Effect of a combination of arterial hypertension and insulin resistance on hemostasis activity

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ABSTRACT

Lasting existence of arterial hypertension in combination with insulin-resistance inevitably disturbs functioning of all the hemostasis elements. Weakening of vascular control over platelets' aggregation, hemocoagulation and fibrinolysis is noted in these conditions. Production lowering of substances with thrombo-resistant properties in vessels, increase of endothelium permeability for macromolecules, accumulation of lipoproteins in vascular wall, adhesion of platelets and leucocytes to it lie in the basis of it. Patients with arterial hypertension and insulin-resistance are characterized by platelets' activation leading to the increase of circulating platelets with changed surface structure in blood and their aggregates. In the given category of patients it is caused by the increased content of biologically active substances in platelets and number increase of different receptors on their surface, including fibrinogen. Combination of arterial hypertension with insulin-resistance inevitably disturbs functioning of coagulative component of hemostasis system – the content of fibrinogen, VII, VIII, IX factors of coagulation, von Willebrand's Factor increases in blood at activity lowering of antithrombin III, protein C and protein S. The complexity of hemostasiopathy in arterial hypertension and insulin resistance dictate the need to continue the search for therapeutic approaches which can balance thrombophilia and simultaneously affect all the components of the hemostatic system.

Keywords: hemostasis, arterial hypertension, insulin-resistance, hyperinsulinemia, disturbance of tolerance to glucose.


INTRODUCTION

Last years cardiologists all over the world are noted to have persistent interest in studying the combination of arterial hypertension (AH) with different elements of metabolic syndrome. It is caused by growing frequency of their occurrence in developed countries.¹,² besides, prevalence of hyperinsulinemia (HI) and disturbance of tolerance to glucose (DTG) is especially high and has a tendency to gradual increase.³ The basic connecting them link is insulin-resistance (IR) what was multiply confirmed in numerous manycenter researches.⁴ As a rule, development of DTG in patients with AH is preceded by HI. There is a supposition about the existence of the common genetic defect promoting the development of both IR and AH.⁵

It is well known that hypertension, especially in combination with IR, adversely affects the functional parameters of the internals, significantly worsens blood rheology, especially in the microcirculation basin. Lasting existence of AH in combination with IR finally leads to complex development of metabolic, hormonic and clinical disturbances which are risk factors of cardio-vascular diseases’ development.⁶ Rapidly progressing hemostasiopathy is a very important mechanism of vascular disorders’ development at AH and IR. It has a complex character in this category of patients and inevitably leads to the development of thrombophilia. This state is the main cause of high frequency of thromboses of any localization, sometimes with fatal consequences.⁷

Modern medicine is continuously looking for ways to reduce cardiovascular mortality, including hypertension burdened by IR. In this regard, it becomes urgent to summarize the main reliable information about the disturbances of platelet, vascular and coagulation components of hemostasis in this category of patients. It can help to chart new directions for future research and find options for eliminating haemostasiopathy in hypertension with AI. Taking into account the fragmented information about haemostatic changes in AH and IR, the aim is to summarize the available information about
disorders in the hemostatic system at hypertension aggravated by IR and highlighten the most clinically significant of them in respect to the prognosis for this category of patients.

**Thrombocyte dysfunction in arterial hypertension and insulin-resistance**

Literature data are evidence of strengthening of platelets’ functional activity at already early stages of AH manifesting itself by increased sensitivity to aggregation inductors, strengthening of their adhesive, aggregative and secretory properties. In patients with AH and IR these changes of platelets are closely correlated with the value of systolic and diastolic blood pressure and evidence of HI. Electronic microscopic study of platelets of patients with hypertension and IR revealed number increase of their activated forms. It turned out that the most characteristic feature for this category of patients is the echinocyte change in the form of platelets in the bloodstream. Patients with AH and IR are also detected to have some increase of circulating in blood platelet aggregates of various sizes. Their quantity is closely correlated with frequency of thrombotic complications.

The levels of chemokins, cytokines, factor of growth, proteins, fibrinogen, von Willebrand’s Factor, the 4th thrombocyte factor and thromboglobulin are very often increased in circulating platelets at AH with IR. The content of dense granules accumulating fine molecules – Ca^{2+}, ADP, ATP, biogenic amines (serotonin, catecholamines and others), also increased in platelets of these patients at that.

Besides, functioning of localized on platelets’ membranes receptors to collagen, thrombin, ADP, catecholamines, serotonin, thromboxane A_2, factor of platelets’ activation, Fc-fragment of immunoglobulins, components of complement, insulin, endothelin and adrenoreceptors can significantly increase in these conditions and lead, irrespective of the initial stimulus, to strengthening of their universal response – aggregation. There is essential number rise of glycoproteins IIb/IIIa playing an important role in aggregation on any stimuli, on platelets of patients with AH and IR at that. Practical significance of given changes was confirmed by data of prospective investigation PROCAM which was conducted among men of 40-60 years of age. It detected that increased risk of cardio-vascular diseases’ development at AH with IR mostly depended on imbalance in the system of platelet hemostasis.

The hyperfunction of platelets which comes together with hypertension, is also associated with the activation of enzyme systems, which enhance and realize their aggregation. If these changes are superimposed on the age-specific increase of platelet aggregation, the risk of thrombotic complications significantly increases. It is probably mostly due to the content increase of magnesium platelets in the cytoplasm, the increase of its pH and the increase of platelets’ sensitivity to arachidonic acid.

Patients with AH and IR (as opposed to healthy persons) are noted to have strong correlate connection between the increase of calcium level in platelets under the impact of aggregation inductors (ADP and factor of platelets’ activation), thickness of left ventricles wall and levels of blood pressure and insulin. It is explained by progressively increasing disturbances in the structure of platelets’ plasmatic membrane, as well as changes in the work of its sodium, potassium and calcium pumps.

The excess level of Ca^{2+} ions in the cytoplasm of platelets at hypertension with IR enhances the phosphoinositol, prostaglandin-thromboxane, tyrosine kinase, phospholipase pathways of platelet activation, inevitably leading to the increase of their aggregation. The level increase of Ca^{2+} in platelets in these conditions correlates not only with the degree of their aggregation activity, but also with the degree of the release reaction. The development of disruption of the transmembrane exchange of Na+ in the blood plate contributes in patients with AH and IR to the decrease of normal platelet capture of serotonin from the peripheral blood. It leads to concentration increase of this inductor of aggregation in the plasma of patients with AH and IR, causing additional stimulation of platelets.

Thus, the development of hypertension with IR leads in patients to the rapid increase of platelet hemostasis activity. The increase of functional readiness of receptor and postreceptor mechanisms of platelets in these patients dictates the necessity of constant control of platelet activity in them. In future studies, it is necessary to solve the problem of the most preferable disagregant for them and to determine the indications for prescribing two disagregants simultaneously.

**Vasopathy in arterial hypertension and insulin-resistance**

It is proved that a long-term IR affects negatively the state of the vessels in many respects due to the stimulation of the development of various growth factors in them. It leads to intensive proliferation and migration to the intima of arterial smooth muscle cells. This situation contributes to vascular remodeling and accelerates the development of atherosclerosis. Stimulating influence of insulin surplus on collagen synthesis in fibroblasts plays definite role in acceleration of these processes in vascular wall at AH with IR. It leads to disturbance
of vascular control over hemostasis and to unbalancing of all its mechanisms. The existence of IR and HI in persons with arterial hypertension inevitably decreases the response of vessels on vasodilators and strengthens it on vasoconstrictive impacts. Given effects can be conditioned by not only changes of metabolism and architectonics of vascular wall but also by negative impacts of activated platelets.\textsuperscript{18,19}

The influence of IR and GI on the vascular tone and level of arterial pressure was studied in detail. Insulin has a normally protective effect on blood vessels through the activation of phosphatidyl-3-kinase in endotheliocytes. It also induces endothelial NO synthase gene expression, enhances NO synthesis, and provides insulin-mediated vasodilation. At the same time, at chronic HI pathological angiospastic mechanisms are started up and lead to progression of AH.\textsuperscript{20}

Persistent metabolic disorders occur at AH with IR in the vascular endothelium leading to the development of severe hemostasopathy. So, at hypertension and IR, there is often a decrease of vascular antiplatelet agents in blood. These are compounds that inhibit vasospasm and coagulation, and substances that enhance fibrinolysis. The leading factors contributing to the violation of vascular hemostasis in these patients are high blood pressure, hyperinsulinemia, as well as the developing hypercholesterolemia and hypertriglyceridemia. Their combination promotes acceleration of atherosclerotic plagues' development, death of endotheliocytes and production rise of von Willebrand's Factor in vascular wall. The impact of the listed factors is realized through activation of lipids' peroxidation in bloodstream.\textsuperscript{21} Besides, in conditions of AH with IR endothelium itself begins to produce free radicals causing deepening of its dysfunction. It was confirmed by morphological investigations which discovered degenerative changes in endothelial cells.\textsuperscript{22,23}

It becomes clear that endothelial dysfunction is an important factor which essentially worsens prognosis and burdens the course of AH and IR on behalf of thickening of vessels' middle coat, decrease of their lumen, degree increase of vasoconstriction owing to the growth of the common! peripheral resistance of vessels. “Vicious circle” is closed: disturbances of hemodynamics at AH and IR rather actively change the structure and function of endothelium what additionally rises blood pressure level.\textsuperscript{24} Forming imbalance between produced in endothelium substances with thrombogenic and thromboresistant properties promotes increase of its permeability for macromolecules, accumulation of lipoproteins, adhesion of platelets and leucocytes to it.\textsuperscript{25,26} Its most probable cause is weakening of vascular enzymatic system of arachidonic acid metabolism and prostacyclin production in endotheliocytes.\textsuperscript{27} It is aggravated by unfavorable changes in the system of microcirculation which are often connected at AH and IR with diameter decrease of afferent microvessels and disturbance of blood outflow. Microvessels at that are turned into passive conductors of bloodstream what leads to its redistribution according to the principle of the least resistance. Given situation causes shunting of bloodstream. Deficiency of blood inflow to metabolically important tissue structures is formed in the result of it. Negative changes of diameter and structure of arteries' wall, and also speed of bloodstream lead to the disturbance of bloodstream laminarity and the rise of pressure on vascular wall what directly activates platelets.\textsuperscript{28}

Thus, patients with AH and IR are characterized by severe vasopathy. It seems to be relevant in future studies to determine the most preferrable antihypertensive drugs for this category of patients according to their ability to reduce the severity of vasopathy and IR.

**Coagulopathy in arterial hypertension and insulin- resistance**

Combination of AH with IR inevitably disturbs functioning of coagulative component of hemostasis system. So, at AH with IR we detected content increase of fibrinogen in plasma which very positively correlates with the levels of blood pressure and insulin. At the same time, the degree of the given dependence can be the same in men and women.\textsuperscript{29}

Synthesis level of VII, VIII, IX factors of coagulation is closely correlated at AH and IR with AP rise and duration of DTG existence.\textsuperscript{30} Even at normal arterial pressure with HI we detected reliable activity rise of VIII and XII coagulation factors and reduction of activated partial thromboplastinic time. At formed AH and IR we described still more evident quantity increase of fibrin-monomers in blood, activity increase of VIII and VII factors of blood coagulation which closely correlate with indices of systolic arterial pressure. Some activity lowering of antithrombin III, protein C and protein S\textsuperscript{21} can also be noted at protractedly existing high level of AP in conditions of IR.

Definite role in the formation of changes in functioning of anticoagulative and fibrinolytic blood systems in patients with AH and IR is evidently played by sex hormones.\textsuperscript{31} So, women being in premenopause, are registered to have
reliable activity increase of the level of inhibitor of tissue activator plasminogen-1 which closely correlates with lowered level of estradiol. At the same time, the rise of the given inhibitor in men with AH and IR is met usually at low content of testosterone in their serum.53

Morning rise of blood pressure in patients with AH and IR, is an independent prognostically important factor of the development of cerebral stroke in the morning. It is associated with the activation of coagulation, increased viscosity and level decrease of plasminogen in blood.34 The risk of a vascular accident leading to disability in this category of patients is also based on the increase of α2-antiplasmin in blood, which can significantly weaken the fibrinolysis process.35,36

Thus, coagulopathy is characteristic for patients with hypertension and IR. It makes a tangible contribution to the development of thrombophilia in them. It remains unclear whether this category of patients needs to use anticoagulants or the decrease of blood pressure and weakened IR will lead to the balancing of coagulopathy.

CONCLUSION
Combination of AH with IR always disturbs functioning of hemostasis. It is manifested by weakening of vascular control over platelets’ aggregation, hemocoagulation and fibrinolysis. Production lowering of substances with thromboreistant properties in vessels, increase of endothelium permeability for macromolecules, accumulation of lipoproteins in vascular wall, adhesion of platelets and leucocytes to it lie in the basis of it. Patients with AH and IR are characterized by platelets’ activation leading to the increase of circulating in blood platelets with changed surface structure and their aggregates. Given patients have content increase of biologically active substances in platelets and number increase of different receptors on their surface. Combination of AH with IR inevitably disturbs functioning of coagulative component of hemostasis system – the content of fibrinogen, VII, VIII, IX factors of coagulation, von Willebrand's Factor rises in blood of these patients at activity lowering of antithrombin III, protein C and protein S. Further studying of hemostatic mechanisms’ state at AH and IR can intensify working out of new methods of prophylaxis and treatment of cardio-vascular disturbances.

CONFLICT OF INTEREST
The authors declare that they don’t have any competing interest regarding manuscript

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