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Influence of Regular Feasible Physical Activity on the Platelet's Functional Activity of the Second Mature Age People

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ABSTRACT

It is known that feasible regular muscle training of an aerobic nature helps to reduce platelet activity of people with high normal blood pressure. At the same time, the physiological reaction of platelets to regular physical activity of the second mature age people with already formed arterial hypertension remains not entirely clear. Purpose of the study is to find out the possibilities of regular moderate aerobic physical activity of the second mature age people with newly developed arterial hypertension. The platelets functional activity of physically exercising and avoiding physical exercises people of the second mature age with arterial hypertension was traced by using optical aggregatometry and cytometry with an assessment of P-selectin level and GP IIb-IIIa on the platelet surface. The platelet aggregation activity and the number of GP IIb-IIIa molecules and P-selectin on platelet membranes of patients who took aspirin and had low physical activity and under the control were comparatively high. Platelet aggregation of patients, who trained physically, was not expressed, and under the ADP action on platelet membranes, the amount of GP IIb-IIIa and P-selectin did not change significantly. The paper shows the possibility of weakening the platelets activity of patients with recent arterial hypertension under the influence of regular physical activity. The results obtained give a reason to consider regular dosed physical activity as an obligatory component of the treatment of this category of patients to minimize the development of their thrombotic manifestations.

Keywords: Arterial hypertension, P-selectin, GP IIb-IIIa, Aggregation, Platelets, ADP, physical exercise.

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INTRODUCTION

Currently, cardiovascular diseases remain very common all over the world of people of different ages[1,2]. At the beginning of their development diseases often proceed without significant clinical manifestations, but in most cases they are accompanied by some vivid activation of platelets[3]. This significantly increases the risk of developing vascular complications of cardiac patients [4,5].

A large proportion of cardiovascular pathology is arterial hypertension (AH). This attracts close attention to AH of modern medicine, which does everything possible to reduce the prevalence of AH, increase the effectiveness of its treatment and effective prevention of thrombosis of any localization, which are very frequent AH complications [6,7].

It has long been noted that platelet aggregation already from the early stages of the arterial hypertension development begins to increase, which creates the need to continue its comprehensive study[8]. At present, it is recognized as one of the most important pathogenetically significant factors in the thrombosis occurrence in AH[9]. For a comprehensive understanding of the platelets functional characteristic features when having hypertension, their further activity rating seems to be necessary when using different inducers of aggregation at different concentrations in this category of patients experiencing drug and non-drug effects [10, 11].

Medicine actively uses various antiplatelet agents to restrain platelet activity [12]. In this respect possibilities of dietary influence and physical activity have also been noticed [13]. The latter variant of recovery seems to be the most physiological and capable of having a positive effect on many components of the pathogenesis of hypertension. Earlier it was noted that feasible and regular physical activity can optimize vascular tone in cardiac pathology, including AH, often reducing the level of blood pressure to standard values [14]. They can significantly improve the quality of life of such patients and significantly improve their overall well-being [15]. It was also noted that regular physical activity can reduce the incidence of vascular complications in patients with AH, which significantly reduces the incidence of their disability[16].

In previous studies, it was noted that feasible muscle training of an aerobic nature, carried out regularly, has a positive effect on platelet activity of people with high normal blood pressure[17]. At the same time, the physiological reaction of platelets to regular physical activity of the second mature age people with already formed AH remains not entirely clear. The solution has not

been found in this field which indicates a serious gap in the system of physiological views on the possibility of regulating platelet activity with the help of feasible regular muscle activity under condition of vascular dysfunction formed in the body. The aim of the study was to find out the possibilities of regular moderate aerobic physical activity of the second mature age people with newly developed AH.

METHOD

The research was approved by the Ethics Committee of Russian State Social University (record №5 from 12.05.2017). The study was carried out on 74 male volunteers of the second mature age who signed an informed consent to participate in it. All of them were divided into 3 considered groups. Study group 1 included 22 people (mean age 55.2±1.9 years), suffering from AH stage 2, stage 2 hypertension for at least 1 year and no more than 2 years, who received enalapril 10 mg 2 times a day and aspirin 100 mg/day. The group of observed 2 consisted of 25 patients (mean age 56.6±2.8 years), suffering from stage 2, stage 2 hypertension for more than 1 year and less than 2 years, who received enalapril 10 mg 2 times a day, aspirin 100 mg/day and for at least one year, daily jogging at a free pace in the evening for 30 minutes a day no later than 2 hours before bedtime. The choice of an antihypertensive agent was dictated by the available information about the absence of the enalapril effect on platelet activity. The control group consisted of 27 volunteers who did not have cardiovascular, metabolic and oncological diseases (mean age 57.1±1.8 years), did not use any antiplatelet drugs and had never physically trained before. To assess the state of platelet aggregation, register the level of GP IIb-IIIa and the severity of the expression of P-selectin molecules on platelet membranes, the blood of the examined patients was taken from a vein and put into plastic vacuum tubes, which contained 3.8% sodium citrate. Platelet-rich blood plasma was obtained by centrifugation at 1500 rpm for 5 minutes at room temperature. By centrifuging platelet-rich plasma at 3000 rpm for 15 minutes, platelet-depleted blood plasma was obtained. It was used when it was necessary to dilute platelet-rich plasma to a concentration of 300 thousand cells/μl, and to calibrate the aggregometer to the level of T = 100%. The severity of ADP-induced platelet aggregation was assessed with the help of a photometric method using a SOLAR aggregometer (Belarus) and an ADP inducer manufactured by Sigma-Aldrich, USA at concentrations of 2.5 μM, 5 μM, and 10 μM. Platelet aggregation was determined by the dynamics of the intensity of light transmission (T,%) at the maximum point and by the level of the rate of aggregation (V,% / min) 30 seconds after the platelet-rich plasma ADP solution entered. The amounts of GP IIb-IIIa and P-selectin on platelets were determined using a CYTOMICS FC 500 flow cytometer (BeckmanCoulter, USA) using fluorescently labeled monoclonal antibodies CD61-FITC and CD62P-PE. For this study, venous whole blood was taken, diluted 50 times with phosphate buffer (1 x PBS). To ensure staining with fluorescently labeled antibodies, 40 μl of diluted blood was incubated with 5 μl of CD61-FITC or CD62P-PE for 15 minutes at room temperature. For the onset of platelet activation, 10 mM ADP was added to the diluted blood together with labeled antibodies. To create a negative control, anti-mouse immunoglobulin antibodies were used that were labeled with FITC and PE. The course of the reaction was interrupted by the addition of 455 μl of 1 x PBS. Subsequently, the samples were placed in a flow cytometer for analysis. The amount of GP IIb-IIIa on the outer membranes of platelets before and after exposure to 10 μM ADP was evaluated as the mean fluorescence intensity (MFI). The level of P-selectin expression on platelets was estimated as the percentage of cells labeled with CD62P-PE before and after exposure to 10 μM ADP. On the basis of the obtained digital values, the ΔGP IIb-IIIa parameter was calculated, which showed an increase in% of the level of GP IIb-IIIa on platelets under the action of ADP in relation to the level of GP IIb-IIIa on platelets not exposed to the action of the inducer. The calculated value of ΔP-selectin showed how much the level of platelets, presenting P-selectin, increased under the action of ADP on them. Statistical processing of the obtained results was carried out using the standard Statistica 6.0 software. The values of the parameters taken into account are given in the article as mean values with their standard error. Comparison of the mean values in the recruited observation groups was carried out using nonparametric methods - Mann – Whitney U-test and Spearman's rank correlation test.

RESULT

Evaluation of ADP-stimulated platelet aggregation carried out in the study did not reveal a significant difference between the non-strenuous control group and the study group 1, who took aspirin as an antiplatelet and had low physical activity. In these groups, there was a high severity of the degree and rate of platelet aggregation development in relation to all concentrations of ADP. In the group of subjects 2, who received aspirin and performed daily jogging at the time of examination, there were statistically significantly lower rates of ADP-induced platelet aggregation (Table 1) compared to the control and group of subjects 1.

Table 1. ADP-Induced Aggregation in Subjects

Groups	ADP inductor 2.5 μM		ADP inductor 5 μM		ADP inductor 10 μM	
	T, %	V, %/ min	T, %	V, %/ min	T, %	V, %/ min
Control group	53.4±4.6	35.5±3.6	69.2±4.7	40.6±4.0	76.3±32.8	41.9±3.2
Observed group 1	54.9±5.3	37.7±5.0	71.8±2.9	43.4±2.3	75.8±2.7	46.8±3.3
Observed group 2	16.9±4.1*	15.6±2.1*	27.5±4.6**	20.2±3.2**	30.3±1.9***	16.1±2.6***

Note. * - p = 0.0003 for T and p = 0.002 for V between the control group and the observed group 2; p = 0.0003 for T and p = 0.03 for V between observation group 1 and observation group 2.

** - p = 0.0002 for T and p = 0.003 for V between control and observation group 2; p = 0.0004 for T and p = 0.005 for V between observation group 1 and observation group 2.

*** - p = 0.0002 for T and p = 0.002 for V between control and observation group 2; p = 0.0003 for T and p = 0.004 for V between observation group 1 and observation group 2.

Evaluation of platelet activity using flow cytometry revealed some increase in the number of GP IIb-IIIa receptors and P-selectin molecules on platelet membranes activated with 10 μM ADP in the control group and in the observed group 1 (Table 2). In the group of subjects 2 who made daily jogging, ADP did not develop a significant increase in the number of neither GP IIb-IIIa molecules nor P-selectin molecules on platelets. This indicated a weak activation of their platelets by ADP. At the same time, the amount of GP IIb-IIIa after the introduction of ADP into the plasma and the level of expression of P-selectin after the introduction of ADP into it were significantly lower in the group of physically active patients. The number of platelets expressing P-selectin without the addition of ADP was slightly higher in the group of observed 2 than in the control group.

Table 2. Levels of GPIIv-IIIa and P-selectin on platelet membranes of patients examined in an intact state and upon their activation by 10 μm ADP

Registered indicators		Control group	Observed group 1	Observed group 2
GP IIb-IIIa, MFI	ADP (-)	18.2±0.7	17.5±2.6	14.8±1.2*
	ADP (+)	21.7±1.1^{+}	23.4±3.8^{+++}	15.4±1.6**
P-selectin, % of cells	ADP (-)	2.8±0.6	3.8±1.1	3.1±1.0
	ADP (+)	30.2±2.9^{++}	17.4±3.5^{++++}	5.6±1.3***

Note. Differences between the 3rd groups: * –p = 0.047; ** - p = 0.02; *** - p = 0.0004.
Differences between ADP (+) and ADP (-): + p = 0.014; ++ - p = 0.0004; +++ - p = 0.03; ++++ - p = 0.03.

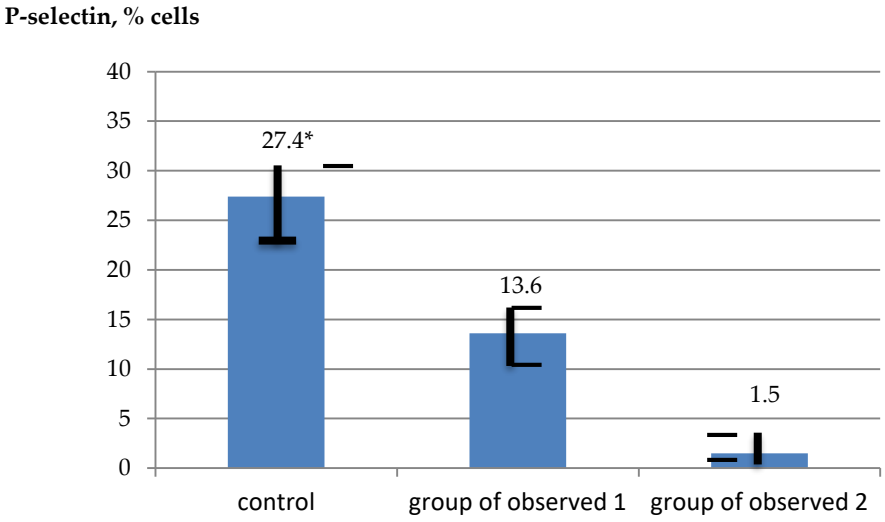
The use of correlation analysis made it possible to establish their relationship between the levels of GP IIb-IIIa and P-selectin and the activity of platelet aggregation. In the general sample, consisting of all examined people, there was a positive and significant correlation between the level of GP IIb-IIIa and the presence of P-selectin after stimulation of platelets with ADP - R = 0.72 (p = 0.000004) and between ΔGP IIb-IIIa and ΔP-selectin - R = 0.44 (p = 0.03). The correlations that were obtained in the study between the considered indicators of platelet aggregation activity and the expression parameters of the considered platelet receptors are presented in Table 3.

Table 3. Correlations between all the considered parameters of platelet activity in the general group of examined

Parameters		GP IIb-IIIa under the influence of ADP	ΔGP IIb-IIIa	P-selectin by ADP	ΔP- selectin
Index T, %	ADP at a dose of 2.5 μM	R = 0.56 p = 0.0006	R =0.33 p =0.04	R = 0.71 p = 0.000008	R =0.45 p =0.009
	ADP at a dose of 5 μM	R =0.37 p =0.04	R = 0.82* p = 0.004	R = 0.65 p = 0.0002	R = 0.57 p = 0.0007
Index V, %/min	ADP at a dose of 2.5 μM	R = 0.28 p = 0.1	No correlation found	R =0.42 p =0.03	R =0.46 p =0.02
	ADP at a dose of 5 μM	R =0.43 p =0.03	No correlation found	R = 0.62 p = 0.00007	R = 0.57 p = 0.0006

Note. * - correlation was found only in group of observed 2.

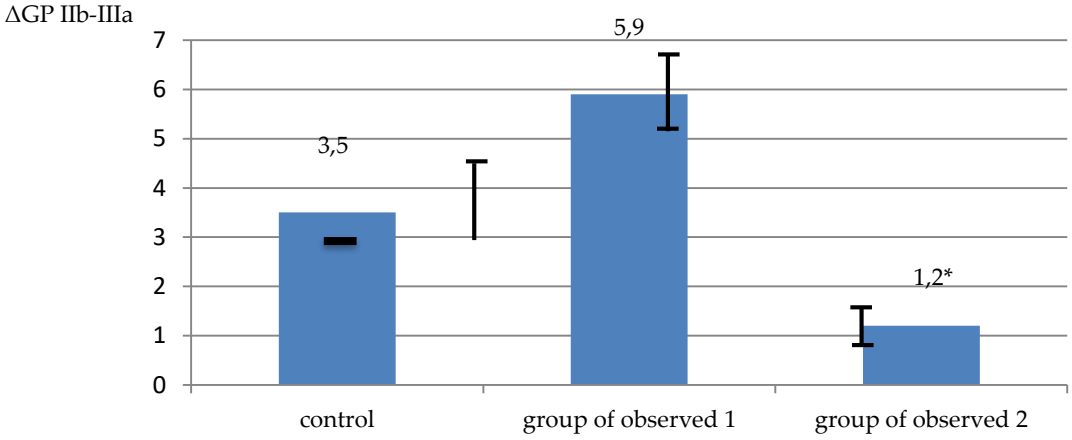
The highest value R = 0.82 was obtained in relation to the relationship between the T index in relation to 5 μM ADP and ΔGP IIb-IIIa in the group of observed 2.



Note: * - p = 0.0002

Figure 1. The severity of P-selectin expression dynamics on platelet membranes under the influence of ADP in the surveyed.

In the study it was found out to what extent the receptor parameters of platelets can change in conditions of regular athletics loads. If the indicators of T and V platelet aggregation caused by ADP in the group of physically active observed decreased by an average of 2.5 times in relation to the control (Table 1), then ΔP-selectin decreased in them by more than 18 times (Figure 1), reflecting the optimization of platelet activation against the background of increased physical activity. The ΔGP IIb-IIIa index was also significantly reduced in the group of observed 2 compared to the rest of the observation groups (Figure 2).



Note: * - p = 0.0002

Figure 2. The degree of change in the surveyed amount of the GP IIb-IIIa receptor on platelet membranes upon activation of ADP

In group 1, the value of ΔP-selectin was lower than the control level (Figure 1), but due to the high ΔGP IIb-IIIa conditions of active ADP-induced aggregation were created. In the absence of regular physical activity the aggregation was not reduced by aspirin intake (Table 1).

DISCUSSION

The presence of vascular dysfunctions in the body always negatively affects the vascular wall, blood system and heart [18, 19]. Platelet activation, which makes a significant contribution to the increased risk of vascular catastrophes, poses a serious threat to the prognosis for patients with hypertension [20]. This is due to the fact that increased platelet aggregation is an important risk factor for the development of thrombosis in the cardiovascular system [21,22]. For this reason, their activity is now being studied especially closely, including the use of an aggregometer and a flow cytometer [23]. The need to monitor the level of

platelet activity in the course of cardiac and oncological patients' therapy is recognized, since it allows to track the individual response to it and its overall effectiveness [24,25]. Previously, it was noted that regular physical activity can weaken to some extent platelet activity of sick and healthy people [14,26]. This effect is very important for people with cardiac pathology [27]. It is connected with the fact that this group of patients is very threatened by thrombosis and often cannot be protected from thrombotic complications because of drug weakening of TxA2 synthesis using aspirin [27,28]. The phenomenon of clopidogrel resistance is also known which is associated with the inability of this drug to block including the ADP receptor - P2Y12 on platelets of cardiac patients, which does not allow to limit their aggregation[29]. In this regard, it becomes clear that there is a need for a wider use of the therapeutic potential of dosed physical activity together with antiplatelet drug therapy in respect of different categories of patients. In view of the great functional significance of platelet receptors GP IIb-IIIa and P-selectin for the realization of their hemostatic potential [30,31], it is of great interest to quantitatively assess their level in patients with hypertension who avoid physical exercise and those who have them regularly.

In this study, a quantitative assessment of the content of glycoprotein receptors GP IIb-IIIa and the level of P-selectin expression on intact platelet membranes and membranes of platelets activated by the addition of 10 μm ADP to the plasma was carried out. It is known that 80% of GP IIb-IIIa are located on the surface of platelets, and 20% of them are in the open tubular system [32,33]. In the examined individuals of the control group, the amount of GP IIb-IIIa under the influence of ADP increased by an average of 20%, which can be explained by the expression of the open tubular system receptors on the surface of platelets due to cytoskeletal rearrangement during their activation. Under these conditions, the GP IIb-IIIa amount of physically inactive patients who received aspirin increased by about 30%, and as for the patients of observed group 2, who took aspirin and made daily jogging, the dynamics of the amount of the GP IIb-IIIa receptor under conditions of ADP action was less than 10%. This should be considered as the appearance of some weakening of the ADP-induced platelet activation mechanisms, possibly largely due to the decrease of the number of ADP-receptor P2Y12 on them [34]. The correlation between the ΔGP IIb-IIIa index and the activity of ADP-platelet aggregation of physically active and physically inactive patients was revealed. At the same time, the degree and rate of this aggregation decreased more significantly against the background of physical exercise in comparison with the control.

Previous studies have shown inhibition of GP IIb-IIIa activation under condition of P2Y12 ADP receptor blocker use [35]. The expression of P-selectin on platelets is very informative regarding platelets functional activity dynamics records, especially in cardiac patients [36,37]. It is connected with the fact that P-selectin is a molecule that is very important for the contact of platelets and leukocytes and which participates in the formation of platelet-leukocyte aggregates[38]. It is believed that it is expressed only on platelets that have undergone activation[39]. A particularly large amount of it is found on platelets in cardiac patients who are often resistant to antiplatelet therapy [40,41]. In this study, the number of platelets expressing P-selectin outside the activation turned to be very low. Thus, we confirmed that inactive platelets almost do not express P-selectin on themselves. Dynamic tracking of this marker is essential for platelets of cardiac patients during therapy, as it helps to predict clinical outcomes for most of these patients[42]. Under activation conditions, the number of platelets interacting with antibodies to P-selectin increased, especially in the observed group 1 who did not experience physical exercise. At the same time, in the physically active subjects of group 2, the number of platelets exhibiting the expression of P-selectin was consistently low, which indicated their weak activation. Apparently obtained in this study the ΔP-selectin indicator, which clearly reflects the activity of platelets, confirms the literature data [43, 44] and shows the possibility of platelet activity inhibition with the help of regular physical exertion. Obviously, in the course of regular physical activity in platelets, the continuously occurring interactions between the platelet's membrane and the cytoskeleton [45] change, bringing intracellular signaling in platelets [46,47] to a more physiological level, contributing to a decrease of total platelet activity.

Using activation by ADP in the course of platelet aggregation assessing and the use of flow cytometry with FITC- and PE-labeled antibodies to the GP IIb-IIIa receptor and P-selectin, the authors managed to obtain new scientific data concerning their dynamics as for hypertensive patients who received aspirin outside regular physical activity and against their background. This helped to understand more clearly the possibilities of regular dosed physical activity in terms of minimizing platelet activity in this category of patients with dangerous development of thrombotic manifestations.

CONCLUSION

In physically exercising and avoiding physical exertion, persons of the second mature age with arterial hypertension, the features of platelet activity were established by using optical aggregatometry and cytometry with an assessment of the level of P-selectin and GP IIb-IIIa on the platelet surface. The platelet aggregation activity and the number of GP IIb-IIIa and P-selectin molecules on platelet membranes in patients who took aspirin and had low physical activity and in control were comparatively high. In patients who trained physically, platelet aggregation was not pronounced, and under the action of ADP on platelet membranes, the amount of GP IIb-IIIa and P-selectin did not change significantly. It is clear that regular dosed physical activity should be a mandatory component of the treatment of patients with arterial hypertension in order to minimize the development of thrombotic manifestations in them.

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CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

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