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Peculiarities of vascular control over platelet aggregation in patients with Arterial hypertension of the 3rd degree at metabolic syndrome.

Medvedev IN*.

Russian State Social University, st. V.Pika,4, Moscow, Russia, 129226

ABSTRACT

In spite of the fact that the great practical signification of evidence of vessels' antiaggregatory control over platelets' activity in patients with metabolic syndrome and arterial hypertension of the 3rd degree, given question can't be considered fully studied. The aim is to ascertain the evidence of vascular wall's antiaggregatory dysfunction at arterial hypertension of the 3rd degree with accompanying metabolic syndrome. We observed 47 patients of middle age with arterial hypertension of the 3rd degree at metabolic syndrome. Control group was composed of 25 healthy people of the same age. We used biochemical, hematological and statistical methods of investigation. Examined patients had an evident strengthening of platelets' aggregatory function and lowering of vascular wall's antiaggregatory ability. These abnormalities were accompanied by deep shears in lipidic metabolism, activation of plasma lipids' peroxidation, weakening of nitric oxide synthesis in the vascular wall, output misbalance of arachidonic acid metabolites in vessels and platelets and strengthening of von Willebrand Factor synthesis in thevascular wall. Patients with arterial hypertension of the 3rd degree at metabolic syndrome on the background of platelets' intense aggregatory activity had anevident lowering of vascular wall's antiaggregatory ability. Given abnormalities surpasses the same ones at arterial hypertension of the 1st and 2nd degree at metabolic syndrome. They are important factors in the rise of thrombogenic danger for examined category of patients.

Keywords: Arterial Hypertension of the 3rd degree; Metabolic Syndrome; Vascular wall; Platelets; Antiaggregation.

Corresponding author

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INTRODUCTION

Vascular control over platelets' aggregation is an important element of hemostasis support in a body [1]. It is mostly provided by the endothelium of vascular wall which has different regulatory functions including control over vascular wall's tone and hemostasis mechanisms at different pathology [2,3]. Being genetically determined, functional features of vascular wall seriously determine blood state of aggregation on the whole [4].Mentioned earlier, investigations in the physiology of vascular wall allowed itemizing the ideas about peculiarities of the work of its regulation mechanisms at different states, including Arterial Hypertension (AH) more and more often loaded by Metabolic Syndrome (MS). At present, MS attracts more and more attention of researchers from different countries [5,6]. It is connected with agradual widening of its prevalence among population [7] and sharp need in search of different variants of its correction [8,9]. Especially great danger from MS is connected with rather frequent development of different thromboses at it. They appear mostly on behalf of some output disturbance of substances weakening hemostasis activity in the vascular wall of these patients [10,11].It was established that synthesis of different hemostatically significant substances can be essentially disturbed already at AH of the 1^{st} and 2^{nd} degree with MS in endotheliocyte. Among these substances are the following: nitric oxide, prostacyclin, antithrombin-III, von Willebrand Factor of plasminogen's tissue activators [2]. Activation of platelets and hemocoagulation, staying the cause of thrombosis, can also often develop at AH of the 1^{st} and 2^{nd} degree with MS [13]. At the same time, In spite of the fact that the great practical signification of evidence of vessels' antiaggregatory control over platelets' activity in patients with MS and arterial hypertension of the 3^{rd} degree, given question can't be considered fully studied. In this connection, we put the following aim in our work to ascertain the evidence of vascular wall's antiaggregatory dysfunction atAH of the 3^{rd} degree with accompanying MS.

MATERIALS AND METHODS

We observed 47 patients of middle age (48.2±1.6 years) with AH of the 3^{rd} degree [14]. The patients had MS consisting of tolerance disturbance to glucose, hyperlipidemia of II b type, abdominal obesity (index of body mass was more than 30 kg/m^2, the relation of waist to thighs was more than 0.85 in women and more than 1.0 in men). The criterion for selection into the group of patients was the durable reception of hypotensive therapy only by enalaprilande medicines having no impact on indices of platelet and vascular hemostasis. Treatment of all the MS manifestations in patients was conducted in all cases with the help of rational diet. The patients didn't consume drugs and alcohol, didn't smoke, had average welfare and good housing conditions. Chronic diseases of five persons (chronic bronchitis, chronic cholecystitis) were in the stage of persistent clinical remission for not less than 1.5 years. Control group was composed of 25 clinically healthy volunteers of the same age. Chronic diseases of 3 persons (chronic tonsillitis and chronic prostatitis) were in the stage of persistent clinical remission for not less than 1.5 years. All the examined persons signed the informed agreement on taking part in the investigation.

For conducting the necessary tests, blood drawing was carried out after 14-hours' starvation of all the examined patients. We determined the content of common cholesterol (CS), CS of High-DensityLipoproteins (CS HDLP) and Triglycerides (TG) in their blood by anenzymatic colorimetric method with the help of a set of the firm "Vital Diagnostikum". The level of common lipids (CL) was estimated with the help of a set produced by the firm "Erba Russ". CS concentration ofLow Density-Lipoproteins (LDLP) and CS of Very Low Density-Lipoproteins (VLDLP),was found by calculating according to standard methods. The results were estimated according to Russian criteria [15]. Tolerance disturbance to glucose was found by determining the concentration of glucose in blood by anortho-toluidine method on an empty stomach and in 2 hours after the reception of 75gr glucose. The activity of plasma lipids' peroxidation (LPO) was determined according to the content of thiobarbituricacid (TBA) – active products in it by a set "Agat-Med" (Russia) and aryl hydroperoxides (AHP) [16]. We also estimated the antioxidant potential of liquid part of blood [17]. In plasma of all the examined patients we determined the content of endothelin-1 by radioimmunological method with the help of reagents of the firm "DRG" (USA), the quantity of thromboxane A_2 metabolite – thromboxane B_2 and prostacyclin metabolite – 6-keto-prostaglandin $F_{1\alpha}$ in the course of enzymoimmunoassay with application of sets of the firm "Enzo Life Science" (USA). The summary quantity of nitric acid metabolites in blood of examined patients was determined according to the method by Metelskaya V.A. and co-authors (2005) [18]. The calculation of platelets' quantity in capillary blood was made in Goryaev's box. Platelets' aggregatory ability was studied by visual micromethod [19] with the usage of the following inductors – adenosine diphosphate (ADP) (0.5×10^{-4} M), collagen (dilution 1:2 of the basic suspension), thrombin (0.125 un/ml),

ristomicin (0.8 mg/ml) and adrenaline (5×10^{-6} M). The antiaggregatory activity of vascular wall was found according to AP weakening in response to all the used inductors in conditions of temporal venous occlusion. It was estimated with the help of index value of the antiaggregatory activity of vascular wall (IAAVW) which was calculated by dividing the period of AP development in plasma, received at temporal venous occlusion, on the period of AP development in blood plasma, taken without application of tourniquet on the vessel.

RESULTS OF INVESTIGATION

Taken into investigation patients with AH of the 3rd degree at MS had hyperlipidemia of II b type (CL – 8.80±0.004 g/l), including hypercholesterolemia (CS 6.23±0.004 mmol/l), rise of CS LDLP till 3.89±0.005 mmol/l, increase of CS VLDLP till 1.18±0.004 mmol/l, lowering of CS HDLP till 1.16±0.004 mmol/l and hypertriglyceridemia(2.60±0.002 mmol/l). At the same time, we found strengthening of LPO in plasma: concentration of TBA-active products in it was equal to 5.80±0.003 mmol/l (in control group – 3.38±0.006 mmol/l), the content of AHP – 3.70±0.004 D_{233}/1 ml (in control group – 1.62±0.002 D_{233}/1ml). The examined patients had an evident weakening of antioxidant plasma activity till 20.5±0.13% (in the control group – 36.8±0.03%) (table 1).

In the blood of patients from the experimental group, we found misbalance of arachidonic acid metabolites: the level of thromboxane B_2 rose on 84.8%, at the level lowering of its functional antagonist's derivative – 6-keto-prostaglandin $F_{1\alpha}$ on 15.2%. It was accompanied by high level of endothelin-1 in the blood(21.1±0.27 pg/ml) of examined patients and lowering of the content of summary nitric acid metabolites on 22.3% in it (Table 1).

Table 1: Biochemical parameters of plasma in the examined

Registered parameters	Patients, n=47, M±m	Control, n=25, M±m
Total cholesterol, mmol/l	6.23±0.004	4.79±0.002 p<0.01
HDLcholesterol, mmol/l	1.16±0.004	1.53±0.001 p<0.01
LDL cholesterol, mmol /l	3.89±0.005	2.56±0.003 p<0.01
VLDL, mmol /l	1.18±0.007	0.7±0.002 p<0.01
TG, mmol /l	2.60±0.002	1.56±0.001 p<0.01
totallipids, mmol /l	8.80±0.005	5.26±0.004 p<0.01
AHP, D_{233} /1ml	3.7±0.004	1.62±0.002 p<0.01
TBA-compounds, mcmol / l	5.80±0.003	3.38±0.006 p<0.01
plasmaantioxidantactivity, %	20.5±0.13	36.8±0.03 p<0.01
thromboxaneA_2, pg/ml	289.3±0.61	156.5±0.66 p<0.01
6-keto-prostaglandin $F_{1\alpha}$, pg/ml	69.9±0.46	82.4±0.49 p<0.01
Total metabolites nitrogen oxide, mcmol / l	26.1±0.45	33.6±0.35 p<0.01
endothelin-1, pg/ml	21.1±0.27	8.2±0.15 p<0.01

Symbols: p – reliability of distinctions of indicators between a group of patients and control. In the subsequent table of designation it is similar.

The amount of platelets in patients' blood related with the normal level. AP in plasma, taken without venous occlusion, was the most accelerated one under the impact of collagen – 23.5±0.07s (in the control group – 32.4±0.04s) (table 2). AP developed a bit slower under the impact of ADP and ristomicin. Thrombin and adrenaline AP also developed faster than in the control group – 36.2±0.32s (in the control group – 56.9±0.10s) and 67.0±0.15s (in the control group – 99.9±0.09s), respectively (p<0.01).

In plasma, received on the background of venous occlusion, patients' AP decelerated weaker than in the group for comparison. It provided the patients with the evident lowering of IAAVW values (Table 2). Therefore, the maximum value of IAAVW was noted for adrenaline – IAAVW 1.38±0.002, whereas in the control group this value was equal to 1.68±0.010. A bit less IAAVW was registered with ristomicin and ADP. Values of IAAVW with thrombin and collagen were still lower – 1.12±0.004 and 1.31±0.004, respectively.

Table 2: Control of vessels over aggregation of platelets at surveyed

Aggregation inductor	Registered parameters	Patients, n=47, M±m	Control, n=25, M±m
ADP	Aggregation of platelets in intact plasma, s	24.2±0.06	42.9±0.10 p<0.01
	Aggregation of platelets in plasma after temporary venous occlusion, s	32.9±0.06	65.4±0.22 p<0.01
	IAAVW	1.36±0.003	1.52±0.012 p<0.01
collagen	Aggregation of platelets in intact plasma, s	23.5±0.07	32.4±0.04 p<0.01
	Aggregation of platelets in plasma after temporary venous occlusion, s	30.8±0.07	48.9±0.09 p<0.01
	IAAVW	1.31±0.004	1.51±0.008 p<0.01
thrombin	Aggregation of platelets in intact plasma, s	36.2±0.32	56.9±0.10 p<0.01
	Aggregation of platelets in plasma after temporary venous occlusion, s	40.7±0.29	84.2±0.12 p<0.01
	IAAVW	1.12±0.004	1.48±0.008 p<0.01
ristomycin	Aggregation of platelets in intact plasma, s	30.1±0.17	45.9±0.12 p<0.01
	Aggregation of platelets in plasma after temporary venous occlusion, s	38.4±0.20	70.8±0.15 p<0.01
	IAAVW	1.27±0.003	1.54±0.009 p<0.01
adrenaline	Aggregation of platelets in intact plasma, s	67.0±0.15	99.9±0.09 p<0.01
	Aggregation of platelets in plasma after temporary venous occlusion, s	92.5±0.60	167.6±0.15 p<0.01
	IAAVW	1.38±0.002	1.68±0.010 p<0.01

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DISCUSSION

It is known that AP and other components of MS separately and, especially at their combination, disturb the function of avascular wall, promoting the development of thrombophilia [20]. At the same time, the activity of vascular hemostasis in the given category of patients needs to be specified. In particular, there is no final clarification about the state degree of basic mechanisms of formation and support of angiopathy in them at AH of the 3rd degree in conditions of MS.

There's no doubt that dyslipidemia of II b type, combining with plasma LPO activation, develops at AH of the 3rd degree and MS. These factors influence rather negatively metabolic processes in vascular walls. Such situation promotes alteration strengthening of all endotheliocytes' structures including their DNA. It weakens their functional features and lightens CS penetration into vascular wall, thus, creating morphological conditions for angiopathy aggravation [21].

High level of arterial pressure, noted in examined patients, influenced negatively functional features of the vascular wall. Apparently, it was caused by not only evident endothelium alteration but also uncovering of sub-endothelial fibers which could activate platelets by contact [22]. In these conditions, the synthesis of biologically active substances, which can decelerate platelet adhesion and aggregation, weakened in the vascular wall. The synthesis of pro-aggregants strengthened in platelets on this background. It was proved by noted in patients evident intensity of thromboxane synthesis and output lowering of its functional antagonist–prostacyclin. It developed more evident misbalance of arachidonic acid metabolites in their blood than at AH of the 1st and 2nd degree and MS [23]. It's possible that on the basis of a given situation we had evident activation of platelet thromboxane synthetase and strong activity weakening of vessels' prostacyclin-synthetase. Found disturbances were evidently deepened by an increase of endothelin-1 synthesis in vascular wall and generation weakening of nitric oxide in it. On the basis of these abnormalities, the examined patients had evident activity disturbance of endotheliocytes' enzymes by, probably, surplus plasma LPO and the presence of dyslipidemia what significantly surpassed the situation at AH of the 1st and 2nd degree on the background of MS [2,13].

At carrying out the test with temporal ischemia of venous wall the patients were found to have a weakening of vessels' ability to repress adhesive features of platelets with the help of at least two mechanisms [24]. The first mechanism was connected with the evident lowering of control from the side of the vascular wall over the density of collagen receptors- glycoproteins Ia-IIa and VI on platelets' membranes. It was found according to weak AP deceleration in response to collagen in plasma after temporal venous ischemia. The second mechanism of strong depression of vascular weakening of platelets' adhesion in persons with AH of the 3rd degree and MS was connected with evident strengthening of von Willebrand Factor's output by structures of vascular wall and its active binding with receptors to it – (glycoproteins I b) on platelets' surface in conditions of vascular antiaggregant' deficiency [25]. We managed to judge the level rise of von Willebrand Factor by early AP with ristomicin which was like subendothelial vessels' fibers as far as its impact on platelets was concerned. It's known that von Willebrand Factor connecting by one end of themolecule with collagen and by the second one through glycoprotein I b – with platelet, formed "adhesion axis": collagen – von Willebrand Factor –glycoprotein I b. Synthesis strengthening of von Willebrand Factor according to the mechanism of positivefeedback increased the amount of receptors to it on platelets' membranes, raising their adhesive readiness [26]. The increase of von Willebrand Factor's quantity in patients' plasma, probably, took place in the result of its active release out of endothelium and to some extent, on behalf of secretion by platelets under hemodynamic impacts and metabolic abnormalities. At the same time, the degree of these processes prevailed over the same ones of the patients with AH of the 1stand 2nd degree at MS. The first mechanism of vessels' control over platelets' adhesive ability is very important in theprovision of hemostasis process in conditions of low shear stress – in large arteries and veins, the second one – at high shear stress in the course of bloodstream in little arteries and arterioles [27].

In conditions of insufficient synthesis of physiological antiaggregant in vessels at AH of the 3rd degree and MS, the strength of fixation of strong aggregation antagonists-collagen and thrombinto their receptors on platelets' membranes rose quickly. It led to evident activation of phospholipase C, stimulation of phospho-inositol way through diacylglycerol and protein kinase C with phospholirirovation of proteins of the contractile system. Forming in these conditions surplus inositol triphosphate promoted Ca^{2+} release out of Intra platelet depo intensifying the involution of actomyosin [28]. Being weak inductors of platelets' aggregation ADP and

adrenaline also more actively than at AH of the 1st-2nd degree with MS, interacted with their own receptors on their membranes. It took place in conditions of deficiency of prostacyclin and nitric oxide formation in vessels, caused evident expression of fibrinogenic receptors (glycoproteins IIb-IIIa) and stimulated the activity of phospholipase A_2. The last one provided the release of asurplus quantity of arachidonic acid out of platelets' phospholipids. In these conditions,cyclooxygenase and thromboxanesynthetase of platelets, activated by metabolic abnormalities and LPO strengthening, increased abundantly thromboxane A_2formation. In physiological conditions of AH of the 1stand 2nd degree with MS thromboxane A_2 and products of inositol way still, could stimulate the yield of prostacyclin out of vessels. Prostacyclin limited the impact ofthromboxane A_2 [29,30]. However, at AH of the 3rd degree with MS the secretion of given substances out of vessels weakened to such extent that couldn't already compensate the activity of proaggregants. It's possible that developing deep abnormalities of hemodynamics in combination with shears in the lipidic range of plasma and strengthening of LPO in it formed all the picture of angiopathy in the given category of patients.

CONCLUSION

Patients with AH of the 3rd degree and MS on the background of strengthened aggregatory activity of platelets had anevident lowering of the antiaggregatory ability of vascular wall. We see the basis of these disturbances in shears in lipidic metabolism, activation of plasma lipids' peroxidation, misbalance of arachidonic acid metabolites in blood and synthesis strengthening of von Willebrand Factor in the vascular wall. Given disturbances surpass the same ones at AH of the 1st-2nd degree and MS and are important factors in the rise of thrombogenic danger for the examined category of patients.

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