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Disaggregating Vascular Impacts on Platelets in Patients with Arterial Hypertension Of The 3rd Degree.

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ABSTRACT

Wide prevalence of high degree arterial hypertension among persons of mature age and large frequency of its complications dictate the necessity of researches' continuation in this group of patients. Special attention should be devoted to antiaggregatory properties of vessels mostly limiting the duration and life quality of patients with arterial hypertension of the 3rd degree. The aim of the research is to detect antiaggregatory activity of vascular wall at arterial hypertension of the 3rd degree. There were observed 54 patients of the second mature age with arterial hypertension of the 3rd degree. The control group was composed of 25 healthy people of the second mature age. We applied biochemical, hematological and statistical methods of investigation in our research. The examined patients were found to have lowering of vessels' antiaggregatory properties at significantly strengthened platelets' aggregation. These disturbances took place against the background of evident strengthening of plasma lipids' peroxidation, inhibition of nitric oxide and prostacyclin yield in vascular walls at the rise of endothelin level in blood. The patients with arterial hypertension of the 3rd degree were noted to have evident lowering of vascular wall's antiaggregatory capability against the background of platelets' strengthened aggregative activity. Development of these disturbances is a serious factor of thrombophilia formation and needs planned lasting correction. It is necessary to determine the approaches to this correction in future researches.

Keywords: arterial hypertension 3 degrees, vascular wall, platelets, antiaggregation, second mature age.

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INTRODUCTION

Deaggregating impacts from the side of vascular wall on platelets is an important element of blood keeping in liquid state in the body of mammals [1]. Given mechanism is provided by functioning of vascular wall's endothelium which continuously generates different biologically active substances influencing hemostasis [2,3]. Previous researches on vascular hemostasis made it possible to detect the dynamics of its functioning at different states, including arterial hypertension (AH). Last years this pathology attracts more and more attention of researchers [5,6]. It is caused by steady growth of its prevalence among working population [7] and by the necessity of continuation of efficient variants' search of its correction [8,9] and complications' prevention [10]. The largest danger of AH is connected with rather frequent development of different thromboses at it which appear on behalf of synthesis weakeningof substances inhibiting hemostasis [11] activity, in vascular wall. Most researches were conducted on patients with AH of the 1st-2nd degree. It was shown in the given category of patients that arterial pressure rise was accompanied by essential synthesis lowering of different hemostatically significant substances, including nitric oxide, prostacyclin, antithrombin-III, tissue activators of plasminogen [12]. Activation of platelets and hemocoagulation forming thromboses' risk [13,14], often takes place at AH of the 1st-2nd degree. At the same time, the evidence of antiaggregatory vessels' control over platelets' activity isn't yet fully detected at AH of the 3rd degree. That's why we put the following aim in our research: to estimate the state of vascular wall's antiaggregatory function in patients with AH of the 3rd degree.

MATERIALS AND METHODS

Our work was made in accordance with ethical principles established by the European convention on vertebrates' protection which are used for experimental and other scientific purposes (adopted in Strasbourg 18.03.1986 and ratified in Strasbourg 15.06.2006). Hhe research was approved by the Ethics Committee of Kursk Institute of Social Education (branch of Russian State Social University) (record №5 from 12.05.2014).

There were observed 54 patients of the second mature age (46.8±2.5 years) with AH of the 3rd degree [15]. The criteria for the enrollment into the research were as follows: AH existence for not less than 6 years, it corresponded to the level of the 3rd degree, absence of systematic pharmacological treatment of AH (because of personal beliefs). The existing metabolic, oncological and allergic diseases were the criteria for the expulsion from the group of observation.

The patients didn't consume drugs and alcohol, didn't smoke, had average welfare and good housing conditions. Chronic diseases of 7 persons (chronic pyelonephritis, 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 4 persons (chronic tonsillitis and chronicbronchitis) 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.

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.

Statistical processing of received data was made with the help of a programme package “Statistics for Windows v. 6.0”, “Microsoft Excel”. The results were processed by Student's criterion (t). Differences in data were considered reliable in case of $p<0.05$.

RESULTSANDDISCUSSION

We found strengthening of LPO in plasma: concentration of TBA-active products in it was equal to 5.11±0.008 mmol/l (in control group – 3.38±0.006 mmol/l), the content of AHP – 3.32±0.009 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 23.6±0.10% (in the control group – 36.8±0.03%) (table).

In the blood of patients from the experimentalgroup, we found misbalance of arachidonic acid metabolites: the level of thromboxane B_2 rose on 40.6%, at the level lowering of its functional antagonist’s derivative – 6-keto-prostaglandin $F_{1\alpha}$ on 14.1%. It was accompanied by high level of endothelin-1 in the blood (18.7±0.19 pg/ml) of examined patients and lowering of the content of summary nitric acid metabolites on 22.2% in it (Table).

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 – 25.1±0.09s (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 – 40.0±0.26s (in the control group – 56.9±0.10s) and 70.1±0.18s (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). Therefore, the maximumvalue of IAAVW was noted for adrenaline – IAAVW 1.41±0.005, 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 – 1.19±0.009 and 1.36±0.005, respectively.

Chronically elevated blood pressure level with AH has a very deleterious effect on blood vessels, disrupting their function, which contributes to 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 activity features of basic mechanisms of formation and support of angiopathy in them at AH of the 3rd degree in conditions.

High level of arterial pressure, noted in examined patients, influenced negatively functional features of the vascular wall [21]. 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 [23]. 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 [24]. 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 [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 [25]. 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 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 [26]. 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 the molecule 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 positive feedback increased the amount of receptors to it on platelets' membranes, raising their adhesive readiness [27]. 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. The first mechanism of vessels' control over platelets' adhesive ability is very important in the provision 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 [27,28].

In conditions of insufficient synthesis of physiological antiaggregant in vessels at AH of the 3rd degree, the strength of fixation of strong aggregation antagonists-collagen and thrombin to 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 plateletdepo intensifying the involution of actomyosin [29]. Being weak inductors of platelets' aggregation ADP and adrenaline also more actively than at AH of the 1st-2nd degree, 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 a surplus quantity of arachidonic acid out of platelets' phospholipids. In these conditions,cyclooxygenase and thromboxane synthetase of platelets, activated by metabolic abnormalities and LPO strengthening, increased abundantly thromboxane A_2 formation. In physiological conditions of AH of the 1stand 2nd degree thromboxane A_2 and products of inositol way still, could stimulate the yield of prostacyclin out of vessels. Prostacyclin limited the impact of thromboxane A_2 [30]. However, at AH of the 3rd degree 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 on the background of strengthened aggregatory activity of platelets had an evident 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 are important factors in the rise of thrombogenic danger for the examined category of patients.

Table: The indicators considered in the surveyed

Registered parameters	Patients, n=54, M±m	Control, n=25, M±m
AHP, D_{233} /1ml	3.32±0.009	1.62±0.002 p<0.01
TBA-compounds, mcmol / l	5.11±0.008	3.38±0.006 p<0.01
plasmaantioxidantactivity, %	23.6±0.10	36.8±0.03 p<0.01
thromboxaneA_2, pg/ml	220.1±0.39	156.5±0.66 p<0.01

6-keto-prostaglandin $F_{1\alpha}$, pg/ml		72.2±0.40	82.4±0.49 p<0.01
Total metabolites nitrogen oxide, mcmol / l		27.5±0.32	33.6±0.35 p<0.01
endothelin-1, pg/ml		18.7±0.19	8.2±0.15 p<0.01
Aggregation inductor ADP	Aggregation of platelets in intact plasma, s	27.4±0.08	42.9±0.10 p<0.01
	Aggregation of platelets in plasma after temporary venous occlusion, s	38.1±0.07	65.4±0.22 p<0.01
	IAAVW	1.39±0.005	1.52±0.012 p<0.01
Aggregation inductorcollagen	Aggregation of platelets in intact plasma, s	25.1±0.09	32.4±0.04 p<0.01
	Aggregation of platelets in plasma after temporary venous occlusion, s	34.1±0.08	48.9±0.09 p<0.01
	IAAVW	1.36±0.005	1.51±0.008 p<0.01
Aggregation inductor thrombin	Aggregation of platelets in intact plasma, s	40.0±0.26	56.9±0.10 p<0.01
	Aggregation of platelets in plasma after temporary venous occlusion, s	47.6±0.34	84.2±0.12 p<0.01
	IAAVW	1.19±0.009	1.48±0.008 p<0.01
Aggregation inductorristomycin	Aggregation of platelets in intact plasma, s	33.1±0.14	45.9±0.12 p<0.01
	Aggregation of platelets in plasma after temporary venous occlusion, s	43.0±0.23	70.8±0.15 p<0.01
	IAAVW	1.30±0.007	1.54±0.009 p<0.01
Aggregation inductor adrenaline	Aggregation of platelets in intact plasma, s	70.1±0.18	99.9±0.09 p<0.01
	Aggregation of platelets in plasma after temporary venous occlusion, s	98.8±0.51	167.6±0.15 p<0.01
	IAAVW	1.41±0.005	1.68±0.010 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.

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