Correctional abilities of regular muscle activity in relation to erythrocytes’ microrheological features of rats with experimentally developed hypertension

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ABSTRACT

Difficulties in the early stage detection of erythrocytes’ microrheological abnormalities during the development of hypertension are connected with falling out of clinicians’ point of view of persons with first signs of this pathology. It dictates the necessity of experimental investigations on laboratory animals with just developed hypertension in them. Earlier at this pathology, it was observed the high efficiency of non-medication impacts in relation to the lowering of arterial pressure and weakening of thrombocyte and vascular dysfunctions. At the same time, there is still no clarity on the question about the impact of regular exercise on erythrocytes’ microrheological features at the beginning of hypertension development. About 87 healthy male rats of Wistar line at the age of 2.5–3 months were taken into the investigation. Twenty-nine animals out of them had experienced no impacts and composed the control group. Fifty-eight rats had hypertension developed by prescribing them cardio angionefo pathogenic semisynthetic diet. Then these rats were casually divided into experimental (31 rats) group and control group (27 rats). Rats from the experimental group during 60 subsequent days experienced daily exercise on a horizontal treadmill. Various subjects like biochemical, hematological, and statistical methods were used for investigation. As the hypertension development, the rats turned out to have a stable developing increase of 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 hypertension development lipids’ peroxidation activated in rats’ erythrocytes because of activity weakening of their antioxidant protection. On the background of muscle activity in rats with hypertension the content of lipids’ peroxidation products in erythrocytes progressively decreased, and by the 60th day of the experiment, they reached the control level of healthy rats. At hypertension development in rats, a reliable decrease of erythrocytes-discocytes quantity in blood was found. It was accompanied by an 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 hypertension development in rats, a quick rise of erythrocytes’ sum in aggregate was found, and the rise in these aggregates’ quantity was due to the decrease of free erythrocytes’ number. Their quantity returned to control values at the end of 60 days of exercise. During experimental hypertension modeling, we noticed very early in rats’ blood decrease of erythrocytes-discocytes’ quantity, the rise of their reversibly and irreversibly level varieties with the 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 hypertension.

Keywords: Rats, erythrocytes, microrheological features, experiment, hypertension, exercise


INTRODUCTION

Modern medical science devotes significant attention to the investigation of early stages of different pathology’s development and initial mechanisms of its realization with the help of numerous models taking into consideration its social consequences. At present, increased interest is shown by researchers to functional and rheological features of different elements of blood. Especially to their most numerous population that is erythrocytes at different diseases including rather wide-spread at present cardiovascular pathologies. Among this group of diseases in the whole civilized world, one of leading positions is occupied by hypertension (AH) leading to the wide invalidation of the population and contributing greatly to mortality figures of able to work persons. It was noticed that at detailed clinical AH picture especially burdened by metabolic abnormalities there is the high activity of platelets, and worsening of erythrocytes’ microrheological features. It significantly lowers microcirculation efficiency and metabolism intensity in all the tissues. At the same time, the state of erythrocytes’ microrheological characteristics at early stages of AH development is not yet studied enough. Difficulties of the early stage detection
of erythrocytes’ microrheological abnormalities’ development in a human being are connected with falling out of clinicians’ point of view of persons with first signs of this pathology including AH.\textsuperscript{27,28} It dictates the necessity of experimental investigations’ fulfillment on laboratory animals with its development modeling in them.\textsuperscript{29,30}

In conditions of AH including metabolic abnormalities, there was shown earlier an efficiency of non-medication impact\textsuperscript{31} of regular muscle activity in relation to arterial pressure lowering and weakening of thrombocyte\textsuperscript{32,33} and vascular dysfunctions.\textsuperscript{34-36} Earlier in the experiment, we showed the ability of exercise to inhibit aging changes of thrombocyte activity.\textsuperscript{37} At the same time, one question is not yet clear - the question concerning the impact of regular exercise on erythrocytes’ microrheological features at the very debut of AH development. The most realistic way of getting the given information is also through experiment. It can be very useful for future clinical investigations directed at the specification of the pathogenic defensible moment of correctional impacts beginning and their character in persons with developing AH.\textsuperscript{38,39} In this connection we put the aim of our work: to watch in conditions of experimental AH the development process of erythrocytes’ microrheological features’ abnormalities having estimated the degree of impact of regular muscle activity on them.

**MATERIALS AND METHODS**

All the investigations in the present work were 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 87 healthy male rats of Wistar 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 210.6±0.52 gr, their abdominal circumference - 13.8±0.28sm. Before the investigation, all the rats had not participated in any experiments and had suffered no diseases. Twenty-nine 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, i.e., simultaneously 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 by one figure which is their simple average. According to the methods,\textsuperscript{40} 58 rats we developed hypertension by prescribing them cardioangionefo pathogenic semisynthetic diet for 2 weeks. Enriched by cholesterol, burdened by salts of twice-substituted sodium phosphate water, and deficient in potassium and magnesium in the background of the daily intramuscular introduction of hydrocortisone acetate suspension of 1.5 mg on 100 gr of animal’s body mass. Changing water for drinking on 1% salt solution and cold impact on animals at the end of fulfilled impact at 4°C during 4 hours for 2-weeks. Later casually these rats were divided into experimental (31 rats) group and a control group of sick rats (27 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 were put into one section of treadmill fixed with rectangular wooden framework form subdivided by wooden partitions into 3-parts for placing animals individually. On the first day of exercise the duration was 1 min, and then it became longer till it reached 25 min a day, and this duration stayed unchanged till the end of investigation.\textsuperscript{41}

The animals, which composed of the control group of sick rats, were examined twice at the moment of pathology development in them and the age of 5–5.5 months, i.e., at the same periods when we finished the investigation of rats with AH 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 that is the simple average between them.

Measuring of animals’ arterial pressure (AP) was fulfilled noninvasively with the help of the device MLU/4c501 by the method of tail cuff application (MedLab, China).

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).\textsuperscript{42} Taking into consideration the level of antioxidant activity (AOA) of liquid blood part.\textsuperscript{43} LPO in erythrocytes was defined with the help of concentrations of malonic dialdehyde (MDA) and AHP in them.\textsuperscript{42} 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 superoxide dismutase (SOD).\textsuperscript{42}

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. Erythrocytes' aggregative activity was found out with the help of light microscope in Goriajev's box by their aggregates' quantity, the quantity of aggregate, and not having entered the aggregation; red corpuscles were found in the meal of washed erythrocytes. The results were processed by Student's criterion (t) and systematic multifactorial analysis.

RESULTS
As the result of AH formation in rats there developed in them stable increase of systolic and diastolic pressure levels. At regular exercise on a treadmill, the given group of rats was noted to have a gradual decrease in the values of systolic and diastolic AP and 60 days of investigation AP figures statistically had no significant differences within the group of healthy control animals (Table 1).

At experimental AH development in rats, we noticed an increase of AHP and TBA-active products' quantity in plasma. At fulfillment of regular exercise by rats with AH, their AHP concentration in plasma gradually decreased at the end of the investigation being 1.64±0.029 D233/1 ml. The quantity of plasma TBA-products in experimental animals underwent the analogical dynamics. It was found an increase of LPO at AH modeling in rats turned out to be possible because of plasma AOA weakening on 18.1%. Regular muscle activity was accompanied by the rise of the given index' level from 24.5±0.52% at the beginning to 28.2±0.36% by the 60th day of investigation (Table 1).

At AH development in experimental rats, the cholesterol quantity in erythrocytes rose a bit (to 1.00±0.031 mmol/1012ar.), while the content of CPL in their membranes had a tendency to decrease (to 0.65±0.036 mmol/1012ar.), what led to a reliable increase of the gradient CS/CPL. On the background of regular muscle activity, we found in erythrocytes gradual CS lowering, and CPL increases what provided value optimization of the ratio CS/CPL.

During AH development LPO activated in rats' erythrocytes owing to weakening activity of their antioxidant protection. On the background of muscle activity on the treadmill, AHP content in erythrocytes of rats with AH progressively lowered and by the 60th day of experiment reached the control level of healthy rats. Experimental rats had analagical dynamics and in the same terms in the concentration of erythrocyte MDA which composed by the 60th day of exercise 0.92±0.020 nmol/1012ar., what corresponded to the values of healthy rats of the control group. Changes of LPO activity was found in erythrocytes of experimental animals at AH development on them, and the background of the following 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 SOD. The levels of their functional features in erythrocytes of experimental rats, having decreased while AH 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 10.8% and 10.9%, correspondingly (Table 1).

At AH development in rats, we found a reliable decrease of erythrocytes-discocytes quantity in the blood which was returning to control the level of healthy rats during 60 days of regular muscle activity. It was accompanied by the blood of experimental animals by corresponding quantity dynamics of changed reversibly and irreversibly erythrocytes, increasing at AH development and decreasing to the control level of healthy rats during exercise (to 10.6±0.36% and 6.9±0.25%, correspondingly). At AH development in rats, we found a sum 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 at 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 all of the abnormalities of biochemical and hematological characteristics, inherent for the invariably high AH level.

Having applied systematic multifactorial analysis, we managed to calculate separately in experimental rats pro-aggregative potential of erythrocytes (PPE) and their de-aggregative potential (DPE), having found the impact degree on them of all the registered parameters, and to realize the calculation of the common erythrocytes' aggregative potential value (CAPE).

In PPE of experimental rats with developed AH the following values were rather heavy: the average aggregate's size (Pi=586.7), aggregates' quantity (Pi=476.8), the quantity of irreversibly transformed erythrocytes (Pi=427.8). Index of aggregation (Pi=426.3), and the sum of all the erythrocytes being in aggregates (Pi=403.1). The value of suspended average PPE estimating on the whole phenomena providing erythrocyte aggregation in rats with AH was equal to 0.112. Very significant in DPE structure in rats with AH were the following values: the activity of erythrocytes' SOD (Pi=518.3), the quantity of erythrocytes-discocytes (Pi=522.6), and catalase functional ability (Pi=531.5). The value of suspended average DPE, estimating the state of
mechanisms which allow erythrocytes to aggregate, in the case of rats with AH was equal to 0.083, and the level of common aggregative potential of their erythrocytes was equal to 0.029.

In PPE of having regular exercise rats with developed AH the following values were the most significant: the average size of an aggregate (Pi=462.1), the number of aggregates (Pi=427.3). The quantity of

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Table 1

<table>
<thead>
<tr>
<th>Indicators</th>
<th>Experimental formation of pathology, M±m</th>
<th>Regular forced jogging in rats with formed pathology, M±m, n=31</th>
<th>Control, M±m</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure, mm Hg.</td>
<td>110.1±0.29</td>
<td>155.3±0.46</td>
<td>20 days</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg.</td>
<td>74.6±0.24</td>
<td>95.1±0.39</td>
<td>20 days</td>
</tr>
<tr>
<td>Acylhydroperoxides of plasma, D_{2/3}/l ml</td>
<td>1.62±0.017</td>
<td>1.91±0.034</td>
<td>20 days</td>
</tr>
<tr>
<td>Thiobarbituric acid-products of plasma, mmol/l</td>
<td>3.71±0.036</td>
<td>4.22±0.047</td>
<td>20 days</td>
</tr>
<tr>
<td>Antioxidant activity of plasma, %</td>
<td>28.7±0.31</td>
<td>24.3±0.49</td>
<td>20 days</td>
</tr>
<tr>
<td>Cholesterol of erythrocytes, mmol/10^{12} erythrocytes</td>
<td>0.92±0.022</td>
<td>1.00±0.031</td>
<td>20 days</td>
</tr>
<tr>
<td>Common phospholipids of erythrocytes, mmol/10^{12} erythrocytes</td>
<td>0.67±0.024</td>
<td>0.65±0.036</td>
<td>20 days</td>
</tr>
<tr>
<td>Cholesterol/common phospholipids of erythrocytes</td>
<td>1.37±0.020</td>
<td>1.56±0.029</td>
<td>20 days</td>
</tr>
<tr>
<td>Acylhydroperoxides of erythrocytes, D_{2/3}/l ml</td>
<td>2.76±0.019</td>
<td>3.36±0.024</td>
<td>20 days</td>
</tr>
<tr>
<td>Malonic dialdehyde of erythrocytes, nmol/10^{12} erythrocytes</td>
<td>0.90±0.016</td>
<td>1.12±0.029</td>
<td>20 days</td>
</tr>
<tr>
<td>Catalase of erythrocytes, ME/10^{12} erythrocytes</td>
<td>9870.0±12.6</td>
<td>8802.0±14.7</td>
<td>20 days</td>
</tr>
<tr>
<td>Superoxidismutase of erythrocytes, ME/10^{12} erythrocytes</td>
<td>1820.0±3.74</td>
<td>1640.0±4.28</td>
<td>20 days</td>
</tr>
<tr>
<td>Erythrocytes-discocytes,%</td>
<td>83.8±0.39</td>
<td>72.7±0.48</td>
<td>20 days</td>
</tr>
<tr>
<td>Reversibly modified erythrocytes,%</td>
<td>9.7±0.32</td>
<td>16.8±0.41</td>
<td>20 days</td>
</tr>
<tr>
<td>Irreversibly modified erythrocytes,%</td>
<td>6.5±0.28</td>
<td>10.5±0.32</td>
<td>20 days</td>
</tr>
<tr>
<td>Sum of all the erythrocytes in an aggregate</td>
<td>37.5±0.09</td>
<td>46.8±0.12</td>
<td>20 days</td>
</tr>
<tr>
<td>Quantity of aggregates</td>
<td>8.7±0.10</td>
<td>11.8±0.09</td>
<td>20 days</td>
</tr>
<tr>
<td>Quantity of free erythrocytes</td>
<td>248.1±0.56</td>
<td>229.0±0.67</td>
<td>20 days</td>
</tr>
</tbody>
</table>

Conventions: p - found reliability of indices’ differences with control group.
irreversibly transformed erythrocytes (Pi=384.7), index of aggregation (Pi=380.5) and the sum of all the red corpuscles in aggregate (Pi=360.1). The value of suspended average PPE fully estimating the mechanisms promoting erythrocytes’ aggregation on the background of exercise in rats with AH was equal to 0.099 what corresponded to control group of healthy rats.

The following values turned out to be very significant in DPE of rats with AH having regular muscle activity: quantity of erythrocytes-discocytes in their blood (Pi=532.4) and also activity levels of catalase (Pi=524.6) and SOD of erythrocytes (Pi=516.0). The value of suspended average DPE reflecting on the whole the state of mechanisms, blocking red corpuscles’ aggregation, in having exercise experimental rats was equal to 0.095, at the value of CAPE 0.009 what corresponded to the control group of healthy rats.

**DISCUSSION**

Despite the fact that on the basis of AH development in human population laid not only environmental impacts but also presence of different genetic abnormalities, the applied model can be considered as quite adequate for the achievement of work involved.

In the result of experimental AH development in rats we created a pathological state very near similar to those genetically determined AH. At the same time, AOA of blood weakens very increase the quantity 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 of their erythrocytes population, thereby negatively influencing their different functions. It is burdened by hypoxia inevitably developing in rats with AH and forming membranopathy in erythrocytes having its basis increase of CS in them with the tendency to CPL lowering at simultaneous activation in erythrocytes of lipids’ peroxidation in the result of their antioxidant protection lowering.

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. Forming changes in erythrocytes lead to increase in the quantity of blood of their reversibly and irreversibly changed forms. So, in rats by the moment of AH 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 spherocytocytic, spherostomatocyte and, finally, spherocyte which soon must be destroyed.

In rats with formed AH strengthening of erythrocytes’ aggregation, it is found that charge of their membrane’s changes because of the degradation of glycoproteins on it. They have a negative charge on the background of active LPO. Intensification of oxygen active forms’ generation in these conditions provides the rats with AH by oxidative alteration of membrane’s structures at the simultaneous damage of plasma globular proteins are able to be connected in the form 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, accelerating the rise of aggregation process between itself and platelets on the background of oxidative damages of their membrane’s lipids.

It becomes clear that very early rise of erythrocytes’ aggregation in rats with developing AH 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 AH significantly increases. As a result of α-receptors’ activation in these conditions functions as mediator the Ca2+-calmodulin system with involvement into the cascade of phosphatidyl inositol’s intracellular reactions. Activation of α-adrenoreceptors takes place by adenylate cyclase suppression owing to the impact of a receptor agonist on Gi-proteins leading to lowering of CAMF quantity in a cell and stimulating Ca2+ inflow into a cell what additionally increases the erythrocytes’ aggregation.

The rising number of freely circulating aggregates in the blood of rats with AH aggregates leads to damage of endothelial bed of their vessels promoting exposure of subendothelial structures what “start” the hemostasis processes and significantly worsens the processes of blood rheology. Rising number of freely circulating aggregates can block the part vasa vasorum, thereby significantly weakening vascular metabolism, promoting depression of deaggregates’ output in endothelial cells.

On the basis of developing in 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 the fast weakening of LPO in them. As the result of regular exercise, the rats with developed AH are noted to have a fast strengthening of antioxidant plasma activity causing lowering of AHP and TBA-products’ concentrations in them. 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, the erythrocytes, positively influencing their characteristics. Simultaneously with the rise of antioxidant protection in erythrocytes what leads to the restraining of lipids’ peroxidation in them.13

Regular muscle activity turned out to be able to change quickly and positively the structural and–functional features of red corpuscles’ membranes and their protein cytoskeleton. Coming from the background of LPO weakening and strengthening of ATF synthesis in erythrocytes, as in other regular blood elements,14 it leads to activity rise of ion pumps which provide optimum content in erythrocytes of Ca2+, Na+ and K+.12,25 It is possible that on the basis of cytoarchitectonics’ stabilization there is also the optimum provision of spectrin net structure with the provision of necessary distance between spectrin molecules. Sixty days exercises of rats with modeled AH 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.

With the change in these conditions in erythrocytes lead to lowering in the quantity of their reversibly and irreversibly transformed forms in animals’ blood. So, in rats with AH 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 those discussed above lighten the process of their circulation along the vessels, especially of the least caliber.30

Aggregative erythrocytes’ abilities of rats with experimentally developed AH in them in the result of 60 days exercises also gradually normalized. It was mostly provided by the changes in their membranes because of optimization on their surface of glycoproteins’ quantity on the background of weakening LPO. Developing with the 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 the weakening of erythrocytes’ adhesion in aggregates.15

It should be supposed that while exercising weakening of erythrocytes’ aggregation in rats is mostly provided by lowering of catecholamines’ impact.29 On the background of α1-receptors’ activity, the functional readiness of the Ca2+-calmodulin system and a cascade of phosphatidyl inositol’s intracellular reactions decreases. The weakening of α1-adrenoreceptors’ activity leads to activation of adenylate cyclase during physiological impact from receptors on Gi-proteins causing the rise of cAMP quantity in a cell which blocks the Ca2+ inflow into it and providing a reduction of erythrocytes’ aggregation.22,68

Quantity lowering to the control level of freely circulating in experimental rats’ blood aggregates on the background of exercise keeps their endothelial bed,31 what leads to a minimum exposition of subendothelial structures and excludes stimulation of hemostasis processes additionally reducing the processes of blood rheology.69 It is especially important for hemocirculation in vasa vasmorum,42 which play a great role in supporting of vascular wall’s tropism and physiological level’s providing of deaggregative impact on erythrocytes through the output of maximally possible quantities of nitric oxide and prostacyclin in endothelium.34,67

CONCLUSION

During experimental AH modeling in rats’ blood we noticed very early lowering of erythrocytes-discocytes content, the rise in the level of their reversibly and irreversibly changed variants with the strengthening of their aggregative ability. It happens in the background of an 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 AH. Coming at that, lowering to control the level of aggregates’ quantity in experimental rats’ blood on the background of exercise keeps their endothelial bed from minimizing accessibility of subendothelial structures and stimulation of hemostasis. Received data gave physicians and cardiologists reason for paying attention once more on the potential of exercise in developing AH treatment.

CONFLICT OF INTEREST

No Conflict of interest to declare.

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