Monograph

Mechanism of the Fåhraeus-Lindquist-Effect

KATIUKHIN LN

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About a Mechanism of the Fåhraeus-Lindquist-Effect

This book chapter is a republication of an article published by Katiukhin LN at Journal of Blood Disorders & Transfusion in May 2014. (Katiukhin LN (2014) About a Mechanism of the Fåhraeus-Lindquist-Effect. J Blood Disorders Transf 5: 1000211. doi: 10.4172/2155-9864.1000211)

Abstract

It was proposed a physiologically and experimentally confirmed explanation of Fåhraeus-Lindqvist-effect in capillaries using osmotic profiles of erythrocyte deformability. It was shown the dose-dependent changes of the erythrocytes deformability after forming artificial water pores (nystatin) and occlusion ($PbCl_2$) of available.The effect was conditioned by interchange of the liquid phases between the erythrocyte and plasma in shear flow.

Keywords

Erythrocytes; Deformability; Aqua Pores; Shear Stress

Introduction

The effect of hematocrit changes in small vessels with a diameter less than 150 microns (R.Fåhraeus-effect) and reducing blood viscosity with decreasing size of the vessel (R.Fåhraeus-T.Lindqvist-effect) [1], first described by the authors in 1931, caused attention to theoretical researches and practical modeling. So, erythrocytes in axial cylindrical flow tube slide in the surrounding layer of plasma. This leads to poor marginal zone cells, which accelerates the movement of the liquid core. Thus, the effect is due to the displacement of red blood cells in shear flow and the plasma acts as a lubricant layer [2-4]. These conclusions are consistent with modern hydrodynamics concepts, but the redistribution of

particles in the bloodstream does not change the ratio of the solid and liquid phases. The real reason of the changes in hematocrit and plasma viscosity of the blood, flowing in small vessels, remains enigmatic. We aimed to elucidate the physiological mechanism of changes in hematocrit and blood viscosity due to increased shear stress and the associated process of deformation changes of erythrocytes.

Materials and Methods

As is known, the most important determinants of the deformation properties of red blood cells are the internal viscosity of the contents or the degree of hydration of hemoglobin, the ratio of surface area to volume, or S/V, and the degree of rigidity of the membrane. In our opinion, the degree of deformability depends also on the presence of lipid membrane pores through which the liquid phases can be exchanged between the internal and external environments of cells in changing shear stress.

The studies were carried out by method of gradient ektacytometry in installation of its own production [5]. The shear rate and shear stress in the gap Couette with viscosity 10 cP at 100 rev/min correspond to 1.050 S^{-1} and 10.5 N/m^2, which are close to the conditions of the blood flow in the capillaries [6,7]. Osmotic deformability profile or osmoskan characterizes changes deformability index I_e versus the osmolality of the suspension medium. Light intensity at high (A) and small (B) axis of the first diffraction ring was measured, and the elasticity (A-B/A+B) or I_e was calculated. On the chart were identified several characteristic points: O_{max}- osmolality at which the highest I_e corresponds to isotonicity value in blood, O_{min}- osmolality at which the minimum I_e observed, it is an accurate measure of the surface-to-volume ratio of erythrocyte population (S/V), and I_{min}- deformability in the point of isotropic erythrocyte swelling.

We used 10 laboratory Wistar rats. The blood was collected after decapitation, heparin used as an anticoagulant (100

U/ml). After centrifugation at 600 g for 10 min the plasma was removed, and the erytrocytes were washed once with HEPES-buffered physiological solution (in mM): 145 NaCl, 7.5 KCl, 10 glucose and 10 HEPES at pH 7.4. Water channels were blocked by $HgCl_2$ (SIGMA-ALDRICH) in concentrations of $2\cdot(10^{-5}\text{-}10^{-3})$ on the phosphate buffer. Erythrocytes and buffer with various concentrations of $HgCl_2$ were mixed in equal proportions and were incubated in 1 hour at 37°C. Water channels in the erythrocytes were formed with help of polyene antibiotic Nystatin, which interacts with membrane sterols, increases water, electrolyte and non-electrolyte permeability of cholesterol-lipid bilayer and causes the formation of pores with a radius of 0.36-0.37 nm. Nystatin (SIGMA-ALDRICH) was dissolved in dimethyl sulfoxide. Incubation of washed erythrocytes with nystatin $(2.10^{-6}\text{-}10^{-5})$ M was carried out in 30 minutes at 37°C. The final solvent concentration in the test medium was less than 0.01% [9]. Experiments were conducted with a suspension of erythrocytes after removal of the supernatant. The data are expressed as mean ±SD. Comparisons between the deformability indexes of red blood cells treated with and without drugs were made by paired T-test. P values <0.05 were considered significant.

Results

These experiments were presented in Figures 1 and 2.

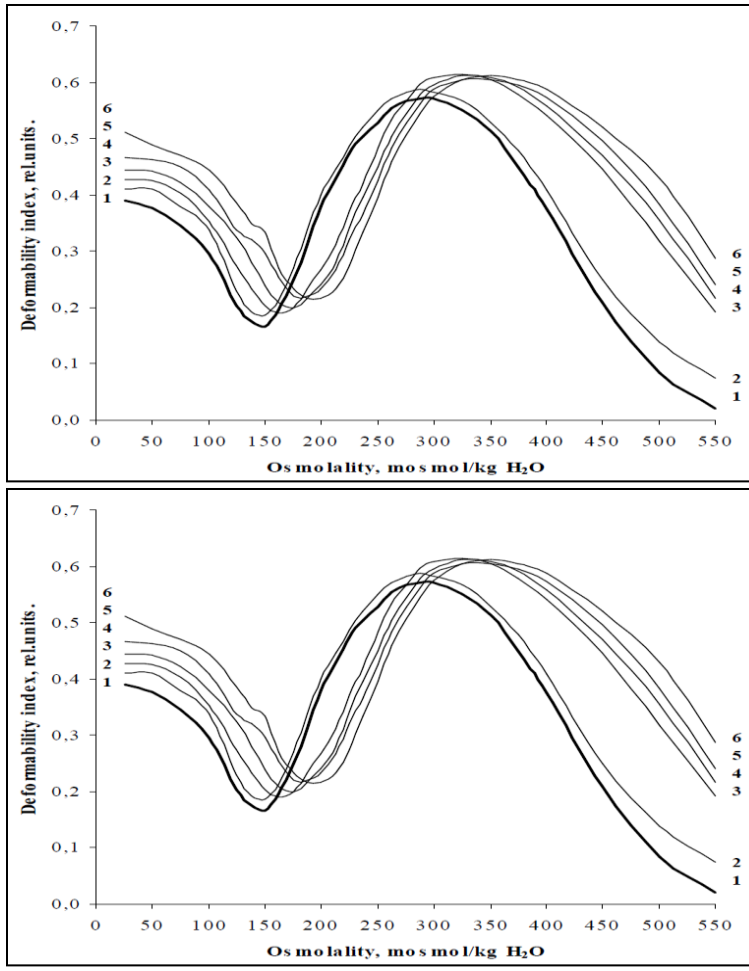

Figure 1: Osmotic deformability profiles of erythrocytes before and after incubation with nystatin. Curves 2-6 represent samples with a progressive increase in the concentration of nystatin: 1- control, 2-1 µM, 3-2 µM, 4-5 µM, 5-10 µM, 6-20 µM.

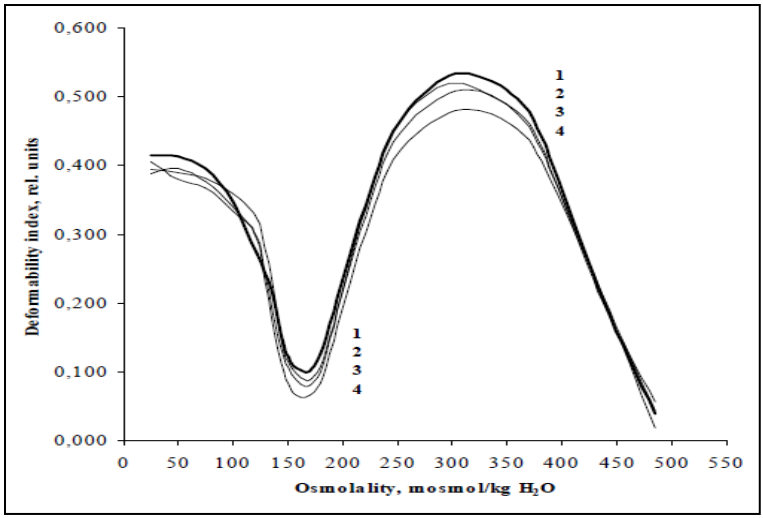

Figure 2: Osmotic deformability profiles of erythrocytes before and after incubation with $HgCl_2$.Curves 2-4 represent samples with a progressive increase in the concentration of HgCl2: 1-control, 2-20 µM, 3-50 µM, 4-100 µM.

There were a clear dose-dependent increase of both indicator I_{min} and the I_{max} depending on the number of pores formed in erythrocyte membranes (Figure 1), whereas Figure 2 showed a dose-dependent decrease in the ability of red blood cells to deform both at isotropic swelling and in isotonic zone depending on the number of blocked pores.

Numerical values of the deformability index I_{min} as result of the impacts with nystatin and mercuric chloride were shown in Table 1.

Table 1: I_{min} values in experiments with nystatin and $HgCl_2$.

Nystatin		HgCl2	
Control, n=5	0,167±0,008	Control, n=5	0,102 ± 0,007
1 mcM, n=5	0,187±0,008	20 mcM, n=5	0,088 ± 0,005
2 mcM, n=5	0,190±0,008	50 mcM, n=5	0,081 ± 0,005*
5 mcM, n=5	0,200 ± 0,008*	100 mcM, n=5	0,063 ± 0,004***
10 mcM, n=5	0,212 ± 0,009***		
20 mcM, n=5	0,219 ± 0,010**		

* -P<0.05; **-P<0.01; ***- P<0.001.
Note: The reliability of differences in relation to the control.

As was seen from the table, I_{min} significantly increased when increasing the number of hydrophilic pores in the membrane of erythrocyte and start falling at their blockade. Numerical values of I_e in isotonic region were shown in Table 2.

Table 2: I_e values in experiments with nystatin and $HgCl_2$

Nystatin		HgCl2	
Control, n=5	0,575 ± 0,007	Control, n=5	0,528 ± 0,010
1 mcM, n=5	0,588 ± 0,008*	20 mcM, n=5	0,517 ± 0,008*
2 mcM, n=5	0,617 ± 0,009***	50 mcM, n=5	0,502 ± 0,008**
5 mcM, n=5	0,613 ± 0,012****	100 mcM, n=5	0,475 ± 0,006***
10 mcM, n=5	0,612 ± 0,008***		
20 mcM, n=5	0,608 ± 0,010**		

Integral deformability I_e was increased significantly with increase in the number of hydrophilic pores and decreased with their blockade. These concentrations of reagents did not destroy the erythrocyte membranes and have demonstrated the picture of quality changes in deformation properties of red blood cells in model experiments.

Discussion

Biological membranes form extended bulk bilayer structures with a relatively small microviscosity and thickness combining the protein and lipid components with different properties. The cell membrane continuity is defined with her barrier and mechanical properties. Membrane lipids possessing mesomorphism reside in the crystalline and liquid states, which differ in packing density and mobility of the protein molecules. The phase transitions lead to an increase in mobility of the acyl chains in bilayer, to an increase in their angle of inclination and to a reducing of packing density. The lateral mobility of membrane proteins is increased, increasing the likelihood of their associates. The native structure of the bilayer can be broken in the process of life with the formation of structural defects. The water permeability of membranes is very high. It is assumed that it can pass through the temporary structural defects formed during thermal vibration tails of fatty acids. These defects (kinks) provide the ability to move across the membrane not only water, but also other small hydrophilic molecules (oxygen, carbon dioxide).

When a red blood cell is placed in hypoosmotic conditions, water rushes into the cell by concentration gradient, the volume increases, and it takes the form of an isotropic sphere before hemolytic stage. Fundamentally at this point deformation properties of the membrane do not play a significant role, erythrocytes is undeformable structure. However, a shear stress in the Couette cell tends to change the spherical shape. While maintaining the volume, the change of the form can occur as a result of increase in surface area only, because a sphere has a maximum volume for the given surface. But the extension module (dilatation), determines the properties of the lipid bilayer as a two-dimensional incompressible fluid is so large that for all non-destructive deformation of the erythrocyte surface area remains unchanged, and the membrane under physiological conditions inextensible [10]. The shear forces cause the rise of the hydrostatic pressure. The volume is reduced due to

output of liquid suspension through hydrophilic pores. Thus, the erythrocyte has an ability to change its shape in shear flow due to the exchange of the liquid phases between its content and suspending medium (in point O_{min}). The extent of these changes depends on the number of the liquid phase put out from the erythrocyte, i.e. on the number of the liquid pores. The method developers [11] in the study with cell populations isolated by density gradient have shown that not all cells reach a critical volume in the same osmolarity. Accordingly, they explain residual deformability of erythrocytes in terms of polymorphism. However, the authors did not consider the possibility of exchanging liquid phases in the deformation of cells. In our opinion, the erythrocyte polymorphism modifies the width of the inversion zone only and to a lesser extent the residual deformability. Meanwhile, in anemic states, particularly in sickle cell anemia, ektacytometry shows the perverse behavior of osmoskans, especially in point O_{min} [12-15]. Many years of our researches suggest that at the native state the deformability in the inversion point is significantly lower than when various impacts, whether pathology or stress.

As seen from the figures, the deformability in inversion point (I_{min}) increases with the concentration of the antibiotic in the suspension medium and is reduced when using a blocking agent. However, the osmoskans, i.e. osmotic profiles of the erythrocytes, also are changing. Thus, the formation of additional pores in membranes (see Figure 1) violated native osmoregulation and the shape of erythrocytes. The hydration of hemoglobin is increased due to water ingress into the cell. Point O_{min} is shifted into hyperosmotic zone, indicating that the erythrocytes are swelling. As for the shift point O_{max}, this is a consequence of increase in the degree of a hemoglobin hydration and shift of characteristic point O' of right wing of the osmoskan. When the pores are blocked (see Figure 2), there is a "conservation" of the inner aqueous phase and the osmoskan does not change. However, the membrane is "loaded" with heavy metal salt and becomes rigid, as evidenced by the O_{max} reduction.

The experiments were carried out in a narrow range of reagent concentrations and caused minimally noticeable effect. They did not destroy the membrane and demonstrated the quality changes of deformation properties of red blood cells in model experiments. Increasing the concentrations, according to a qualitative change in the osmoscans, causes severe disturbance of osmoregulation systems and marked hemolysis.

Conclusion

Evolving shear stress in vessels smaller than 150 microns causes stimulated reshaping oxygen carriers. As a consequence of these changes, liquid phase moves under pressure gradient from the erythrocyte to the capillary lumen. The hematocrit and the blood viscosity in the vessel are reduced. These transformations are reversible. When the erythrocyte leaves capillary, the shear stress is reduced, cell shape is restored and the water reenters into the erythrocyte. Using labeled media and fluorescent dyes, as well as experiments with cooking buffers on heavy water and subsequent stress by passing the erythrocyte suspension through millipore filters or by syringe hopefully confirms our conclusion.

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Erythrocyte Aggregation and the Fåhraeus-Lindquist-Effect

This book chapter is a republication of an article published by Katiukhin LN at Journal of Biochemistry & Molecular Medicine in January 2019. (Katiukhin LN. (2019) Erythrocyte Aggregation and the Fåhraeus-Lindquist-Effect. J Biochem Mol Med, 1(1): 22-24.)

Abstract

The message provides an analysis of changes in the aggregation properties and orientation of erythrocytes in the shear flow in small vessels. It is suggested that the mechanisms under consideration do not participate in the manifestation of the Fåhraeus-Lindquist effect. The decrease in apparent viscosity and hematocrit is mediated by the transformation of erythrocytes in the shear flow and the exchange of the aqueous phase of erythrocytes and blood plasma.

Keywords

Erythrocyte, Aggregability, Fahraeus-Lindquist effect, Shear stress

Introduction

Many years have passed since the discovery of a decrease in blood viscosity and hematocrit with a decrease in the size of a vessel with a diameter of less than 150 μm (Fåhraeus-Lindquist effect), but the mechanism has not yet been clarified. Numerous attempts to computational modeling of the effect in small vessels based on the paradigm of redistribution of erythrocytes in the bloodstream and that describes the interaction of plasma with red blood cells, appear unconvincing. The real reason for the change in

plasma viscosity and hematocrit of the blood flowing in small vessels remains enigmatic.
Indeed, erythrocytes slide around the plasma layer in axial cylindrical tubes. Plasma acts as a lubricant layer that reduces endothelial injury. It is believed that the movement of blood leads to the depletion of marginal zone concentration by cells, which accelerates the movement of the liquid core. Thus, red blood cell aggregation along with inward radial migration in small vessels are two significant mechanisms determining the effect. But the redistribution of particles in the bloodstream does not can change the ratio of the solid and liquid phases in the vessel, i.e., decrease of the apparent viscosity and hematocrit of the blood. By the way, the widely used term "apparent viscosity" requires clarification. It should be noted that the term “apparent” (or “effective”) viscosity means the derived value of blood viscosity and reflects the viscosity of a Newtonian fluid that would yield the same flow under otherwise identical conditions. As we suggested, increased shear stress in vessels less than 150 μm in size stimulates the transformation of erythrocytes. The pressure gradient causes the liquid phase to move from the erythrocyte to the capillary lumen, which leads to a decrease in blood viscosity and hematocrit. These transformations are reversible. When the erythrocyte emerges from the capillary, the shear stress decreases, the cellular form is restored and water returns to the cell [1]. Generally speaking, the participation of the aggregation properties of red blood cells in the rheology of blood should, in our opinion, is reconsidered. In this context, it is appropriate to realistically assess the aggregation phenomenon of red blood cells.

Erythrocytes have a tendency to aggregate and form what are known as “rouleaux”, but at low shear rates. The effects of such formations are to increase low shear viscosity. Figure 1 shows the tendency of the erythrocytes to form aggregates at the shear forces for normal blood.

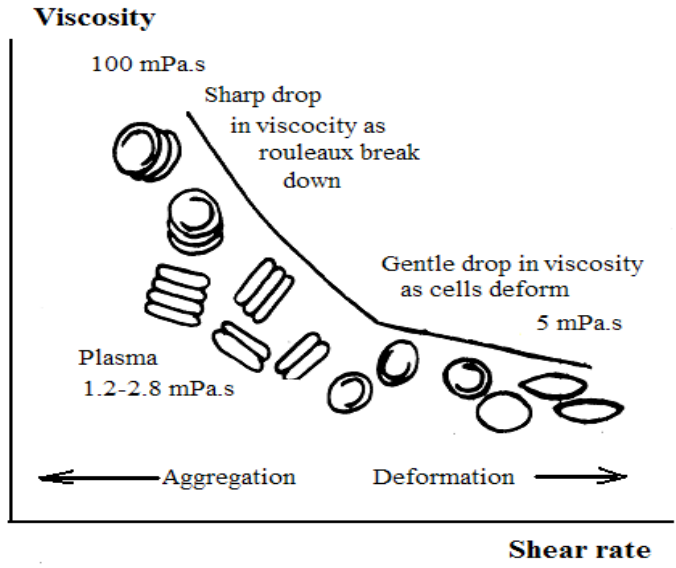

Figure 1: Log/log plot of viscosity versus shear rate in autologous plasma.

If the shear forces acting on blood drop, the erythrocytes tend to form stacks or aggregates. These stacks are held together by weak forces that are mediated by certain of the plasma proteins. The shear rate is calculated as the speed gradient $\gamma=\partial V_x/\partial y$ in fluid flow tubes in the direction perpendicular to the movement vector Y. Considering parabolic distribution of velocities in the vessel section (Bernoulli effect for viscous fluids flowing slowly in the laminar mode), the shear rate in the vessel clearance is measured linearly, from zero value in the vessel center to the maximum at its wall. Consequently, the true ratio is $\gamma_{threshold}/\gamma_{max}=D_{threshold}/D_{max}$. Thus, for vena cava, the ratio of diameters with the threshold shear rate and the maximum reaches 50/100 or ½, that is, $D_{threshold}$=5 mm at D_{max}=10 mm. Consequently, the conditions for RBC aggregation phenomenon manifestation in vena cava are only created when the vessel clearance is occluded by 4 times. This is true to the condition if the blood flow rate will not increase when the clearance narrows. For venules with the diameter of 0.02 mm, this ratio reaches 50/1000, that is, the clearance should decrease by 40 times. For arterioles with the diameter of 0.007 mm, the ratio makes up 50/8000, that is,

aggregation is possible if the clearance decreases by more than 25 thousand times! As for capillaries whose diameter sometimes comes to one third from the RBC diameter and where all the main metabolic processes occur, there is no point in talking about them [2-4]. Thus, as aggregates are easily destroyed in the normal blood flow under the influence of slight shear efforts, the tendency for their formation in bloods under physiological conditions in vivo does not considerably influence the blood flow. Thus, the phenomenon of RBC aggregation is shown only in case of complete blood flow stoppage. In our opinion, RBC aggregation is a minor physiological phenomenon, the phenomenon of resting blood, comparable with the establishment of hydrogen bonds on the formation of the spatial structure of biological molecules and Van der Waals forces between particles [5, 6]. Strengthening of aggregation capacity of a large number of oxygen carriers should be considered as the protective reaction of the organism to change in the protein pattern of plasma in case of pathology on the whole and inflammation in particular, which in fact improves blood supply to tissues. Really, it has been suggested that the effects of aggregation on hemodynamic mechanisms (e.g. plasma skimming, Fåhraeus-Lindquist effect, microvascular hematocrit) may promote rather than impede vascular blood flow [7].

Increased aggregation contributes to accumulation of RBC in central areas of vessels, formation of plasmatic lining and sliding layer near endothelial lining. The presence of rouleaux in the low shear rate central core of large vessels causes the velocity profile to become blunted. So called “plug flow” occurs where the mass of cells is lubricated by a slip film of plasma at the vessel walls. This benefits the distribution of erythrocytes, as well as promoting the margination of leucocytes and platelets towards the vessel endothelium where they may detect injury more readily. And this is observed precisely in large vessels with low shear stresses. It seems unreasonable to actively fight it. It is appropriate to support the mechanism of struggling, which was generated by the organism in the course of evolution for support of blood flow properties in case of pathological processes. For

example, with means of medicines like immunoglobulins, that increases pro-aggregation effect along with raising high-density lipoprotein cholesterol level as attractive treatment strategy, by concentrating attention on deformation properties of red blood cells.

The work was made as part of the state assignment "Physiological and biochemical mechanisms of homeostasis and their evolution".

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Again About the Fåhraeus-Lindquist Effect

This book chapter is a republication of an article published by Katiukhin LN at Journal of Blood Transfusions and Diseases in December 2019. (Katiukhin LN. (2019) Again About the Fåhraeus-Lindquist Effect. J Blood Transfusions Dis, 2(3): 124-125.)

In 1929, Fåhraeus (1888-1968) reported on a rheological effect in microvessels [1]. When blood flowed from a large diameter tube into a capillary tube, the average hematocrit of the capillary blood was less than that of the blood in the larger tube. This phenomenon was called the the Fåhraeus-effect. The effect was interpreted as a feature of particulate flow, when the hematocrit in the capillary is a function of radial position of erythrocytes. An article was later published by Fåhraeus and Lindquist [2], which demonstrated that if blood flows through glass capillary tubes of decreasing radius, a decrease in hematocrit was accompanied by a progressive decrease in apparent blood viscosity (the "Fåhraeus-Lindqvist effect").

Some later works showed that mean velocity of the red blood cells in capillary tubes is higher than the mean bulk flow velocity [3,4]. The erythrocytes move away from the boundary toward the channel center, while the suspending plasma fluid is displaced to the cell free layer regions left by the migrating cells. It results in the formation of a cell-free layer next to the tube wall (skimming). Thus, in small tubes the plasma acts as a lubricant layer [5-9]. Subsequent studies have shown that apparent viscosity continues to decline at diameters that correspond to the arteriolar segments of the systemic vascular tree, where the majority of the total peripheral resistance resides and is actively regulated *in vivo*. The Fåhraeus-Lindqvist effect thus reduces microvascular resistance, thereby maintaining local tissue perfusion at a relatively lower blood pressure [10].

There are some works on the practice of theoretical modeling of the effects [11-13]. It is assumed that in the observed effects in microvessels aggregation properties of erytrocytes participate [5,14-17]. It is worth noting that shear rate in vessels of asuch diameters is much higher than the threshold for complete destruction of aggregates (50 C^{-1}) [18,19]. Given this circumstance, such participation is very hypothetical [20,21].

The effects considered are reduced to a parallel decrease in hematocrit and blood viscosity in microvessels. However, it is worth noting that the redistribution of erythrocytes in the bloodstream according to a widely admitted hypothesis does not change the ratio of the solid and liquid phases in the blood wessel. There is one paper where it has been shown that, contrary to a widely admitted hypothesis, the Fåhraeus-effect does not account for the Fåhraeus-Lindqvist effect [22]. To date, the true reason of the decrease in hematocrit and blood viscosity flowing in small vessels was remained unclear. In our deep conviction, events in the microworld of the microwessels occur as follows. Given that the erythrocyte membrane is inextensible, the developing shear stress in small vessels causes a forced change in the shape of oxygen carriers with a decrease in their volume while maintaining the surface area. Due to these changes, under the influence of a pressure gradient the liquid phase moves from the red blood cell into the lumen of the capillary. The hematocrit and viscosity of the blood in the vessel are reduced accordingly. These transformations are reversible. When the red blood cell leaves the capillary, shear deformations decrease, the shape of the cell is restored and water with electrolytes returns inside the red blood cell [23].

The work was made as a part of the state assignment “Physiological and biochemical mechanisms of homeostasis and their evolution”.

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