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The Effect of Complex Treatment on Platelet Aggregation Activity in Patients with Grade 3 Arterial Hypertension with Metabolic Syndrome

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Abstract

The combination of arterial hypertension and metabolic syndrome causes a whole complex of disorders in the patients' body, contributing to the risk of developing thrombosis in them. In this regard, it is very important to develop a comprehensive therapy for this patient population, which positively influences the activity of platelets, which is an important factor in the formation of thrombophilia in them. The aim of the work is to establish the intensity of the dynamics of platelet aggregation ability and the state of functional capabilities, the individual mechanisms of their determining in patients with arterial hypertension of the third degree in the metabolic syndrome. 24 patients with arterial hypertension of the 3rd degree, risk 4, including 10 men and 14 women of mature age, were under observation. The control group consisted of 25 clinically healthy people of similar age. The surplus platelet activity observed in the in vitro and in vivo patients is based on an increase in the adhesive and aggregation activity of platelets with a weakening of their ability to disaggregate, largely due to an imbalance in their blood pressure and anti-aggregational compounds. The complex therapy, including amlodipine, valsartan, pioglitazone, hypocaloric diet and dose physical exercise, provided patients with arterial hypertension 3 degrees with metabolic syndrome after 4 months. Stable normalization of initially high platelet activity, significantly reducing their risk of developing thrombosis, despite the non-strict compliance with the non-drug component of treatment after 16 weeks of treatment.

Keywords: Arterial hypertension; Metabolic syndrome; Thrombocytes; Amlodipine; Valsartan; Non-drug treatment

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Introduction

Until now, one of the leading places in the development of complications and deaths in the structure of the overall incidence belongs to cardiovascular pathology [1]. In this case, a very large proportion of it has arterial hypertension (AH) and its complications, which have pronounced negative effects on the cardiovascular system and significantly increase the risk of thrombosis [2]. At the same time, the adherence to the AH of metabolic syndrome (MS), including hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, abdominal obesity (AO), insulin resistance, manifested by impaired glucose tolerance (STH) or diabetes mellitus, dramatically increases the risk of cardiovascular disasters [3]. The most vulnerable in this regard are persons with MS who have AH of high degree due to pronounced activation of platelets, which significantly increases the risk of recurrent thrombosis of different localization [4].

There is no doubt that patient with a high degree of hypertension with MS need a complex correction [5]. According to modern views, the use of drugs that maximally affect the elements of pathogenesis of hypertension and MS, which include combinations of modern and safe antihypertensive drugs (angiotensin receptor blocking agent ACE, for example, valsartan and calcium antagonist, for example, amlodipine), hypoglycemic drug (e.g., pioglitazone) and non-drug therapy, including rational diet and exercise doses [6,7]. In this connection, the effect of this complex on the important mechanism of formation and maintenance of thrombophilia is of great scientific and practical interest-high platelet activity and individual mechanisms of its control in patients with AH of grade 3 in MS.

In this regard, the goal of the study was formulated: to establish the intensity of the dynamics of platelet aggregation ability and the state of functional capabilities, of the individual mechanisms of their determinants in patients with AH of grade 3 in MS.

Materials and Methods

The study included 24 patients with AH of 3 degrees, risk 4, incl. 10 men and 14 women of mature age (49.1 ± 1.9 years). All patients had a combination of AH with a diagnosis in strict accordance with the generally accepted criteria of MS, consisting of a violation of glucose tolerance, hyperlipidemia II b type, abdominal obesity (body mass index more than 30 kg/m^2, the ratio of waist volume to hip volume more than 0.85 in women and more than 1.0 in men). The control group consisted of 25 clinically healthy people of similar age. A group of patients and a group of healthy people had a normal amount of platelets

in their blood. The blood in both groups was taken after 14 hours of starvation. The content of total cholesterol, high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) was determined by the enzymatic colorimetry method using the Vital Diagnosticum kit, the total lipids concentration was determined using the Erba Russ kit. Low-density lipoprotein (LDL) cholesterol was calculated according to W. Friedwald, the cholesterol-lowering lipoprotein cholesterol (VLDL) was calculated by the formula: TG / 2.2. The lipid composition was evaluated in full accordance with the Russian recommendations on the diagnosis and correction of lipid metabolism disorders [8]. The activity of lipid peroxidation (LPO) of plasma was detected by the content of thiobarbituric acid (TBA) -active products by a set of the firm "Agat-Med" and acyl hydroperoxides (AGP) [9]. In all patients, the antioxidant potential of the liquid part of the blood was determined [10].

All the subjects surveyed in the plasma determined the endothelin-1 content by radioimmunoassay using DRG reagents (USA), as well as the levels of thromboxane A_2 thromboxane B_2 metabolite and prostacyclin metabolite 6-keto-prostaglandin F1α by enzyme immunoassay using the "Enzo Life science»(USA). The total content of observed metabolites of nitrogen oxide in the blood was determined by the method of [11]. Aggregation of platelets was evaluated on a two-channel laser analyzer aggregation of platelets ALAT2-"BIOLA" (model LA230-2, Russia) using as inductors ADP (0.5 × 10.4 M), collagen (1:2 dilution of the basic suspension), ristomycin (0.8 mg/ml). Intravascular activity of thrombocytes was determined with phase contrast.

In order to correct blood pressure (BP) patients were prescribed amlodipine 10 mg once a day and valsartan 160 mg once a day, to optimize carbohydrate metabolism-pioglitazone at a dose of 30 mg once a day. Non-pharmacological therapy included a hypocaloric diet and feasible regular physical training. Assessment of clinical and laboratory indicators was performed at the beginning of treatment, at 2,4,12 and 36 months of therapy. The non-compliance with the non-pharmacological component of the ongoing correction was allowed after 4 months therapy.

Statistical processing of the obtained results was carried out using Student's t-test.

Results and Discussion

The initial level of arterial pressure in the patients under observation (systolic - 186.1 ± 4.3 mm Hg, diastolic - 114.8 ± 3.2 mm Hg) corresponded to grade 3 hypertension. After 2 weeks of therapy, the blood pressure level in the observed patients stabilized at the level: systolic-135.0 ± 2.1 mm Hg, diastolic-85.3 ± 1.3 mm Hg, and remained at the achieved level until the end of the observation.

In the blood of patients, increased amounts of OL and OXC prevailed over control values of 1.67 and 1.30 times, respectively (Table 1). At the same time, in the blood of the observed patients with complicated hypertension of grade 3, MS also showed an increase in LDL cholesterol, cholesterol and VLDL in 1.52, 1.68 and 1.67 times, respectively, combined with a decrease in HDL cholesterol 1.32 times. Against this background, the expressed activation of plasma LPL was revealed in the patients-the content of AGP in it (3.70 ± 0.003 D_{233}/1 ml) exceeded the control 2.28 times, TBA-active products (5.80 ± 0.003 μmol/l)-in 1.71 times with a decrease in the value of the antioxidant potential of the liquid part of the blood by 79.5%.

As a result of the use of complex therapy in the blood of patients, a gradual decrease in the levels of OL and OXC, reaching the control values after 4 months, was noted (Table 1). This was accompanied

Table 1. Biochemical characteristics of blood plasma in patients with grade 3 arterial hypertension in metabolic syndrome.

Indicators	Observed Patients, n = 24, M ± m					Control, n=25, M ± m
	initial state	2 months of therapy	4 months of therapy	12 months of therapy	36 months of therapy	
Concentration cholesterol, mmol/l	6.25 ± 0.07	5.79 ± 0.06 p<0.05	4.83 ± 0.06 p<0.05	4.88 ± 0.03	5.18 ± 0.04	4.79 ± 0.02 p<0.01
Concentration HDL cholesterol, mmol/l	1.14 ± 0.003	1.31 ± 0.001 p<0.05	1.50 ± 0.002 p<0.05	1.51 ± 0.006	1.43 ± 0.01	1.53 ± 0.001 p<0.01
Concentration of LDL cholesterol, mmol/l	3.92 ± 0.06	3.42 ± 0.05 p<0.05	2.60 ± 0.08 p<0.05	2.62 ± 0.04	2.87 ± 0.03	2.56 ± 0.03 p<0.01
Concentration Cholesterol VLDL, mmol/l	1.19 ± 0.002	1.06 ± 0.003 p<0.05	0.73 ± 0.003 p<0.01	0.75 ± 0.008 p<0.01	0.88 ± 0.002	0.70 ± 0.002 p<0.01
Concentration triglycerides, mmol/l	2.63 ± 0.02	2.34 ± 0.008 p<0.05	1.61 ± 0.006 p<0.05	1.65 ± 0.01 p<0.05	1.93 ± 0.02 p<0.05	1.56 ± 0.01 p<0.01
Level of total lipids, g/l	8.79 ± 0.03	7.53 ± 0.04 p<0.05	5.29 ± 0.02 p<0.01	5.34 ± 0.03	5.92 ± 0.04	5.26 ± 0.04 p<0.01
Concentration acylhydroperoxides plasma, D_{233}/1 ml	3.62 ± 0.03	3.24 ± 0.02 p<0.05	1.66 ± 0.005 p<0.01	1.65 ± 0.006	1.89 ± 0.002 p<0.05	1.62 ± 0.02 p<0.01
Thiobarbituric acid-products of plasma, μmol / l	5.76 ± 0.002	5.32 ± 0.003 p<0.05	3.41 ± 0.002 p<0.01	3.44 ± 0.002	3.86 ± 0.004	3.38 ± 0.006 p<0.01
Antioxidant activity of plasma, %	21.4 ± 0.06	26.6 ± 0.4 p<0.05	36.3 ± 0.05 p<0.01	36.7 ± 0.12	34.4 ± 0.5	36.8 ± 0.03 p<0.01
Thromboxane B_2, pg / ml	291.4 ± 0.68	212.6 ± 0.54 p<0.01	157.1 ± 0.42 p<0.01	156.7 ± 0.36	157.0 ± 0.46	156.5 ± 0.66 p<0.01
6-keto-prostaglandin F1α, pg / ml	70.2 ± 0.42	74.9 ± 0.35 p<0.05	81.9 ± 0.46 p<0.01	82.3 ± 0.29	82.2 ± 0.38	82.4 ± 0.49 p<0.01
Total metabolites of nitric oxide, μmol / l	26.3 ± 0.52	29.6 ± 0.45 p<0.05	33.7 ± 0.40 p<0.05	33.9 ± 0.48	33.7 ± 0.37	33.6 ± 0.35 p<0.01
Endothelin-1, pg / ml	20.9 ± 0.26	12.8 ± 0.19 p<0.01	8.1 ± 0.22 p<0.01	8.2 ± 0.16	8.2 ± 0.14	8.2 ± 0.15 p<0.01

Legend: p - reliability of differences between the group of patients and control, p1 - reliability of the dynamics of the indicators taken against the background of correction. In the following table, the notation is similar.

in the observed patients by a decrease in plasma concentrations of LDL cholesterol, LLDPE and TG cholesterol and an increase in HDL cholesterol to control figures after 4 months, with their preservation at the achieved level until the end of the observation. Against this background, the stable normalization of LPO plasma activity was noted in the blood of patients at the same time-4 months later. The content of AGP in it was 1.66 ± 0.005 D233 / 1 ml, TBA-active products - 3.41 ± 0.002 μmol / l with optimization of the antioxidant potential of the liquid part of the blood (36.3 ± 0.05%).

The imbalance of metabolites of arachidonic acid-thromboxane B_2-was found to be increased in the blood of the persons who made up the observation group, by 84.8%, whereas the level of the derivative of its functional antagonist, 6-keto-prostaglandin F1α, was reduced by 17.9% (Table 1). This was accompanied in the patients with high level of endothelin-1 (21.1 ± 0.27 pg/ml) with a decrease in the amount of total metabolites of nitric oxide in their blood plasma reduced by 28.7%.

The complex therapy was accompanied in patients by gradual normalization of the metabolites of arachidonic acid in blood, a decrease in thromboxane B_2 by 85.5%, and an increase in 6-keto-prostaglandin $F_1\alpha$ by 14.3% (Table 1). This was accompanied by a decrease in the blood of the examined patients to the level of control of endothelin-1 (8.1 ± 0.22 pg / ml) and an increase in the amount of total metabolites of nitric oxide (by 21.9%).

At the end, platelet aggregation in patients with AH of grade 3 in MS was enhanced (Table 2). Most actively, their platelets reacted to collagen, while the degree of aggregation with this inductor exceeded the control by 25.0% and the aggregation rate by 27.5%. Slightly less platelets of patients responded by aggregation to ristomycin. At the same time, the degree of aggregation with it in patients was above the control by 25.7%, and the aggregation index exceeded it in healthy individuals by 46.4%. Even less active platelets of the examined patients aggregated in response to the addition of ADP. In this case, the value of ADP aggregation and the aggregation index with this inducer exceeded the control values by 25.7% and 58.4%, respectively.

As a result of the use of complex therapy in observed patients, platelet aggregation experienced a gradual weakening, maximally expressed by 4 months observations, which allowed it to reach the level of control (Table 2). Thus, during these periods of treatment, the normalization of collagen aggregation was noted, manifested by a decrease in the degree of aggregation of platelets with this inducer by 26.2% and a decrease in the aggregation index by 28.9%. The achieved normalization of the aggregation response of platelets of patients in these terms to ristomycin was provided by a decrease in the degree of aggregation with it by 28.8% with a decrease in the aggregation index by 57.4%. Regarding the third tested inductor-ADP platelets examined patients after 4 months. Therapies responded with aggregation to the same extent as in the control. This was due to a decrease in the degree of ADP aggregation and the aggregation rate with this agonist by 29.2% and 45.6%, respectively. Continuation of therapy allowed fixing the AT the reached level until the end of the observation.

When studying intravascular activity of platelets (Table 2) in patients with AH of the third degree in MS, a decrease in the number of discocytes to 48.6 ± 0.40% (in control-82.1 ± 0.10%) was revealed. The content of disco-echinocytes in their blood was doubled. The number

Table 2. Functional activity of platelets in patients with grade 3 arterial hypertension in metabolic syndrome.

Indicators		**Observed Patients, n=24, M ± m**					**Control, n=25, M ± m**
		initial state	**2 months of therapy**	**4 months of therapy**	**12 months of therapy**	**36 months of therapy**	
Aggregation of platelets with collagen	degree of aggregation, units	10.1 ± 0.25	9.4 ± 0.32 p_1<0.05	8.0 ± 0.27 p_1<0.01	8.1 ± 0.25	7.9 ± 0.29	8.0 ± 0.32 p<0.01
	aggregation rate, units	8.9 ± 0.32	7.8 ± 0.36 p_1<0.05	6.9 ± 0.40 p_1<0.05	6.8 ± 0.24	6.9 ± 0.20	6.9 ± 0.27 p<0.01
Aggregation of platelets with ADP	degree of aggregation, units	9.3 ± 0.34	8.3 ± 0.30 p_1<0.05	7.2 ± 0.22 p_1<0.05	7.1 ± 0.25	7.0 ± 0.27	7.1 ± 0.24 p<0.01
	aggregation rate, units	8.3 ± 0.29	7.2 ± 0.27 p_1<0.05	5.7 ± 0.23 p_1<0.01	5.6 ± 0.15	5.5 ± 0.22	5.6 ± 0.16 p<0.01
Aggregation of platelets with ristomycin	degree of aggregation, units	9.4 ± 0.22	8.5 ± 0.29 p_1<0.05	7.3 ± 0.28 p_1<0.05	7.4 ± 0.18	7.3 ± 0.23	7.4 ± 0.15 p<0.01
	aggregation rate, units	8.5 ± 0.30	7.2 ± 0.26 p_1<0.05	5.4 ± 0.22 p_1<0.01	5.3 ± 0.26	5.2 ± 0.19	5.3 ± 0.22 p<0.01
number of platelets in the aggregates, %		15.5 ± 0.04	12.5 ± 0.07 p_1<0.05	6.9 ± 0.03 p_1<0.01	7.1 ± 0.04	7.8 ± 0.03	6.7 ± 0.08 p<0.01
number of small aggregates of 2-3 platelets per 100 free-standing platelets		18.2 ± 0.09	14.4 ± 0.04 p_1<0.05	3.1 ± 0.02 p_1<0.01	3.3 ± 0.02	3.7 ± 0.05	2.9 ± 0.06 p<0.01
number of medium and large aggregates, 4 or more platelets per 100 free-standing platelets		5.7 ± 0.03	2.5 ± 0.01 p_1<0.05	0.28 ± 0.004 p_1<0.01	0.25 ± 0.002	0.29 ± 0.003	0.2 ± 0.06 p<0.01
erythrocytes-discocytes, %		49.4 ± 0.20	59.5 ± 0.40 p_1<0.05	80.7 ± 0.20 p_1<0.01	79.8 ± 0.40	77.5 ± 0.70	82.1 ± 0.10 p<0.01
Disco-echinocytes, %		27.3 ± 0.09	23.8 ± 0.15 p_1<0.05	13.8 ± 0.09 p_1<0.01	14.3 ± 0.05	15.6 ± 0.09	13.5 ± 0.04 p<0.01
Spherocytes, %		14.5 ± 0.08	10.9 ± 0.08 p_1<0.05	2.7 ± 0.04 p_1<0.01	2.6 ± 0.03	3.2 ± 0.04	2.1 ± 0.12 p<0.01
Sphero-echinocytes, %		6.7 ± 0.01	4.2 ± 0.07 p_1<0.05	1.8 ± 0.01 p_1<0.01	2.1 ± 0.02	2.3 ± 0.04	1.5 ± 0.08 p<0.01
Bipolar forms, %		2.1 ± 0.004	1.6 ± 0.01 p_1<0.05	1.0 ± 0.002 p_1<0.01	1.2 ± 0.01	1.4 ± 0.02	0.8 ± 0.04 p<0.01
Sum of active forms, %		50.6 ± 0.15	40.5 ± 0.05 p_1<0.05	19.3 ± 0.03 p_1<0.01	20.2 ± 0.10	22.5 ± 0.30	17.9 ± 0.09 p<0.01

of spherocytes, sphero-echinocytes and bipolar platelet forms also significantly exceeded the control values and reached 14.4 ± 0.08%, 7.0 ± 0.06% and 2.2 ± 0.07%, respectively, in patients. The sum of active forms of platelets in patients was 51.4 ± 0.12%, (in control - 17.9 ± 0.09%). Small and large aggregates in the blood of the subjects of the observation group contained 18.6 ± 0.08 and 5.4 ± 0.04, against control - 2.9 ± 0.06 and 0.2 ± 0.06 per 100 free-standing platelets, respectively. At the same time, the number of platelets in the aggregates in patients prevailed over the level of the comparison group 2.2 times, which indicated a marked increase in intravascular activity of platelets.

Conduction of complex therapy provided for the observed patients rapid weakening of BAT, which allowed, after 4 months. To achieve normalization level of discocytes (80.7 ± 0.20%). At the same time, the number of disco-echinocytes in their blood decreased twice, and initially increased number of spherocytes, sphero-echinocytes and bipolar forms of platelets after 4 months. The monitoring also reached the indicators characteristic of control. This provided a decrease in the total number of active platelet forms to the level of the control group (19.3 ± 0.03%), also in the blood of individuals to the observation of group to 4 months. The number of small and large aggregates reached the control level (13.1 ± 0.02 and 0.28 ± 0.004 per 100 free-standing platelets, respectively) when the number of platelets in the aggregates was normalized. Further complex therapy provided stable maintenance of normal platelet activity in all patients until the end of observation.

At the time of taking under observation in blood all patients detected an increase in the concentration of TG, OL, OXC, VLDLP cholesterol, LDL cholesterol, which threatened rapid progression in this category of atherosclerosis patients. At the basis of the formation of atherogenic danger, an increase in LPO in the blood, which causes not only peroxide changes in plasma lipids, but also damage to endotheliocytes, played a big role, which facilitated the penetration of lipids into the vessel wall, thereby creating conditions for the subsequent occurrence of thrombosis in them [18]. The complex correction provided stable elimination of dyslipidemia within 4 months. Therapy, which, combined with an increase in antioxidant plasma safety and a decrease in the concentration of primary and secondary LPO products, minimized the risk of progression in observed patients of atherosclerosis.

In previous studies, it was found that hypertension in patients with MS actively violate the functions of the vascular wall and platelets, thereby contributing to the appearance of sometimes thrombotic phenomena [12]. At the same time, the activity of platelet hemostasis in these patients is still not fully understood, and needs additional evaluation. Moreover, in this category of patients, the degree of violation of the main mechanisms of the formation of thrombocytopathy, as the basis of thrombophilia, is not fully understood [13].

The observed elevated BP present in itself has a negative effect on the vascular wall, causing damage to the endothelium and exposing subendothelial fibers that are able to contact platelets actively. The hypercholesterolemia existing in patients, in turn, significantly aggravates this process, accelerating the development of vasopathy [14]. In the emerging conditions in the vascular wall, the synthesis of biologically active substances that is able to limit the adhesion and aggregation of platelets, in which the synthesis of proaggregants is increased [15]. Thus, the intensification of thromboxane formation and the weakening of the production of its functional prostacyclin antagonist, observed in the observed patients, create an imbalance in the metabolites of arachidonic acid, apparently based on the activation of platelet thromboxane synthetase and depression of vascular prostacyclinsynthetic activity. These disorders are exacerbated by the developing increase in production in the wall of the vessels of edothelin-1 and the weakening of the production of NO in it; probably as a result of suppression of endothelial NO synthase by excessive LPO and dyslipidemic changes in plasma [16].

The normalization of blood pressure achieved on the background of treatment quickly eliminates the negative effect of hemodynamic disturbances on the vascular wall peculiar to hypertension, minimizing the alteration of the endothelium and the expression of subendothelial fibers capable of activating platelets [17]. Early relief of hypercholesterolemia also significantly weakened the vasopathy by activating in the vessel wall the synthesis of biologically active substances inhibiting adhesion and aggregation of platelets while physiological weakening of the synthesis of proagregantes in them. This manifested itself in patients after 4 months, recovery against the background of complex therapy to the level of control of the balance of thromboxane and prostacyclin, as judged by the dynamics of the concentration of their metabolites. The rapidly advancing positive changes were combined with the suppression of the production in the wall of the edothelin-1 vessels and the increase in the production of NO in it, probably as a result of the activation of endothelial NO synthase against the background of normalization of LPO and elimination of dyslipidemia.

Developing with AH and MS biochemical changes in blood plasma are inevitably accompanied by an increase in AT, which was noted for all tested inductors. Excessively formed on their membranes, plasma thromboplastin stimulates thrombin formation, leading to the growth of aggregates of the blood platelets and the acceleration of the formation of fibrin fibers on them with the formation of platelet-fibrin clots capable of embolizing small vessels [18,19].

As a result of the therapy, after 4 months not only the optimization of the biochemical plasma disorders present in patients, but also the attenuation of AT, which was noted for all tested inducers. Thromboplastin generation was reduced on thrombocyte membranes of treated patients, which can inhibit thrombin formation, reducing the formation of aggregates of blood plates and suppressing fibrinogenesis, which eliminated the formation of mobile platelet-fibrin clots.

The initially high sensitivity of platelets to the aggregation inducers found in the examined patients was provided through the activation of a number of mechanisms. Thus, on the surface of platelets, a significant increase in the density of glycoproteins Ia-IIa and VI, participating in the adhesion of blood platelets, occurred at the surface of platelets at the time of enrollment, as could be judged by the intensification of AT in response to collagen. Intensification of adhesion of blood platelets in the observed patients is also associated with excessive expression of receptors to the Willebrand factor on their surface. This mechanism of enhancing the adhesive activity of platelets in patients was documented by the intensification of AT with ristomycin affecting platelets, identical to the subendothelial structures of the vessels. In this case, in view of the fact that for the onset of ristomycin AT, the von Willebrand factor is required that fixes one side of the molecule to ristomycin (as to collagen) and the second to the blood plates through their receptor-Ic, in this category of patients it can be ascertained that the formation of the "adhesion axis »: Ristomycin (collagen)-WF-GPIv. Moreover, it is the significant increase in the number of binding sites of von Willebrand factor on the membranes of the blood platelets of the observed patient category that is an important mechanism for the onset of excessive adhesive capacity of thrombocytes [20].

At the same time, against the background of the inadequate synthesis in the vessels of physiological antiplatelet agents in patients with AH of the third degree in MS on the surface of platelets, the number of receptors to collagen increases, this increases their sensitivity to it. This is inevitably accompanied by activation of phospholipase C, stimulation of the synthesis of diacylglycerol and protein kinase C, followed by pronounced phosphorylation of the proteins of the contractile system. Under these conditions, inositol triphosphate actively stimulates the entry of Ca^{2+} from the depot of the blood plates, contributing to the rapid reduction of actomyosin [21,22].

The ADP inductor, which belongs to the weak inducers of platelet aggregation, under conditions of lack of formation in the vessels of nitric oxide and prostacyclin also actively, interacts with its own receptors on the membranes of the blood platelets. This causes on them a powerful expression of fibrinogen receptors with activation of phospholipase A2, which provides the cleavage of arachidonic acid from membrane phospholipids [23,24].

The performed therapy was able not only to increase the production of NO and prostacyclin in the vessels, but also to lower the sensitivity of platelets to the inducers of their aggregation. So, on their surface in treated patients after 4 months. observations developed, judging by the weakening of AT in response to collagen, a significant decrease in the density of glycoproteins Ia-IIa and VI, involved in the adhesion of blood platelets. The observed normalization of adhesion of the blood platelets against the background of therapy in the patients was also weakened due to a decrease in the number of receptors to the von Willebrand factor, as indicated by inhibition to the level of control of AT with ristomycin.

The use of complex therapy provided in patients with AH of 3 degrees with MS a decrease in the platelet surface of the sites of fixation of a strong collagen inducer. This was based on a decrease in the activity of phospholipase C, a weakening of the synthesis of diacylglycerol and protein kinase C with inhibition, phosphorylation of proteins in the contractile system of platelets. The decrease in the amount of inositol triphosphate ensured the slowing down of the intake of Ca^{2+} from the depot of the blood plates, contributing to a decrease in the reduction of actomyosin [25,26].

At the same time by 4 months the observed inhibition of AT with ADP indicated a physiological analysis of the expression of fibrinogen receptors on platelets and the activity of phospholipase A2 in them, ensuring the cleavage of optimal amounts of arachidonic acid from membrane phospholipids [27].

Excess blood of patients with active forms of platelets has its basis on the one hand, insufficient formation in vascular walls of nitric oxide and prostacyclin, and, on the other, increasing the activity of platelets themselves. In addition, the high BAT indicates excessive availability of platelet collagen vascular endothelial damage as a result of her with the constant presence in the blood of patients with elevated concentrations of dissolved inducers aggregation of a large number of lipid peroxidation and active, leading to chemical endothelial injury [28]. Constantly high blood pressure leads to mechanical microtrauma of the vascular walls, which also inevitably leads to an increase in BAT in the examined contingent of patients. Developing increase in the content of active forms of platelets contributes to the increase of blood-moving aggregates of different sizes, also capable of damaging endotheliocytes, which further reveals subendothelial structures [29]. These processes close the "vicious circle", causing a significant weakening of vascular hemostasis and an increased risk of thrombosis [30]. Also circulating aggregates generalized block vasa vasorum that in the context of existing metabolic disorders and rheological blood of people with hypertension in MS leads to a further weakening of the functions of blood vessels and progression of atherosclerosis.

Complex therapy caused a rapid reduction in the blood of patients in the number of active forms of blood platelets, which was based, on the one hand, on the increase in the formation of nitric oxide and prostacyclin in the vascular walls, and on the other, the weakening of the activity of the platelets themselves. At the same time, inhibition of BAT on the background of the performed treatment speaks about optimization of accessibility of collagen to the vascular wall for blood clots due to minimization of chemical damage to its endothelium by a drop in the amount of dissolved aggregation inducers, lipids and LPO products in the blood of patients. Stable normalization of blood pressure eliminated mechanical microtraction of the vascular walls, which also led to a decrease in BAT in the surveyed patients [31]. The reduction in the active platelet form in these conditions was accompanied by a normalization of the number of aggregates of different sizes moving across the blood, which also played a role in normalizing mechanical effects on endotheliocytes, reducing the contact of the subendothelial structures with blood to the minima. The effects achieved by treatment disrupt the "vicious circle", providing a significant increase in vascular control over platelets, significantly reducing the risk of recurrent thrombosis [32] and improving the quality of life of patients [33,34].

Conclusion

Excessive platelet activity, which is detected in vitro and in vivo in patients with hypertension with MC, is based on an increase in the adhesive and aggregation activity of platelets with a weakening of their ability to disaggregate. This was due to an imbalance in the blood of these patients and anti-aggregation compounds. The most significant causative factors of this imbalance are arterial hypertension, negative changes in the lipid composition of the plasma, and the enhancement of LPO in it. The complex therapy, including amlodipine, valsartan, pioglitazone, hypocaloric diet and dose physical exercise, was provided in patients with AH of grade 3 with MS after 4 months, stable normalization of initially high activity of platelets, significantly reducing their risk of developing thrombosis.

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