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Development of Platelet Dysfunctions at Arterial Hypertension with Dyslipidemia.

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ABSTRACT

Patients with arterial hypertension and dislipidemia are characterized by strengthening of platelets' adhesive, aggregative and secretory abilities against the background of their normal quantity which is realized in vessels of any size and produces the danger of initiation of hemostasis process at minimal damages of atherosclerotic plaques in them. It is possible that at the given pathology we have simultaneous activation of receptor and intraplatelet ways of platelets' activation in response to all the physiological inductors and their combinations. That's why, blood of patients with arterial hypertension and dislipidemia is noted to have high level of platelets' active forms. Their increased intravascular activity indirectly points at availability of vascular wall's endothelial collagen for them in the result of endothelium damage and at increased concentration of different aggregation inductors in their blood (thrombin, adenosine diphosphate, adrenaline). It becomes clear that dislipidemia leads to chemical microtraumas of vascular walls and arterial hypertension – to mechanical ones what in total causes strengthening of intravascular platelets' activity. At arterial hypertension in combination with dislipidemia platelets can stimulate the synthesis of pro-oxidants, vasoconstrictors, aggregants and thrombogenic factors in vascular walls and weaken the formation of endothelial vasoconstrictors and disaggregants.

Keywords: arterial hypertension, dislipidemia, platelets, aggregation, secretion.

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INTRODUTION

Development of arterial hypertension (AH) is always accompanied by many disturbances in a body. Formation of firmly increased arterial pressure leads to myocardial hypertrophy, remodeling of vessels, nephoratia and some other disturbances what significantly worsens life quality of patients [1]. Modern science pays great attention to investigation of AH aspects, especially in case of its combination with different metabolic disturbances [2]. One of such very frequent disturbances is dislipidemia [3]. It is acknowledged that combination of AH with dislipidemia greatly accelerates the course of atherosclerosis and is often complicated by different thrombotic manifestations [4]. It becomes clear that platelet dysfunctions [5] lie in the basis of thrombotic complications at this state. At the same time, information about mechanisms of their activation can't be considered full and and needs summation, generalization and, sometimes, correction. Taking high social danger of thrombophilia at AH with dislipidemia into account, we put the following aim in our research: to conduct the review of available literature concerning platelet dysfunctions in persons with combination of arterial hypertension and dislipidemia.

Foundations of platelets' hemostatic activity in the processes of thrombosis

Platelets are nuclear-free fragments of megacaryocytes' cytoplasm. These megacaryocytes, notwithstanding the absence of ability to synthesize DNA, have a lot of functions and complex metabolism [6,7]. The average life of platelets is 6.9±0.3 days. In their cytoplasm there are granules which contain proteins – fibrinogen, von Willebrand's Factor, the 4th platelet factor, thromboglobulin and platelet factor of growth [8].Dense granules of platelets contain finer molecules – Ca^{2+}, ADP, biogenic amines (serotonin, catecholamines and others).Lysosomal granules of platelets are stuffed with hydrolases.

A lot of receptors are located in the membrane of platelets (receptors to collagen, thrombin, ADP, catecholamines, serotonin, thromboxane A_2, the factor of platelets activation, Fc – fragment of immune-globulins, components of complement, insulin, α-adreno-receptors, receptors to endothelin) and receptor-like proteins which bind and hold complexes of coagulation factors and integrins participating in cellular adhesion, on the surface of platelets.

The reactions which take place in platelets, are complicated enough but, regardless of the initial stimulus, lead to the development of universal answer – aggregation of platelets (AP) [9]. At the contact with collagen of a damaged vessel's sub-endothelium platelets stick to it through protein bridges – von Willebrand's Factor formingmonostratal lining which other platelets stick to. Stimulators of aggregation are thrombin, circulating immune-complexes, activated C3a component of complement, degranulation products of mast cells, catecholamines, basophilic factor activating platelets, and others. Activation affects all the components of platelets. The inductor's impulse is transferred from receptors to internal structures of a cell [10].

Platelets play an important role in pathogenesis of cardio-vascular disturbances, first of all, by changing their functional properties what is accompanied by emission of vasoactive mediators. They provoke local vasospasm and increase platelets' aggregation what rises the risk of thrombotic manifestations [11,12]. Activation of platelets is caused by increased arterial pressure [13], hypoxia [14], active lipids' peroxidation (LPO) [15], erythrocytes' fragments [16], dislipidemia [17], and also sub-endothelial structures of vascular wall which are exposed in the result of endotheliocytes' death [18]. At the same time, cholesterolemia can independently stimulate the activity of platelets with the release of more active lipoid factor than in healthy people [19], out of them.

So, platelets – is an important component of hemostasis system which can be activated at different pathological impacts and produces the danger of thrombosis.

Adhesion of platelets at AH with dislipidemia

Platelets stick to sub-endothelium at participation of von Willebrand's Factor. It is the first stage of thrombus' formation. Besides endothelium von Willebrand's Factor (approximately 15% of circulating quantity) is synthesized by megacaryocytes. That's why it is contained in α-granules of platelets. The main quantity of circulating von Willebrand's Factor has endothelial origin in its usual state. However, platelets' activation can lead to its contents' increase in bloodstream on behalf of its emission out of platelets. Von

Willebrand's Factor is secreted by endothelial cells into both bloodstream and sub-endothelium where it is contained into the composition of extracellular matrix [20].

The level of von Willebrand's Factor is reliably higher in hypertensive patients in comparison with healthy people and positively correlates with diastolic arterial pressure, mass index of aortic ventricle's myocardium, thickness of back wall of aortic ventricle and mass of interventricular septum. Quantity increase of von Willebrand's Factor at AH with dislipidemia in blood is very often accompanied by reliable growth of P-selectin concentration (an adhesive molecule – a marker of platelets' activity) [21].

High content of cholesterol in platelets' membranes which is typical for AH with dislipidemia, stimulates their receptor and post-receptor mechanisms. Changes in lipid composition of platelets' membranes promote lowering of platelets' antioxidant protection what is spoken by activity lowering of catalase, superoxide dismutase and platelets' antioxidant state in patients with AH and dislipidemia [22]. Strengthening of freely radical processes in platelets and content increase of primary and secondary LPO products in them are developed as consequence of the given changes. Quantity increase of free radicals causes damage of platelets' structure stimulating their adhesion [23,24].

Overload of platelets' membranes by cholesterol also promotes secretion of some biologically active substances out of them. These substances additionally provoke adhesion and aggregation of still inactive platelets. Already after adhesion the platelets of such patients stimulate quick formation of fibrin threads on their surface what leads to impetuous formation of a large platelet-fibrin clot [25].

It was found out in conducted earlier researches that in the given category of patients activation of platelets' adhesive ability could be realized with the help of at least two mechanisms. The first mechanism was number increase of collagen receptors – glycoproteidsIa-IIa and VI on membranes of patients' platelets. The second mechanism of platelets' adhesion strengthening in persons with AH and dislipidemia was realized through concentration rise of von Willebrand's Factor in blood – cofactor of platelets' adhesion and/or increase of receptors number to it – (GPI b) on the surface of platelets. The first mechanism of strengthening of platelets' adhesive ability had significance in hemostasis realization at low shift tension – in large arteries and veins, the second one – in fine arteries and arterioles [26].

So, found strengthening of platelets' adhesive ability in patients with AH and dislipidemia against the background of platelets' normal quantity which is registered in fine and large blood vessels, produces danger of activation of platelets' aggregation in any site of vascular course.

Aggregation and secretion of platelets at AH with dislipidemia

It is typical for patients with AH and dislipidemia to have AP strengthening with all the inductors. Fixation of strong aggregation agonists – collagen and thrombin – to receptors on platelets' membranes causes activation of phospholipase C with stimulation of phosphor-inositol way through diacyl glycerol and proteinkinase C and strengthens phospholiration of proteins of platelet contractile system [27]. Inositol-triphosphate promotesthe yield of Ca^{2+} out of intraplateletdepos providing intensification of actomyosin reduction. ADP and adrenaline being weak inductors of platelets' aggregation, cause expression of fibrinogenic receptors (GPIIb-IIIa) at interaction with their receptors of platelet membrane. They stimulate phospholipase A_2 at that what leads to the yield of arachidonic acid out of membrane phospholipids. Activated by dislipidemia and intensive LPOcyclo-oxygenase and thromboxane-synthetase accelerate metabolism of arachidonic acid with the increase ofproaggregant prostaglandins' yield, including thromboxane A_2. It accelerates platelets' aggregation by stimulating phospholipase A_2, phospholipase C and evident yield of Ca^{2+} into cytoplasm. May be, strengthening of functioning of receptor and intraplatelet ways of signal transmission into platelets at AH with dislipidemia takes place mostly on behalf of activity growth of phospholipase A_2 and phospholipase C with stimulation of phosphor-inositol way and metabolism of arachidonic acid [28].

Content increase of thromboxane A_2 at AH with dislipidemia can be also caused by accumulation of cholesterol and lipids' peroxides in blood. In particular, patients with AH and dislipidemia are found to have the ability of low-density lipoproteids to strengthen biosynthesis of thromboxane A_2 in platelets and in endothelial cells of vessels. Given fact can be explained by high content of arachidonic acid's endoperoxides in them. Surplus of thromboxane A_2 in blood of patients with AH and dislipidemia quickly increases availability of

platelets' receptors for fibrinogen, activates coagulation, narrows blood vessels. Thromboxane A_2 causes evident content increase of Ca in platelets' cytoplasm, activates phospholipase A_2, embossing arachidonic acid out of lipid bilayer, and strengthens activity of cyclo-oxygenase and thromboxane-synthetase. In these conditions Ca strongly activates platelets' contractile proteins in the course of aggregation and reaction of release [29].

Platelets of patients with AH and dislipidemia differ by not only increased content of Ca but also lowering of Mg content in cytoplasm, increased pH, regulation disturbance of α_2-adrenoreceptors and high sensitivity to ADP and arachidonic acid [23]. It is established that patients with AH, especially in combination with dislipidemia, have increased expression of some genes in megacaryocytes what rises the marker's level of high functional activity in platelets – β-thromboglobulin [30].

It isn't still clear whether AP disturbance is the consequence of arterial pressure rise or pathogenic factor of arterial hypertension development. That's why, the results which were received after examination of young people with predisposition to AH, are very interesting. It is established that at normal level of arterial pressure they are noted to have surplus AP in response to all the applied inductors. It isn't noted in the group of young people whose parents had normal arterial pressure [20].

It was typical for patients with AH and dislipidemia to have increase of platelets' active forms in blood. Increased intravascular activity of platelets indirectly pointed at availability of collagen of vascular wall's subendothelium in these patients. May be, it happened in the result of endothelium damage and increase of different aggregation inductors in blood of these patients (thrombin, ADP, adrenaline). Dislipidemia evidently leads to chemical microtraumas of vascular walls, AH – to mechanical ones what in total causes strengthening of intravascular platelets' activity in patients with AH and dislipidemia [19].

Number growth of circulating aggregates of different sizes in bloodstream of patients was inevitable consequence of high content of platelets' active forms in blood of patients. Freely moving in bloodstream aggregates damage endotheliocytes exposing subendothelial structures, including fibers of collagen [13]. Circulating aggregates can block vasa vasorum what in combination with rheological and barometric bloodstream changes in persons with AH and dislipidemia can change transcriptional activity of vessels' cellular elements leading to progression of atherosclerosis manifestations [31].

High intravascular platelets' activity in patients with AH and dislipidemia has in its basis strengthening of platelets' adhesive and aggregative activity invivo. Arterial hypertension, changes of lipid composition of platelets' membranes with LPO activation in them and thromboxane-formation [32,33] can be considered the basic mechanisms of it.

Besides, strengthened reaction of release of biologically active substances possessing mitogenetic, vasoconstrictor and oxidative impact out of platelets promotes worsening of hemostasis system functioning. The most significant role in this field belongs to substances which are released by activated platelets – thromboxane and platelet factor of growth. These compounds damage endothelium, promote migration of lissocells into subendothelium and activation of collagen synthesis in them [34].

So, there is an opinion in literature that patients with AH and dislipidemia are noted to have strengthening of platelets' aggregation and secretion. However, this information is not enough for final judgment about mechanisms of the given process, especially in the debut of the given pathology formation.

CONCLUSION

Modern science pays great attention to investigation of of different AH aspects, especially in case of its combination with dislipidemia. Given combination can accelerate the course of atherosclerosis and cause platelet dysfunctions. Information about aspects of thrombocytopathy formation in the given category of patients can't be considered full and needs generalization and clarification. Patients with AH and dislipidemia are often noted to have strengthening of platelets' adhesive, aggregative and secretory abilities in fine and large blood vessels. It produces danger of thrombosis development in vessels of any size. Its main mechanisms are sensitivity increase of platelets' receptors and intraplatelet ways of their activation. The basic stimules of platelets at AH with dislipidemia are increased arterial pressure, hypoxia, active lipids' peroxidation, fragments

of erythrocytes, hypercholesterolemia, hypertriglyceridemia and exposing subendothelial structures of vascular wall.At the same time, existing data in available literature are rather poor for final judgment about mechanisms of platelet activity increase in debut of AH with dislipidemia. Effective approaches to prophylaxis of thrombocytopathy development in the given category of patients are not worked out yet.

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