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Formation of Hemostasiopathy in Arterial Hypertension and Insulin Resistance

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Abstract

The long existence of arterial hypertension in combination with insulin resistance inevitably impairs the functioning of all elements of hemostasis. In these circumstances, there is a weakening of the vascular control of platelet aggregation, hemocoagulation and fibrinolysis. This is based on the decreased production in the blood vessels of substances with thromboresistant properties, increasing the permeability of the endothelium to macromolecules, accumulation in the vascular wall lipoproteins, adhesion of platelets and leukocytes. For patients with hypertension and insulin resistance characteristic of platelet activation, leading to increased circulating blood platelets with a modified surface structure and their aggregates. It caused such patients, a high content in platelets of biologically active substances and the increase in the number of different receptors on their surface, including fibrinogen. The combination of hypertension with insulin resistance inevitably impairs the functioning and coagulation component of hemostasis in the blood increases the content of fibrinogen, VII, VIII, IX coagulation factors, von Willebrand factor by lowering the activity of antithrombin III, protein C and protein S.

Keywords: Hemostasis; Hypertension; Insulin resistance; Hyperinsulinaemic; Impaired glucose tolerance

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Introduction

In recent years, cardiologists have shown a strong interest in studying the combination of arterial hypertension (AH) with various elements of the metabolic syndrome. This is due to the increasing frequency of their occurrence in developed countries [1-3] with the prevalence of hyperinsulinemia and impaired glucose tolerance are particularly high and tend to gradually increase [4]. The main link of their link is insulin resistance, which has been repeatedly confirmed in a large number of multicenter studies [5]. As a rule, the development of a violation of glucose tolerance in patients with AH is preceded by hyperinsulinemia [6]. The reasons for the onset of insulin resistance are not fully understood. It is assumed that there is a common genetic defect that promotes development and insulin resistance and AH [7-9].

The prolonged existence of AH in combination with insulin resistance ultimately leads to the development of a complex of metabolic, hormonal and clinical disorders that are risk factors for the development of cardiovascular diseases, which are based on insulin resistance and compensatory hyperinsulinemia, which are the basis of MS formation [10,11].

The combination of hypertension and impaired glucose tolerance has been known for a long time. As early as 1922, Georgii Fyodorovich Lang pointed out the relationship between hypertension and metabolic disturbances, while still young at that time his students Grotelle et al. [12] noted in hypertensive patients a sufficiently high frequency of the pathology of carbohydrate metabolism.

Subsequently, it was found that the basis for lowering the sensitivity to insulin may be a violation of its ability to suppress the production of glucose in the liver and/or stimulate the capture of glucose by peripheral tissues. Since 75-80% of glucose is consumed in skeletal muscles in healthy people, it became clear that the main cause of insulin resistance is the disturbance of insulin-stimulated glucose utilization in skeletal muscles [13]. It has been found that disorders leading to insulin resistance can occur at several levels: pre-receptor (abnormal insulin), receptor (decrease in the number or affinity of receptors), glucose transport level (decrease in the number of GLUT4 molecules) and post-receptor (signal transduction and phosphorylation) [14,15]. Anomalies of the insulin molecule are rare and have no clinical significance. The density of insulin receptors can only sometimes be reduced in patients with insulin resistance by the mechanism of negative feedback against hyperinsulinemia [16]. There are serious reasons to believe that the main defects that determine insulin resistance are localized at the post-receptor level. They are not the same for different patients, but the acquired disorders in the body, in particular, in the hemostatic system, are important for the manifestation of existing genetic defects [17]. The presence of these disorders can greatly increase the risk of thrombosis, which shortens the duration of the life of patients. In this connection, the goal is to summarize the available information on haemostasis disorders in hypertension and insulin resistance.

Long-existing hyperinsulinemia negatively affects the state of the vessels largely due to stimulation of the development of various growth factors in them, which leads to intensive proliferation and migration

to the intima of arterial smooth muscle cells. This is accompanied by excessive production of an inhibitor of plasminogen activator-1. All this contributes to vascular remodeling and accelerates the development of atherosclerosis [18,19]. A definite value in the acceleration of these processes in the vascular wall with hypertension with insulin resistance is the stimulating effect of excess insulin on the synthesis of collagen in fibroblasts [20]. It has also been established that the thickness of the intima-media complex of arteries and the number of circulating blood in the blood desquamated endotheliocytes in patients with AH with insulin resistance are closely correlated with an increase in insulin levels [21,22].

The presence of persons with arterial hypertension and insulin resistance inevitably reduces the response of the vessels to vasodilator and strengthens it on vasoconstrictor effects. These effects can be caused not only by changes in the metabolism and architectonics of the vascular wall, but also by negative effects on the vascular endothelium and platelets, accompanied by increased production of endothelin, thromboxane A2, prostaglandin F2α, and a decrease in prostacyclin synthesis [23,24]. In this connection, the effect of excess insulin on the synthesis of lipids, not only in the liver, but also directly in the vascular wall, is very pathogenetically important [25].

The influence of insulin resistance and hyperinsulinemia on the vascular tone and level of arterial pressure was studied in sufficient detail. Insulin has a normally protective effect on blood vessels due to the activation of phosphatidyl-3-kinase in endothelial cells and micro vessels, induces endothelial NO synthase gene expression, enhances NO release by endothelial cells and insulin-induced vasodilation. At the same time, with chronic hyperinsulinemia, pathological vasospastic mechanisms are triggered, leading to AH progression [26,27].

Normally, the vascular endothelium has a leading role in the clear modulation of the entire haemostatic potential. With hyperinsulinemia in the vascular endothelium, persistent metabolic disorders occur leading to the development of severe hemostasiopathy [27]. So, with insulin resistance, there is often a decrease in the blood of substances of vascular origin with antiaggregatory activity, compounds limiting vasospasm and coagulation and enhancing fibrinolysis. The leading factors contributing to the disruption of vascular hemostasis in these patients are elevated blood pressure, hyperinsulinemia, as well as the onset of hypercholesterolemia and hypertriglyceridemia. Their combination promotes the acceleration of the development of atherosclerotic plaques, the death of endotheliocytes and an increase in the production in the vascular wall of von Willebrand factor. The effect of over-listed factors is realized through activation of lipid peroxidation in the bloodstream [28], which in itself is able to weaken the antithrombotic abilities of the vascular wall in normal and pathological conditions [29,30]. First of all, this is manifested by a decrease in the formation in the vascular endothelium of substances that provide vasodilation, inhibiting the adhesion and aggregation of platelets that inhibit the proliferation of smooth muscle cells [31]. In addition, under conditions of AH with insulin resistance, the endothelium itself begins to produce free radicals that cause a deepening of its dysfunction. This was confirmed by morphological studies that found degenerative changes in endothelial cells [32].

It becomes clear that endothelial dysfunction is an important factor that significantly worsens the prognosis and aggravates the course of hypertension due to thickening of the middle shell of the vessels, a decrease in their lumen, an increase in the degree of vasoconstriction due to the growth of total peripheral vascular resistance [33,34]. The vicious circle closes: violations of hemodynamics in hypertension are very active in changing the structure and function of the endothelium, which further increases hypertension [35]. The emerging imbalance between substances produced in the endothelium with thrombogenic and thrombotic resistance promotes an increase in its permeability for macromolecules, accumulation of lipoproteins, adherence to it of platelets and leukocytes [36-38]. The most likely cause of this is the weakening of the vascular enzymatic system of arachidonic acid metabolism and the production of prostacyclin in endotheliocytes under the influence of free radical oxidation, which is activated as the body ages, develops hypertension and metabolic disorders [39,40]. Also, with AH with insulin resistance, the ability of endothelial cells to release NO decreases, leading not only to weakening of vasodilation but also to the process of remodeling the vascular wall, but also to weakening the inhibition of adherence and aggregation of platelets and monocytes, atherogenesis and thrombosis [41,42]. This aggravates unfavorable changes in the microcirculation system, which, with hypertension with insulin resistance, is often associated with a decrease in the diameter of the micro vessels and the violation of blood outflow. At the same time micro vessels are transformed into passive conductors of blood flow, which leads to its redistribution according to the principle of least resistance. The emerging situation causes a shunting of blood flow, as a result of which a lack of blood flow to the metabolic tissue structures is formed [43]. Negative changes in the diameter and structure of the arterial wall, as well as the rate of blood flow, lead to a violation of laminar flow and increased pressure on the vascular wall, which directly activates platelets, which occupy an important place in the cell-humoral interaction of the hemostatic system [44,45].

Data from the literature indicate an increase in the functional activity of platelets already in the early stages of hypertension, manifested by an increase in sensitivity to aggregation inducers, an increase in their adhesive, aggregation, and secretory properties [32,37]. In patients with AH and insulin resistance, these platelet changes closely correlate with the magnitude of systolic and diastolic arterial pressure and the severity of hyperinsulinemia. Electron microscopic study of platelets of AH patients with insulin resistance revealed the presence among them of various morphological forms, caused by their increased activation. At the same time, the most characteristic for them is the echinocyte change in shape. Also in hypertensive patients with insulin resistance, there is an increase in circulating blood of various sizes of platelet aggregates, the number of which closely correlates with the frequency of thrombotic complications [46].

With AH with insulin resistance in circulating platelets, the levels of chemokines, cytokines, growth factor, proteins, fibrinogen, von Willebrand factor, the 4th platelet factor and thromboglobulin are very often increased. Moreover, in the platelets, the content of dense granules accumulating small molecules-Ca2+, ADP, ATP, biogenic amines (serotonin, catecholamines, etc.) can also increase [47]. In addition, under these conditions, the functioning of platelet-localized receptors for collagen, thrombin, ADP, catecholamines, serotonin, thromboxane A2, platelet activating factor, immunoglobulin Fc fragment, complement components, insulin, endothelin, adrenoreceptors can significantly increase from the initial stimulus, to the strengthening of their universal response - aggregation [15]. At the same time, the number of glycoproteins IIb/IIIa, which play an important role in aggregation for any stimuli, is significantly increased on platelets of hypertensive patients with insulin resistance. The practical significance of these changes was confirmed by the prospective study PROCAM, conducted among men aged 40-60 years, who showed that the

increased risk of cardiovascular disease in hypertension with insulin resistance largely depends on the imbalance in the system of platelet hemostasis [48,49].

The hyper function of thrombocytes, which comes with AH with insulin resistance, is also associated with the activation of enzyme systems in them, which strengthens aggregation, which ultimately increases the risk of thrombotic complications. This is also caused by an increase in the content of magnesium platelets in the cytoplasm, an increase in its pH and an increase in the sensitivity of platelets to arachidonic acid [49].

In patients with hypertension with insulin resistance, in contrast to healthy individuals, there is a high degree of correlation between the increase in calcium level in platelets under the influence of aggregation inducers (ADP and platelet activating factor), the thickness of the wall of the left ventricle and the level of arterial pressure. This is due to the development of abnormalities in the structure of the plasma membrane of platelets, changes in the work of sodium, potassium, and calcium pumps that develop with hypertension and deeper as the duration of its duration increases [50].

In view of the fact that Ca^{2+} ions directly participate in the realization of phosphoinositol, prostaglandin-thromboxane, tyrosine kinase, and phospholipase pathways of platelet activation, its excessive intracellular content inevitably leads to AH with insulin resistance to enhance their aggregation. The rise in these conditions of Ca^{2+}level in platelets, stimulated by various inducers, correlate with the severity of their aggregation activity and the degree of the release reaction. Disruption of the trans-membrane exchange of Na^{+} in the blood plates helps to reduce the normal capture of serotonin from the peripheral blood by platelets, since this process is highly Na^{+}-dependent, which can lead to an increase in the concentration of aggregation inducers in the blood plasma of AH patients with insulin resistance and additional platelet stimulation [51,52].

The combination of hypertension with insulin resistance inevitably disturbs function and coagulation component of hemostasis system. So, in hypertension with insulin resistance detected elevated levels of fibrinogen in plasma, which is strongly positively correlated with blood pressure. The degree of this dependence varies somewhat for men and women [53].

The level of synthesis of VII,VIII, IX coagulation factors is normally clearly genetically determined [54] closely correlates with hypertension with insulin resistance with an increase in arterial pressure and the duration of the violation of glucose tolerance [55]. Even with a high normal arterial pressure with hyperinsulinemia, a significant increase in the activity of VIII and XII coagulation factors and a decrease in activated partial thromboplastin time are found [56]. With the formation of hypertension with insulin resistance, an even more pronounced increase in the amount of fibrin monomers in the blood, the activity of VIII and VII clotting factors, closely correlated with the systolic blood pressure [57]. In addition, with AH with insulin resistance, there is often an increase in WF, which, however, may not be recorded in all cases because of the varying degree of endothelial damage. Also, with a long-term high blood pressure level under conditions of insulin resistance, a decrease in the activity of anti-thrombin III [55], protein C and protein S [55,58] can be noted.

A certain role in the formation of changes in the functioning of the anticoagulant and fibrinolytic blood systems in AH patients with insulin resistance is apparently played by sex hormones. Thus, in women with pre-menopausal hypertension, a significant increase in the activity of the level of the inhibitor of the tissue activator plasminogen-1, which closely correlates with a decreased level of estradiol, is recorded. In this case, the increase of this inhibitor in men with AH and insulin resistance occurs, as a rule, with a low content of testosterone in their serum [59].

Morning rise in blood pressure in patients with AH and insulin resistance, which is an independent prognostically important factor in the development of cerebral stroke in the morning hours [9], is associated with pronounced activation of coagulation, increased viscosity, reduced fibrinolytic blood properties and platelet hyperactivation. Also at the heart of the danger of a vascular catastrophe in this contingent lies the onset of instability of atherosclerotic plaques and the multifocality of endothelial alteration [53], the increased susceptibility to which is largely genetically determined [60].

Conclusion

A systematic study of hemostasis dysfunctions in patients with arterial hypertension with elements of the metabolic syndrome is a very promising and practically sought-after direction, which is rightly given great attention. In connection with the important role of hemostasis in the regulation of vital body functions, it can be assumed that further elucidation of the state of its mechanisms in arterial hypertension with insulin resistance can lead to the development of new methods for the prevention and treatment of cardiovascular disorders.

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