same time, ET plays an important role in the mechanisms of development of acute and chronic disorders of cerebral circulation, ischemic heart disease, myocardial infarction, cardiac arrhythmias, atherosclerotic vascular injuries, pulmonary and cardiac hypertension and other pathological processes [Kawanabe Y., et al., 2011]. It





is the main vasoconstrictor peptide hormone from the group of cytokines; its vasoconstrictor potential is 10 times higher than that of angiotensin II. Currently isolated and purified four isoforms of endothelin, consisting of 21 amino acid residues: ET-1, -2, -3 and -4 [Stepanova Yu.I., et al., 2013].

The detected increased expression of inflammatory markers in the arterial wall (IL-6, adhesion molecules IcAM-1, vcAM-1) proves that hypertension is accompanied by an inflammatory process at the vascular level, which accelerates the development of atherosclerosis. Relatively recently, the involvement of the pro inflammatory cytokine IL-17 in hypertension has been described. This cytokine is produced by CD4 +, CD8 + cells, neutrophils, and killer T cells.

It is known that IL-17 is important in the pathogenesis of psoriasis, rheumatoid arthritis, inflammatory diseases of the respiratory system and intestines. In the experiment, it was found that mice lacking this cytokine are incapable of maintaining a stable blood pressure level, in contrast to the control. It was found that the use of the cytokine IL-17, which activates RhoA / Rho kinase, can reduce endothelium-dependent vasodilation and cause an increase in systolic blood pressure in the experiment, and the introduction of antibodies neutralizing this cytokine into the bloodstream of laboratory animals is accompanied by normalization of blood pressure and restoration of the functional state of the endothelium.

In experimental conditions, it was found that the deficiency of IL-4, a cytokine with anti-inflammatory properties, can play a significant role in the development of hypertensive eclampsia. An important role in the formation of the pro-inflammatory phenotype of the vascular wall is played by the aforementioned nuclear factor for the correction of light chains, kappa of activated B cells (nF-KB), a protein complex that is a key regulator of gene expression in the cell's response to external, including immune, influences.

In order to study the state of immunity in combination with indicators of the carbohydrate and lipid spectrum, we carried out a comparative assessment of indicators depending on the degree of hypertension. There was a statistically significant increase in the absolute number of leukocytes up to 8.3 ± 0.2 in patients of group 2 versus control - 7.3 ± 0.32 ($P < 0.05$). Leukocytes, as the main representatives of the cellular link of immunity, usually increase with the development of an inflammatory process in the body. In the study, the revealed relative leukocytosis indicates the development of complications of the underlying disease, in our studies - complications of hypertension. At present, the morphofunctional aspects of various complications of hypertension, such as coronary artery disease, acute coronary circulation disorder, myocardial infarction, are known and disclosed. In clinical





practice, the complex mechanisms of the relationship between hypertension and metabolic changes in blood leukocytes have been little studied.

In recent years, ideas about changes in hemorrhagic parameters in hypertension have been further developed due to the increased attention of scientists to the issue of the role of leukocytes in the dynamics of blood flow in microvessels. It is believed that the role of leukocytes in determining the rheological properties of blood is determined by the following:

1. Increased leukocyte volume, exceeding the erythrocyte volume.
2. Relative leukocyte stiffness, i.e. its low deformability in comparison with an erythrocyte.
3. The ability of a leukocyte to adhere to the walls of blood vessels.

It is assumed that it is these features that determine the 2-3 times slower passage of the leukocyte through the glass capillary in comparison with the erythrocyte. Of particular importance in the rheology of blood in microvessels is the ability of leukocytes to adhere to the wall of blood vessels. It is believed that the phenomena of adhesion of leukocytes are the main cause of microcirculation disorders under various pathological conditions. At the same time, activated leukocytes synthesize and secrete various biologically active substances (metabolites of arachidonic acid, growth factors, proteases, reactive oxygen species, cytokines, etc.) that affect vascular permeability, vascular tone, chemotaxis, tissue damage, thrombosis, angiogenesis.

Leukocytes can also cause obstruction of the microvasculature at the site of ischemia and a further decrease in tissue blood flow [Zakirova A.N., et al., 2013]. Since the process of vascular remodeling is also influenced by the infiltration of the media of the vessel by inflammatory cells, as noted above, we can talk about the important, although to date, insufficiently studied role of leukocytes in the pathogenesis of hypertension. Scientists have found that acute increases in blood pressure in patients with hypertension are accompanied by the activation of blood leukocytes and a significant increase in the adhesive and aggregation properties of leukocytes in comparison with healthy people [Zakirova A.N., et al., 2013]. Activation of leukocytes contributes to damage to the endothelium, deterioration of the rheological properties of blood, activation of platelets and, ultimately, a violation of microcirculation [Zakirova A.N., et al., 2013].

Taking into account the abovementioned, the obtained reliable result on the increase in the level of leukocytes in patients of the 2nd group indicates the beginning of the development of metabolic disorders and damage to the vascular endothelium with impaired microcirculation. When studying the leukocyte formula, it is imperative to determine the relative number of lymphocytes, which are responsible for the full





functioning of cellular immunity (T-lymphocytes), humoral immunity (B-lymphocytes), as well as for the destruction of atypical cells (NK-lymphocytes).

The study of the relative and absolute concentration of the total pool of lymphocytes in hypertension also showed a statistically significant increase in patients of the 2nd group, against the control - $31.2 \pm 1.78\%$ and 2.3 ± 0.14 in $1 \mu\text{l}$, up to $38.1 \pm 0.9\%$ and 3.18 ± 0.06 in $1 \mu\text{l}$, respectively ($P < 0.05$).

It should be noted that the obtained result is statistically significant for the increase in the absolute number of lymphocytes in both groups of examination of patients with hypertension. At the same time, an increase in the absolute number of lymphocytes was found to 2.7 ± 0.08 in $1 \mu\text{l}$ with AH of the 1st degree and up to 3.18 ± 0.06 in $1 \mu\text{l}$ in the 2nd group, against the control values - 2.3 ± 0.14 in $1 \mu\text{l}$ ($P < 0.05$). And the relative concentration of lymphocytes in the 1st group had a tendency to increase - $35.0 \pm 1.38\%$, in the 2nd group it was significantly increased to $38.1 \pm 0.9\%$ versus the control values - $31.2 \pm 1.78\%$.

The obtained results of studying the leukoformula are as follows: relative and absolute lymphocytosis in patients with hypertension indicate concomitant chronic diseases (viral, bacterial, parasitic and allergic diseases) with hypertension. Consequently, the obtained results of studying the leukoformula of blood in patients with hypertension show, firstly, depending on the degree of hypertension in dynamics, leukocytes in the blood increase as a result of damage to the vascular endothelium and disturbance of microcirculation; secondly, the effect of concomitant chronic viral and bacterial diseases on the course of the underlying disease and the development of complications of hypertension has been proven.

Thus, given the importance of the influence of concomitant chronic bacterial and viral diseases on the course of hypertension, for early prevention of the development of complications of the underlying disease, dynamic study, analysis of the number of leukocytes and blood lymphocytes and timely treatment of viral-bacterial diseases, as well as the remediation of foci of chronic infection are necessary.

Analysis of the cellular composition of T-lymphocytes made it possible to determine the relative and absolute values of the subpopulations. It is known that the study of CD3 + - lymphocytes allows the identification of mature intact T cells. In a study in patients with grade 1 hypertension, a decrease in the relative number of CD3 + lymphocytes was found to $53.6 \pm 1.31\%$ and to $50.2 \pm 0.9\%$ in grade 2 hypertension ($P < 0.05$), in relation to the control values - $56.2 \pm 1.67\%$. The obtained result is statistically significant only in relation to patients of the 2nd group of examination and indicates a relationship with the severity of the course of hypertension. Consequently, a decrease in the level of CD3 + -lymphocytes indicates hyporeactivity



or immunological paralysis in hypertension of the 2nd degree. The absolute values of CD3 + lymphocytes in this case showed an increase to 1.59 ± 0.04 in $1 \mu\text{l}$ in patients with hypertension of the 2nd degree ($P < 0.05$), in relation to the control values - 1.29 ± 0.08 in $1 \mu\text{l}$.

At the same time, the patients of the 1st group showed a tendency to increase to 1.45 ± 0.05 in $1 \mu\text{l}$ of blood. Quantification of the subpopulation of CD3 + lymphocytes allows differential diagnosis of primary and secondary immunodeficiencies. Based on the analysis of a subpopulation of CD3 + lymphocytes, we were able to determine the nature of immunodeficiency. All that has been established confirms the conclusion that in dynamics, depending on the severity of hypertension, immunological paralysis is formed, which in turn contributes to the development of immuno-metabolic disorders and complications of hypertension.

In the diagnosis of the state of cellular immunity and antibody production, the number of CD4 + lymphocytes is of particular importance. It is known that CD4 + cells are functionally divided into two types of helper lymphocytes: 1st order T-helpers (Th1 cells) and 2nd order (Th2 cells). Different CD4 + T cells produce different sets of cytokines. Th1 cells (also called delayed-type hypersensitivity cells - DHC) are cytokines for the cellular immune response: interleukin 2 (IL-2), IL-3, IFN- γ , TNF-a, TNF-b, - among which a discriminate cytokine is IFN- γ . Th2 secrete a set of cytokines necessary for the humoral immune response: IL-3, 4, 5, 6, 10, 13, TNF-b, among which the discriminate cytokine is IL-4.

To clarify the nature of the inflammatory process (viral, bacterial or allergic) in the patients of the examined groups, the quantitative and qualitative composition of CD4 + lymphocytes was analyzed.

There was a decrease in the relative percentage to $31.0 \pm 0.77\%$ in patients of the 1st group ($P < 0.05$), and to $29.6 \pm 0.47\%$ in patients of the 2nd group ($P < 0, 05$), against the control group - $34.3 \pm 0.91\%$, which is statistically significant in both groups and indicates a state of hypo reactivity and secondary immunodeficiency in hypertension. At the same time, the absolute value of CD4 + lymphocytes showed a significant increase to 0.94 ± 0.02 in $1 \mu\text{l}$ of blood with hypertension of the 2nd degree ($P < 0.05$), against the control group - 0.79 ± 0.05 in $1 \mu\text{l}$ of blood. And in patients with grade 1 hypertension, its value tended to increase to 0.83 ± 0.03 in $1 \mu\text{l}$ of blood. The result obtained showed the body's response to the inflammatory process.

Statistically significant results were obtained for CD8 + lymphocytes. A significant increase in both the relative and absolute values of CD8 + lymphocytes in hypertension was established, regardless of the severity of its course. In patients of the 1st group, the relative concentration increases to $25.3 \pm 0.58\%$ ($P < 0.05$), in the



2nd group to $29.4 \pm 0.46\%$ ($P < 0.05$), against the control group - $22.5 \pm 0.77\%$. The absolute values were also increased up to 0.68 ± 0.02 in $1 \mu\text{L}$ of blood ($P < 0.05$) with AH of the 1st degree and up to 0.93 ± 0.01 in $1 \mu\text{L}$ of blood in AH of the 2nd degree ($P < 0.05$), against control group - 0.51 ± 0.03 in $1 \mu\text{L}$.

The results obtained led to the conclusion that in patients with hypertension, an increase in the suppressor activity of lymphocytes is observed against the background of a decrease in killer activity. Consequently, with hypertension, depending on the severity, an immune-metabolic imbalance develops; against the background of immunological paralysis, a compensatory response to an acute and chronic inflammatory process is observed.

Today, the prognostic value of the ratio between CD4 / CD8 + lymphocytes (immune-regulatory index - IRI) is known. It is an indicator of the state of the immune system, which shows the changes taking place in the body. The study found a statistically significant decrease in IRI regardless of the severity of AH. At the same time, with AH of the 1st degree, IRI is reduced to 1.22 ± 0.03 ($P < 0.05$), and with AH of the 2nd degree - to 1.0 ± 0.03 versus control - 1.52 ± 0.04 ($P < 0.05$). All the results confirm the formation of a secondary immune deficiency state in hypertension, regardless of the severity. Since patients with hypertension have comorbid pathology and the body's response to the inflammatory process has been established, it was interesting to determine the level of CD16 + - lymphocytes responsible for antiviral immunity. They are also called natural killer cells (NK cells). CD16 + - lymphocytes have cytotoxic activity against various intracellular infections and tumor cells.

To study the state of antiviral and antibacterial immunity, the concentration of CD16 + - lymphocytes in the blood of patients with hypertension was determined. A significant increase in their absolute values was established in patients of the 1st and 2nd groups to -0.41 ± 0.02 in $1 \mu\text{L}$ and 0.59 ± 0.02 in $1 \mu\text{L}$, respectively, in relation to the control - 0.28 ± 0.03 in $1 \mu\text{L}$ of blood ($p < 0.05$), which confirms the body's response to inflammation of a viral and bacterial nature. In hypertension, the killer activity was significantly increased in patients of the 2nd group - $19.0 \pm 0.8\%$ versus control - $12.4 \pm 1.1\%$ ($p < 0.05$). And with AH of the 1st degree, the relative concentration of CD16 + lymphocytes tended to increase to $15.2 \pm 1.03\%$. This means that killer activity increases in hypertension, depending on the severity of hypertension.

To differentiate the stage of the inflammatory process, the level of CD25 + lymphocytes was analyzed, showing an early stage of inflammation. A statistically significant increase in the absolute values of CD25 + lymphocytes was revealed both in the 1st degree and in the 2nd degree of AH up to 0.58 ± 0.03 in $1 \mu\text{L}$ and 0.86 ± 0.02



in 1 μ l, respectively, against the control indicator - 0.41 ± 0.04 in 1 μ l ($p < 0.05$). At the same time, a higher, 2-fold increase in the absolute values of CD25 + lymphocytes in AH of the 2nd degree was revealed, which allows the conclusion that a more severe course of AH is accompanied by activation of the compensatory response of the organism. At the same time, the functional activity of CD25 + lymphocytes increases 1.5 times in AH of the 2nd degree to $27.2 \pm 0.93\%$ versus $18.1 \pm 1.29\%$ in the control ($p < 0.05$). A mild course of hypertension is accompanied by a tendency to increase the relative number of CD25 + lymphocytes to $21.6 \pm 1.34\%$.

The results obtained allowed us to conclude that in hypertension in patients with immune-metabolic imbalance, the absolute number of CD20 + lymphocytes increases 3.5 times ($p < 0.05$), CD25 + lymphocytes - 1.5 times ($p < 0, 05$), CD16 + lymphocytes by 2.1 times ($p < 0.05$), versus control values. AH in patients develops against the background of an immune-metabolic imbalance and is accompanied by the activation of compensatory anti-inflammatory responses of the body. Consequently, the compensatory anti-inflammatory reaction of the body in response to viruses, bacteria, allergens, parasites, intracellular infections and the risk factors established in the study over time contributes to the depletion of immunity, aggravation of the metabolic syndrome, predicts the development of immunological paralysis depending on the degree of hypertension. Over time, such a complex biological process undoubtedly leads to the formation of focal changes and tissue decay of internal organs with the formation of multiple organ failure and complications of hypertension.

Assessment of the state of cleansing the body from damaged, infected and old cells in hypertension showed a significant increase in both absolute and relative indicators of CD95 + - lymphocytes, regardless of the degree of hypertension. With AH of the 1st degree, the concentration of CD95 + - lymphocytes increases to $26.9 \pm 1.35\%$ ($p < 0.05$), with AH of the 2nd degree, up to $28.4 \pm 1.07\%$ ($p < 0.05$), against the control - $21.0 \pm 1.38\%$ and has a statistical significance. And the absolute value of CD95 + - lymphocytes increases to 0.72 ± 0.03 in 1 μ l with AH of the 1st degree and to 0.9 ± 0.03 in 1 μ l in relation to the control - 0.48 ± 0.04 in 1 μ l ... The analysis of apoptosis showed a 2-fold increase in the absolute number of CD95 + - lymphocytes in AH of the 2nd degree, and in AH of the 1st degree it was increased by 1.5 times.

As a result, the results obtained indicate the activation of the process of apoptosis in hypertension against the background of immune-metabolic imbalance and secondary immunodeficiency. AH often occurs against the background of an immune-metabolic imbalance and is accompanied by the activation of compensatory anti-inflammatory responses of the body. At the same time, with the aggravation of the metabolic syndrome in hypertension, a decrease in immunity occurs. The development of



immunological paralysis depends on the degree of hypertension. The established immune-metabolic imbalance, depending on the length of time and the severity of hypertension, contributes to the formation of focal changes in cardiovascular tissue and multiple organ failure, in general, as a complication of hypertension.

References

1. Gavriilyuk E.V., Sheban L.I., Konoplya E.N., Mikhin V.P. Immune disorders in patients with ischemic heart disease. // *Allergology and Immunology*. - 2008. -- 9 (1). - P.41
2. Golovach I.Yu. Left ventricular hypertrophy and arterial hypertension: new pathogenetic and therapeutic concepts. *Medicine today*. 2013; 460 (9): 3-5.
3. Dmitriev V.A. et al. C-reactive protein and interleukin-6 in target organ damage in the early stages in hypertensive patients. // *Cardiological Bulletin*. - 2007. - XIV (2). - S. 55–61
4. Zakirova A.N., Fatkullina E.Z., Zakirova N.E. Profibrotic factors and remodeling of the left ventricular myocardium in women with arterial hypertension and metabolic syndrome. // *Medical Bulletin of Bashkortostan*. - 2013. -- 8 (3). - C.44–48
5. Kozlovsky, V.I., Akulenok A.V. Leukocyte activation, role in damage endothelium and the development of cardiovascular pathology // *Vestnik VSMU*. - 2005. - T. 4, no. 2. - S. 5-13.
6. Krivoshey I.V. Study of cytokine gene polymorphism in hypertensive patients. // *Medicine and education in Siberia*. - 2013. - 6: - C.42–44
7. Mansimova O.V., Gavriilyuk E.V., Konoplya E.N. Immunomodulatory and cardioprotective effects of mildronate and mexicor in acute coronary syndrome. // *System analysis and control in biomedical systems*. - 2010. -- 9 (1). - S. 191-194.
8. Morozova O.S., Popovskaya E.V. Immunological reactivity in men with hypertension in the Arctic. // *Bulletin of the Ural Medical Academic Sciences*. - 2014. – 2. – P. 86–88.
9. Stepanova Yu.I., Gonchar I.A. Endothelin-dependent effects in cerebrovascular pathology of ischemic genesis // *Medical News*. - 2013. - No. 10. - P. 12-18.
10. Shavrin A.P., Golovskoy B.V. Study of the relationship of markers of inflammation with blood pressure level. // *Cytokines and inflammation*. - 2006.- 5 (4). - C.10–12
11. Kawanabe Y., Nauli S.M. // *Cell. Mol. Life Sci*. 2011. Vol. 68 (2). - P.195-203.

