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Orderly muscle activity in elimination of erythrocytes microrheological abnormalities in rats with experimentally developed obesity

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ABSTRACT

Background: Difficulties of the earliest stages' detection of erythrocytes' microrheological abnormalities' development at obesity are connected with falling out of clinicians' field of view of persons with first signs of this pathology. It dictates the necessity of experimental investigations' fulfillment on laboratory animals with just developed obesity in them. Earlier in this pathology, there was shown high efficiency of non-medication impacts in relation lowering of the value of body mass and weakening of thrombocyte and vascular dysfunctions. At the same time, there is still no clarity in the question about the impact of regular exercise on erythrocytes' microrheological features at the beginning of obesity development.

Methods: 91 of health male-rats of Vistar line at the age of 2.5-3 months , into the investigation. 29 animals of them had experienced no impacts and composed the control group. 62 rats had obesity developed by prescribing them cardioangionefopathogenic semisynthetic diet. Then these rats were casually divided into experimental (32 rats) group and control group (30 rats). Rats from the experimental group during 60 subsequent days experienced daily exercise on a horizontal treadmill. There were used biochemical, hematological and statistical methods of investigation.

Result: As the result of obesity development the rats turned out to have steady developing increase in systolic and diastolic pressure. At regular exercise, on the treadmill, the rats were noted to have a gradual decrease of their values during 60 days of investigation to the level of the norm. During obesity development lipids' peroxidation activated in rats' erythrocytes because of activity weakening of their antioxidant protection. On the background of muscle activity in rats with obesity the content of lipids' peroxidation products in erythrocytes progressively decreased and by the 60th day of experiment reached the control level of healthy rats. At obesity development in rats, there was found a reliable decrease of erythrocytes-discocytes quantity in blood. It was accompanied by the increase of reversibly and irreversibly changed erythrocytes' quantity in examined animals' blood. Their values were returning to control the level of healthy rats during 60 days of regular muscle activity. At obesity development in rats, there was found the quick rise of erythrocytes' sum in aggregate and these aggregates' quantity at lowering of free erythrocytes' number. Their quantity returned to control values to the end of 60 days of exercise. During experimental obesity modeling, we noticed very early in rats' blood decrease of erythrocytes-discocytes' quantity, the level rise of their reversibly and irreversibly varieties with a strengthening of their aggregative ability. It takes place in the background of the weakening of erythrocytes' antioxidant protection and activation of lipids' peroxidation in them. Regular lasting muscle activity can eliminate existing erythrocytes' microrheological features' abnormalities in rats with recently developed obesity.

Keywords: Rats, erythrocytes, microrheological features, experiment, obesity, exercise.
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INTRODUCTION

At present fundamental medicine attentively examines early development stages of different pathology and mechanisms of its realization.[1-4] taking into consideration their social aspects.[5] Traditionally in the focus of many researchers' attention, we can find functional and rheological features of basic regular blood elements and especially - their most numerous population - erythrocytes at rather widespread at present cardio-vascular and metabolic diseases.[6-14] Among them, one of the leading positions is occupied by developing under the impact of genetic predisposition and way of life obesity (OB) of abdominal type leading to dyslipidemia, hypertension and metabolic syndrome.[15-20] It was noted that at hemodynamic and metabolic abnormalities we could notice high activity of neutrophils, platelets and worsening of erythrocytes' microrheological features what significantly lowers microcirculation efficiency and metabolism intensity in all the tissues in comparison with healthy people.[21-26] Absence of ability to trace the earliest stages of erythrocytes' microrheological abnormalities' development in a human being at first OB signs because of these persons' fall out of clinicians' field of view dictates

Table 1 **Dynamics of Arterial Pressure, Biochemical and Hematological Parameters in Experimental Rats (Conventional signs: p - found the reliability of indices' differences with the control group of healthy animals)**

	Experimental formation of pathology, M ± m		Regular forced jogging in rats with formed pathology, M ± m, n = 32				Control, M ± m	
Indicators	initial state, n = 62	end of pathology modeling, n = 62	initial state	20 days	40 days	60 days	sick, n = 30	healthy, n = 29
Value of body mass, kg	224.1 ± 0.48	281.3 ± 0.34 p<0.01	280.9 ± 0.40 p<0.01	263.4 ± 0.59 p<0.01	242.0 ± 0.29 p<0.01	226.5 ± 0.46	284.6 ± 0.58 p<0.01	215.1 ± 0.43
Abdominal cavity, cm	13.9 ± 0.24	16.9 ± 0.27 p<0.01	17.0 ± 0.29 p<0.01	15.3 ± 0.35 p<0.01	14.6 ± 0.12 p<0.05	13.7 ± 0.37	17.2 ± 0.46	215.1 ± 0.43
Acylhydroperoxides of plasma, D233/l ml	1.60 ± 0.012	1.92 ± 0.032 p<0.01	1.93 ± 0.030 p<0.01	1.86 ± 0.027 p<0.01	1.74 ± 0.025 p<0.05	1.62 ± 0.022	1.96 ± 0.032 p<0.01	1.63 ± 0.019
Thiobarbituric acid-products of plasma, mkmol/l	3.68 ± 0.031	4.29 ± 0.044 p<0.01	4.25 ± 0.042 p<0.01	4.14 ± 0.036 p<0.01	3.90 ± 0.032 p<0.01	3.72 ± 0.024	4.28 ± 0.041 p<0.01	3.69 ± 0.32
Antioxidant activity of plasma, %	28.9 ± 0.29	24.4 ± 0.44 p<0.01	24.3 ± 0.47 p<0.01	25.5 ± 0.42 p<0.01	26.8 ± 0.36 p<0.05	28.6 ± 0.40	24.0 ± 0.49 p<0.01	28.8 ± 0.29
cholesterol of eryth rocytes, mkmol/10^{12} erythrocytes	0.91 ± 0.019	1.06 ± 0.027 p<0.01	1.05 ± 0.030 p<0.01	0.99 ± 0.029 p<0.05	0.95 ± 0.025	0.92 ± 0.027	1.07 ± 0.040 p<0.01	0.92 ± 0.023
common phosp holipids of erythro cytes, mkmol/10^{12} erythrocytes	0.67 ± 0.022	0.61 ± 0.034 p<0.01	0.61 ± 0.035 p<0.01	0.63 ± 0.032 p<0.05	0.65 ± 0.029	0.67 ± 0.026	0.60 ± 0.033 p<0.01	0.68 ± 0.022
cholesterol/common phospholipids of erythrocytes	1.36 ± 0.032	1.74 ± 0.037 p<0.01	1.72 ± 0.040 p<0.01	1.57 ± 0.032 p<0.01	1.46 ± 0.027 p<0.05	1.37 ± 0.024	1.55 ± 0.038 p<0.01	1.35 ± 0.019
acylhydroperoxides of erythrocytes, D233/10^{12} erythrocytes	2.75 ± 0.016	3.51 ± 0.025 p<0.01	3.49 ± 0.030 p<0.01	3.22 ± 0.031 p<0.01	3.02 ± 0.028 p<0.05	2.76 ± 0.025	3.55 ± 0.039 p<0.01	2.74 ± 0.017
malonic dialdehyde of erythrocytes, nmol/10^{12} erythrocytes	0.92 ± 0.015	1.16 ± 0.027 p<0.01	1.15 ± 0.029 p<0.01	1.08 ± 0.025 p<0.01	1.01 ± 0.022 p<0.05	0.90 ± 0.017	1.17 ± 0.040 p<0.01	0.91 ± 0.018
catalase of erythrocytes, ME/10^{12} erythrocytes	9920.0 ± 14.9	8750.0 ± 17.3 p<0.01	8780.0 ± 19.2 p<0.01	9050.0 ± 17.7 p<0.01	9420.0 ± 16.2 p<0.05	9900.0 ± 14.8	8735.0 ± 18.4 p<0.01	9880.0 ± 11.9
superoxidismutase of erythrocytes, ME/10^{12} erythrocytes	1835.0 ± 2.90	1600.0 ± 4.65 p<0.01	1606.0 ± 5.29 p<0.01	1690.0 ± 4.76 p<0.01	1785.0 ± 5.33 p<0.05	1825.0 ± 5.06	1590.0 ± 7.10 p<0.01	1830.0 ± 4.05
erythrocytes-discocytes,%	84.4 ± 0.35	71.8 ± 0.49 p<0.01	72.0 ± 0.51 p<0.01	75.0 ± 0.48 p<0.01	79.1 ± 0.41 p<0.05	83.9 ± 0.37	70.5 ± 0.54 p<0.01	84.0 ± 0.34
reversibly modified erythrocytes,%	9.5 ± 0.34	17.0 ± 0.48 p<0.01	17.2 ± 0.45 p<0.01	14.7 ± 0.38 p<0.01	11.9 ± 0.35 p<0.05	9.8 ± 0.34	17.5 ± 0.49 p<0.01	9.5 ± 0.29
irreversibly changed erythrocytes,%	6.1 ± 0.24	11.2 ± 0.31 p<0.01	10.8 ± 0.32 p<0.01	10.3 ± 0.30 p<0.01	9.0 ± 0.26 p<0.01	6.3 ± 0.24	12.0 ± 0.38 p<0.01	6.5 ± 0.25
the sum of all the erythrocytes in an aggregate	37.2 ± 0.08	46.2 ± 0.11 p<0.01	46.0 ± 0.10 p<0.01	43.0 ± 0.08 p<0.01	40.4 ± 0.07 p<0.05	37.6 ± 0.05	46.7 ± 0.14 p<0.01	37.3 ± 0.07
the quantity of aggregate	8.6 ± 0.07	12.0 ± 0.10 p<0.01	12.2 ± 0.09 p<0.01	10.6 ± 0.07 p<0.01	9.5 ± 0.09 p<0.05	8.7 ± 0.07	12.4 ± 0.10 p<0.01	8.8 ± 0.04
the quantity of free erythrocyte	247.5 ± 0.52	226.1 ± 0.64 p<0.01	226.4 ± 0.65 p<0.01	232.4 ± 0.54 p<0.01	241.8 ± 0.45	250.1 ± 0.32	227.3 ± 0.65 p<0.01	249.2 ± 0.52

the need to conduct experimental investigations on laboratory animals with OB modeling in them.[27,28]

In conditions of complicated metabolic abnormalities, we showed earlier high efficiency of non-medication impact of regular muscle activity with hypertension lowering and weakening of thrombocyte and vascular dysfunctions.[29-34] Earlier in the experiment, we showed the ability of exercise to inhibit aging changes of thrombocyte activity.[35] At the same time, one question isn't yet clear - the question concerning the impact of regular exercise on erythrocytes' microrheological features at the very debut of OB development. The most realistic way of getting the given information is also through experiment. It can be beneficial for future clinical investigations directed at a specification of the defensible pathogenetic moment of correctional impacts beginning and their character in persons with developing OB.[36,37] In this connection we put the aim of our work: to watch in conditions of experimental OB the development process of erythrocytes' microrheological features' abnormalities having estimated impact degree of regular muscle activity on them.

METHODS

All the investigations in the present work conducted in full correspondence with ethical norms and recommendations on humanization of work with laboratory animals containing "The European Convent on the protection of vertebrate animals used for experiments or in other scientific purposes" (Strasbourg, 1986).

We took into investigation 91 healthy male-rats of Vistar line at the age of 2.5-3 months received from healthy females by the first-second farrow. Animals' body mass at the moment of taking them into investigation composed 209.7 ± 0.49 gr, their abdominal circumference – 13.5 ± 0.24sm. Before the investigation, all the rats hadn't participated in any experiments and had suffered no diseases. 29 animals of them experienced no impacts and a composed control group of healthy rats. They were examined twice: at the beginning and the age of 5-5.5 months, those are simultaneous with the end of experimental rats' investigation. Because of the absence of statistically significant differences between the results of both control rats' investigations received data are presented in one figure - their simple average.

In 62 rats after their putting into small cages (one specimen - in a cage) during 30 days there was developed OB as the result of giving them of high-caloric diet from combined feed (47%), sweet condensed milk (44%), vegetable oil (8%) and vegetable starch (1%).[38]

Later casually these rats were divided into experimental (32 rats) group and a control group of sick rats (30 rats). Rats from the experimental group during 60 subsequent days had daily exercise on horizontal treadmill TORNEO by firm KETLER moving with the speed 5 m/min. The animals put into one section of fixed on the wooden treadmill framework of rectangular form subdivided by wooden partitions into three parts for animal's individual placing. On the first-day exercise duration was 1 min, then it became longer on 1 min a day, till it reached 25 min a day, and this period stayed unchangeable till the end of investigation.[39]

The animals, which composed control group of sick rats, were examined twice - at the moment of pathology development in them and the age of 5-5,5 months, those are the same periods when we finished the investigation of rats with OB having experienced exercise. Because of the absence of statistical differences between results of the first and the second investigations the results are presented by one figure - simple average between them.

The level of lipids' peroxidation (LPO) in animals' plasma was found according to the quantity of thiobarbituric-acid (TBA)-active products in it with the help of a set "Agat-Med" and according to the content of acylhydroperoxides (AHP) taking into consideration the level of antioxidant activity (AOA) of blood liquid part.[40,41] LPO in erythrocytes was defined with the help of concentrations in them of malonic dialdehyde (MDA) and AHP.[40] We estimated in them enzymatically the level of common cholesterol (CS) by a set "Vitaldiagnostikum" (Russia) and found the concentrations of common phospholipids (CPL) according to phosphorus content with the calculation of the ratio CCS/CPL. In erythrocytes, we defined the activity of catalase and superoxiddismutase (SOD).[40]

Cytoarchitectonics of red corpuscles was defined with the help of light phase-contrast microscopy. All the erythrocytes were subdivided into discocytes, reversibly deformed and irreversibly changed forms.[42] Erythrocytes' aggregative activity was found out with the help of light microscope in Goriajev's box by their aggregates' quantity, the quantity of aggregated and not having entered the aggregation red corpuscles in the meal of washed erythrocytes.[43] The results were processed by Student's criterion (t).

RESULTS

In the result of OB model's reproduction, the rats have developed a stable increase of body mass and bulk of abdominal cavity. At regular exercises on a treadmill, the rats with developed OB were noticed to have a gradual lowering of their body mass and bulk of abdominal cavity, and their values in 60 days of investigation reached the level of healthy control animals (Table 1).

At experimental OB development in rats, we noticed an increase of AHP and TBA-active products' quantity in plasma. At fulfillment of regular exercise by rats with OB AHP concentration in plasma gradually decreased being at the end of investigation 1.62 ± 0.022 D233/1 ml. A numbef plasma TBA-products in experimental animals underwent the analogical dynamics. Found LPO increase at OB modeling in rats turned out to be possible because of plasma AOA weakening on 18.4%. Regular muscle activity was accompanied by the rise of the given index' level from 24.3 ± 0.47% at the beginning to 28.6 ± 0.40% by the 60th day of investigation (Table 1).

At OB development in experimental rats cholesterol quantity in erythrocytes rose a bit (to 1.06 ± 0.027 mkmol/10^{12}ar.), while the content of CPL in their membranes tended to decrease (to 0.61 ± 0.034 mkmol/10^{12}ar.), what led to reliable increase of the gradient CS/CPL. On the background of regular muscle activity, we found in erythrocytes gradual CS lowering and CPL increase what provided value optimization of the ratio CS/CPL.

During OB development LPO activated in rats' erythrocytes owing to activity weakening of their antioxidant protection. On the background of muscle activity on the treadmilll, AHP content in erythrocytes of rats with OB progressively lowered and by the 60th day of experiment reached the control level of healthy rats. Experimental rats had analogical dynamics and in the same terms in the concentration of erythrocyte MDA which composed by the 60th day of exercise 0.90 ± 0.017 nmol/10^{12}ar., what corresponded to the values of healthy rats' control group. Found changes of LPO activity in erythrocytes of experimental animals at OB development in them and on the background of the foingllowing exercise turned out to be possible as the result of depression being changed by activation of their antioxidant system, the state of which was judged by the activity of catalase and superoxiddismutase. The levels of their functional features in erythrocytes of experimental rats, having decreased while OB development, on the background of exercise reached values near to the same ones in the control group of healthy rats owing to their activation on 12.7% and 13.6%, correspondingly (Table 1).

At OB development in rats, we found a reliable decrease of erythrocytes-discocytes quantity in the blood which was returning to control level of healthy rats during 60 days of regular muscle activity. It was accompanied in blood of experimental animals by the quantity dynamics of changed reversibly and irreversibly erythrocytes, increasing at OB development and decreasing to the control level of healthy rats during exercise (to 9.8 ± 0.34% and 6.3 ± 0.24%, correspondingly). At OB development in rats, we found some increase of red corpuscles in aggregate and quantity of these aggregates at simultaneous number lowering of free red corpuscles having returned to control values of healthy animals to the end of 60 days of exercise (Table 1).

The absence of regular exercise in the control group of sick rats was accompanied by keeping of all the abnormalities of biochemical and hematological characteristics, inherent for invariably high OB level.

DISCUSSION

Despite the fact that in the basis of OB development in human population lie not only environmental impacts but also presence of different genetic abnormalities, the applied model can be considered as quite adequate for the achievement of putting in the work purpose.[44,45]

In the result of experimental OB development in rats, we created pathological state very near to such one at genetically determined OB.[46,47] At the same time, AOA of blood weakens very fast promoting quantity increase in it of AHP and TBA-products and negatively influencing metabolism in tissues. Besides, activation of LPO processes in liquid part of blood causes alteration of vascular endothelium of regular blood elements' outer structures including the most numerous their population - erythrocytes, thereby negatively influencing their different functions.[10,11,48-51] It is burdened by hypoxia inevitably developing in rats with OB and forming in erythrocytes membranopathy having in its basis increase of CS in them in them with the tendency to CPL lowering at simultaneous activation in erythrocytes of lipids' peroxidation in the result of their antioxidant protection lowering.[52]

Forming situation mostly promotes the loss by a part of erythrocytes of normal biconcave form what makes the process of their moving along capillaries difficult.[19] Forming changes in erythrocytes lead to quantity increase in the blood of their reversibly and irreversibly changed forms.[22] So, in rats by the moment of OB development in them, the quantity

of erythrocytes transformed by echinocytosis into spheres, with the appearance of different forms' acanthas on their surface and stomatocytosis to unilaterally arched disk, significantly exceeds the same at the beginning. Further transformation inevitably goes in the direction of spheroechinocyt, spherostomatocyt and, finally, spherocyte which soon must be destroyed.[10]

Found in rats with formed OB strengthening of erythrocytes' aggregation has mostly in its basis appearing changes of their membrane's charge because of glycoproteins' degradation on it. They have negative charge on the background of active LPO.[53] Intensification of oxygen active forms' generation in these conditions provides the rats with OB by oxidative alteration of membrane's structures at simultaneous damage of plasma globular proteins able to be connected in the kind of "bridges" between separate erythrocytes and realize the process of their aggregation. Besides, LPO products gradually increase the threshold of erythrocytes' deaggregation on behalf of erythrocytes' adhesion strengthening in aggregates, speed rise of aggregation process between itself and platelets on the background of oxidative damages of their membrane's lipids.[54,55]

It becomes clear that found very early rise of erythrocytes' aggregation in rats with developing OB is mostly connected with the impact of catecholamines, the concentration of which, as it is known, from the first development stages of cardiovascular pathology and especially OB significantly increases. As the result of α1-receptors' activation in these conditions as mediator functions the system Ca^{2+}-calmodulin with involvement into the cascade of phosphatidyl inositol's intracellular reactions. Activation of α2-adrenoreceptors takes place by adenylate cyclase suppression owing to the impact of a receptor-agonist on Gi-proteins leading to lowering of cAMP quantity in a cell and stimulating Ca^{2+} inflow into a cell what additionally rises erythrocytes' aggregation.[60,61]

The number rise of freely moving in the blood of rats with OB aggregates leads to damage of endothelial bed of their vessels promoting exposure of subendothelial structures what "starts" hemostasis processes and significantly worsens the processes of blood rheology.[54,59] Rising number of freely circulating aggregates can block the part vasa vasorum, thereby significantly weakening vascular metabolism, promoting depression of de-aggregates' output in endothelial cells.[60,61]

In the basis of developing on the background of regular exercise positive dynamics of erythrocytes' microrheological features lies the growth of antioxidant protection of not only blood plasma but erythrocytes themselves with a fast weakening of LPO in them.[62,63] As the result of regular exercise the rats with developed OB are noted to have a fast strengthening of antioxidant plasma activity causing lowering of AHP and TBA-products' concentrations in it. LPO lowering in the liquid part of blood promotes endothelium stabilization of vessels and receptors on the outer membranes of regular blood elements including the most numerous their population - erythrocytes, positively influencing their characteristics. Simultaneously with it, antioxidant protection rises in erythrocytes what leads to restraining of lipids' peroxidation in them.[10]

Regular muscle activity turned out to be able to change quickly and positively structural-functional features of red corpuscles' membranes and their protein cytoskeleton. months, 60-days-exercises of rats with modeled OB turned out to be able to normalize erythrocytes' cytoarchitectonics with content lowering in the bloodstream of their activated forms to the level of control group indices.

Coming in these conditions changes in erythrocytes lead to quantity lowering in animals' blood of their reversibly and irreversibly transformed forms. So, in rats with OB, while exercising, we noticed significant quantity lowering of erythrocytes having experienced the process of echinocytosis to the state of spheres, and particularly, with the appearance of acanthas of different forms on their membranes. The process of erythrocytes' transformation through stomatocytosis to unilaterally arched disk minimizes, especially in these conditions. All that lightens the process of their circulation along the vessels, especially of the least caliber.[27]

Aggregative erythrocytes' abilities of rats with experimentally developed OB in them in the result of 60-days-exercises also gradually normalized. It was mostly provided by coming changes of their membranes' charge because of optimization on their surface of glycoproteins' quantity on the background of weakening LPO. Developing at that damage minimization of plasma globular proteins having the ability to be connected as "bridges" between erythrocytes also led to the decrease of their aggregation evidence. At the same time, lowering of LPO-products in plasma and erythrocytes lowers their deaggregation threshold because of weakening of erythrocytes' adhesion in aggregates.[12]

It should be supposed that found while exercising weakening of erythrocytes' aggregation in rats is mostly provided by lowering of catecholamines' impact. On the background of α1-receptors' activity lowering decreases the functional readiness of the system Ca^{2+}-calmodulin and cascade of phosphatidyl inositol's intracellular reactions. Weakening of α2-adrenoreceptors' activity leads to activation of adenylate cyclase during physiological impact from receptors on Gi-proteins causing rise

of cAMP quantity in a cell blocking Ca^{2+} inflow into it and providing minimization of erythrocytes' aggregation.[19,65]

Quantity lowering to the control level of freely circulating in experimental rats' blood aggregates on the background of exercise keeps their endothelial bed, what leads to a minimum exposition of subendothelial structures and excludes stimulation of hemostasis processes additionally lightening the processes of blood rheology.[20,66] It is especially important for hemocirculation in vasa vasorum, which play a great role in supporting of vascular wall's trophism and physiological level's providing of its de-aggregative impact on erythrocytes through output of maximally possible quantities of nitric oxide and prostacyclin in endothelium.[31,39,63]

CONCLUSION

During experimental OB modeling in rats' blood, we noticed very early lowering of erythrocytes-discocytes content, rise the level of their reversibly and irreversibly changed variants with the strengthening of their aggregative ability. It happens in the background of the increase in erythrocytes of cholesterol/common phospholipids' gradient, weakening of their antioxidant protection and activation of lipids' peroxidation in them. Regular long muscle activity in the form of jogging can eliminate existing abnormalities of erythrocytes' microrheological features in rats with experimentally developed OB. Coming, at that, lowering to control a level of aggregates' quantity in experimental rats' blood on the background of exercise keeps their endothelial bed minimizing accessibility of subendothelial structures and stimulation of hemostasis. Received data give physicians and cardiologists reason the attention once more on the potential of exercise in developing OB treatment.

CONFLICT OF INTEREST

All authors declare there is no conflict of interest regarding publication of this manuscript.

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