

RHEOLOGICAL PROPERTIES OF ERYTHROCYTES IN PATIENTS WITH A NEW CORONAVIRUS INFECTION

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Abstract. The paper focuses on studying the rheological properties of erythrocytes in patients with a new coronavirus infection in the acute period and during early convalescence. A significant decrease in erythrocyte membrane plasticity was found in all patients in the acute period of the disease and every second recovering patients in the early post-COVID period. An increase in the degree and rate of erythrocyte aggregation in a quarter of cases, regardless of the observation period, was accompanied by inhibition of erythrocyte disaggregation mechanisms, which can serve as a pathophysiological basis for the formation of hemorheological disorders both in the micro- and macrovasculature in the first 3 months after recovery.

Keywords: COVID-19, hemorheology, erythrocytes, deformability, aggregation, disaggregation, post-COVID period.

List of Abbreviations

CT – computed tomography
CRP – C-reactive protein
Hb – hemoglobin
MCV – mean corpuscular volume
MCH – mean corpuscular hemoglobin
MCHC – mean corpuscular hemoglobin concentration

Introduction

Endothelial damage, hemostatic and hemorheological disorders are of great importance in the pathogenesis of an acute inflammatory response and complicate the course of various infectious diseases, contributing to the development of hypoxia, acidosis, and microthrombosis (Ami *et al.*, 2001; Subramaniam *et al.*, 2018; Gillespie *et al.*, 2021). Patients with the new coronavirus infection COVID-19 are also at risk for thrombotic complications. Thromboses in veins and pulmonary arteries have been reported (Iba *et al.*, 2020); thrombosis of microvasculature vessels in COVID-19 may underlie internal organ dysfunction up to the development of multiple organ failure (Marchandot *et al.*, 2020; Giannis *et al.*, 2020; Becker *et al.*, 2020). It is now abundantly clear that a proportion of patients who have had COVID-19 suffer from complications of this disease (Yong *et al.*, 2021). The condition characterized by the consequences of a new coronavirus infection has been termed «Long COVID» or «post-

-COVID syndrome» (Callard *et al.*, 2021). Coagulopathy and endotheliopathy are thought to be one of the mechanisms underlying the post-COVID syndrome, along with changes in the immune response (dysregulation of the immune system, the development of autoimmune reactions), multiple organ damage in the acute period of the disease, a persistent inflammatory reaction, and intestinal dysbiosis (Fernández-Lázaro *et al.*, 2021). The consistency of microcirculation is determined not only by the functional activity of the endothelium, platelets, plasma coagulation factors but also by the rheological properties of blood, mainly provided by erythrocytes, their deformability and the ability to aggregate and disaggregate (Byrnes *et al.*, 2017; Weisel *et al.*, 2019). The role of erythrocytes in a new coronavirus infection is not limited to oxygen transport; their contribution to the development of inflammation and hemocoagulation has also been demonstrated (Soma *et al.*, 2022). Meanwhile, the analysis of the literature showed that against the background of a large volume of publications on hemostasiological disorders in COVID-19, only a limited amount of information is found regarding studies of erythrocyte rheology in both the acute and post-COVID period (Renoux *et al.*, 2021; Grau *et al.*, 2022; Nader *et al.*, 2022), which determined the relevance of this work.

The aim of the study was to investigate the rheological properties of erythrocytes in patients with a new coronavirus infection COVID-19.

Materials and Methods

The study was of a pilot, single-center, continuous, observational, prospective nature. We examined 74 patients (31 males and 43 females) aged 30 to 74 years (52.7 ± 11.2 years) with COVID-19-associated pneumonia who were treated at the infectious diseases hospital of the University Clinic of the Federal State Budgetary Educational Institution of Higher Education «Privolzhsky Research Medical University» (PRMU) of the Ministry of Health of the Russian Federation and who were observed after recovery in the PRMU's follow-up care center for 3 months after discharge. The diagnosis of new coronavirus infection COVID-19 was confirmed by polymerase chain reaction (rhino and oropharyngeal swab test). According to chest computed tomography (CT), all patients were diagnosed with bilateral polysegmental pneumonia with varying degrees of severity of lung parenchymal lesions (from CT1 to CT4). The following comorbidities were verified: hypertension (35%), obesity (2%), diabetes mellitus (14%), coronary heart disease and chronic heart failure (14%), diseases of the gastrointestinal tract (15%), and kidney diseases (1%). Almost half (45%) of the patients had two or more comorbidities. The outcome of treatment in all patients was favorable.

The study was conducted in accordance with the Declaration of Helsinki (2013) and approved by the Ethics Committee of the Privolzhsky Research Medical University (Protocol No. 12, dated August 26, 2020). Informed voluntary consent to participate in the study was obtained from each patient.

Venous peripheral blood was collected from a patient upon admission to the COVID hospital (stage 1) and next 3 months after the onset of the disease during early convalescence (stage 2) in the dispensary room of the University Clinic. Hemolysed blood samples were not used for research.

The deformability ability of red blood cells was studied in an artificial shear flow in a rigidometer by counting deformed erythrocytes (Levin *et al.*, 2018).

The process of erythrocyte aggregation and disaggregation was studied using a rheoscope designed according to the method of H. Schmid-Schönbein *et al.* (Schmid-Schönbein *et al.*, 1973) modified by G.Y. Levin (Levin *et al.*, 2006). The degree of erythrocyte aggregation (Ma, maximum amplitude of the aggregation, mm), the rate of aggregation (A40, the amplitude of the aggregation 40 s after the beginning of the aggregation process, mm), the degree of disaggregation at shear rates of 5 s^{-1} , 10 s^{-1} , 15 s^{-1} , 20 s^{-1} (D5, D10, D15, D20, respectively, cal-

culated as the ratio of the amplitude of disaggregation to the degree of aggregation, expressed as a percentage).

Basal erythrocyte parameters, including the erythrocyte count, hemoglobin concentration (Hb), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), were determined in whole blood on a Pentra 60 hematology analyzer (Horiba ABX, France).

We also determined the concentration of fibrinogen according to the Clauss method on an ACL Elit pro coagulometer (Instrumentation Laboratory Company, USA) and the concentration of C-reactive protein (CRP) on an Indiko biochemical analyzer manufactured by Thermo scientific (Finland). Reagents from the analyzer manufacturer were used.

The comparison group consisted of 30 relatively healthy volunteers comparable in sex and age with the observed patients.

Statistical analysis of the data was performed using the Statistica 6.1 software (StatSoft, Inc.). The normality of data distribution was checked using the Shapiro-Wilk test. Median and interquartile range (Me [IQR]) were calculated for data whose distribution differed from the normal. The statistical significance of differences in the data obtained at the stages of the study was determined using the non-parametric Mann-Whitney U test. Correlation analysis and calculation of the gamma correlation coefficient (γ) were used to identify the relationship between variables. The significance value (p) was taken equal to 0.05.

Results

In the acute period of the disease, at the 1st stage, there was a decrease in erythrocyte volume and hemoglobin content ($p < 0.05$). Three months after the disease manifestation, during the early convalescence period, only the erythrocytes volume returned to normal (Table 1). The volume of erythrocytes and their hemoglobin content correlated with the severity of the disease ($\gamma = -0.51$, $p = 0.021$, and $\gamma = 0.43$, $p = 0.032$, respectively).

It was found that in 100% of cases, there was a sharp deterioration in the deformation properties of erythrocytes in the acute period of the disease; only 10% of red cells had the maximum possible ability to deform (Table 2). The erythrocyte deformability index correlated with their volume and hemoglobin content in the cell ($\gamma = 0.41$, $p = 0.013$, and $\gamma = 0.48$, $p = 0.028$, respectively).

Table 1

Selected hematological parameters of erythrocytes in patients with COVID-19, Me [IQR]

Parameter	Relatively healthy individuals	Stage 1	Stage 2
RBC, $\cdot 10^{12}/l$	4.7 [0.50]	4.5 [0.7]	4.5 [0.9]
Hb, g/dl	137.0 [18.0]	132.2 [20.5]	136.0 [27.0]
MCV, fl	92.2 [4.6]	88.8 [6.5] ¹	93.1 [7.3] ²
MCH, pg	31.2 [1.0]	30.4 [2.0] ¹	30.4 [2.2] ¹
MCHC, g/l	334.0 [19.0]	337.0 [7.0]	322.0 [13.0] ²

Note: ¹ – statistical significance of differences compared to relatively healthy individuals, ² – statistical significance of differences compared to the indicator at stage 1 ($p < 0.05$)

Table 2

Indicators of erythrocyte deformability in patients with COVID-19, Me [IQR]

Indicator	Relatively healthy individuals	Stage 1	Stage 2
Erythrocyte deformability, %	90.1 [19.6]	33.0 [18.5] ¹	50.0 [24.0] ^{1,2}
High degree of erythrocyte deformability, %	70.5 [15.4]	10.0 [9.5] ¹	20.0 [16.0] ^{1,2}
Medium degree of erythrocyte deformability, %	18.5 [11.2]	20.0 [15.5]	26.0 [12.0] ^{1,2}

Note: ¹ – statistical significance of differences compared to relatively healthy individuals, ² – statistical significance of differences compared to the indicator at stage 1 ($p < 0.05$)

At the 2nd stage of observation, in the period of early convalescence, despite the improvement, the deformation properties of the erythrocyte membrane were significantly inferior to those in relatively healthy individuals (Table 2). The plasticity of the erythrocyte membrane correlated with the hemoglobin content in erythrocytes ($\gamma = -0.30$, $p = 0.001$).

Along with a sharp deterioration in deformability, all patients in the acute period of the disease (stage 1) showed an increase in the degree and rate of erythrocyte aggregation by 24%, $p = 0.012$ and 33%, $p = 0.034$, respectively (Table 3).

At the 2nd stage, the degree and rate of erythrocyte aggregation did not recover and significantly exceeded those in relatively healthy individuals ($0.011 \leq p \leq 0.050$).

The reversibility of the aggregation process, the ability of red blood cells to disaggregate, plays an important role in the deterioration of hemorheology. An analysis of the relationship between the aggregation and disaggregation ability of erythrocytes revealed a weak/medium dependency level at different shear rates ($-0.32 \leq \gamma \leq -0.53$, $0.024 \leq p \leq 0.05$), indicating that the more active the process of erythrocytes conglomeration was, the stronger the formed aggregates were and the worse they were subjected to dispersion. Disruption of disaggregation

pro-cesses at low shear rates was observed in 53/72% of patients at the 1st stage of the examination.

Depending on the severity of disaggregation processes, patients at the 1st stage were divided into two groups, which were observed at the 2nd stage, respectively. The first group (group A, $n = 12$) consisted of patients with inhibition of disaggregation processes; the second group (group B, $n = 41$) included patients with activation of disaggregation mechanisms (Table 4).

In patients of group A, there was no dispersion of aggregates at the 1st stage; moreover, the process of erythrocyte aggregation continued at a shear rate of 5 s^{-1} . With an increase in the shear flow rate, a significant disruption of the disaggregation properties of red blood cells persisted. During the period of early convalescence (stage 2), there was no restoration of the disaggregation properties of erythrocytes in these patients. In group B, an increase in disaggregation was detected at the 1st stage at all shear flow rates; as in group A, it didn't recover during the convalescence period.

Deviations in the rheological properties of erythrocytes during the acute period of a new coronavirus infection occurred against the background of rapid development of an inflammatory reaction, which was evidenced by an increase in the concentration

Table 3

Degree and rate of erythrocyte aggregation in patients with COVID-19, Me [IQR]

Indicator	Relatively healthy individuals	Stage 1	Stage 2
Ma, mm	74.2 [6.7]	92.0 [18.0] ¹	80.0 [24.0] ^{1, 2}
A ₄₀ , mm	51.8 [8.5]	68.9 [17.0] ¹	57.5 [20.0] ^{1, 2}

Note: ¹ – statistical significance of differences compared to relatively healthy individuals, ² – statistical significance of differences compared to the indicator at stage 1 ($p < 0.05$)

Table 4

Erythrocyte disaggregation rates in patients with COVID-19, Me [IQR]

Indicator	Relatively healthy individuals	Group A		Group B	
		Stage 1	Stage 2	Stage 1	Stage 2
D ₅ , %	21.3 [8.4]	5.0 [12.0] ¹	12.0 [9.5] ^{1, 2}	34.0 [19.0] ^{1, 2}	37.8 [17.5] ¹
D ₁₀ , %	41.8 [10.0]	35.0 [19.0] ¹	35.0 [9.0] ¹	52.0 [16.0] ^{1, 2}	54.0 [13.0] ¹
D ₁₅ , %	52.4 [11.2]	45.4 [5.2] ¹	42.0 [13.0] ¹	62.0 [10.0] ^{1, 2}	64.0 [10.5] ¹
D ₂₀ , %	62.5 [9.3]	55.0 [6.0] ¹	50.0 [12.0] ¹	70.2 [14.0] ^{1, 2}	76.0 [16.0] ¹

Note: ¹ – statistical significance of differences compared to relatively healthy individuals, ² – statistical significance of differences compared to the indicator at stage 1 ($p < 0.05$)

of fibrinogen (5.1[2.2] g/l, $p = 0.001$) and C-reactive protein (31.0[25.0] g/l, $p = 0.001$) in the blood compared with the parameters of relatively healthy individuals. An association was found between increased fibrinogen concentration and increased aggregation rate ($\gamma = 0.51$, $p = 0.012$), as well as a decrease in the dispersion of aggregates at a shear flow rate of 5 s^{-1} ($\gamma = -0.63$, $p = 0.034$). The level of C-reactive protein also correlated with the indicators of erythrocyte disaggregation at shear flow rates of 15 s^{-1} and 20 s^{-1} ($\gamma = -0.55$, $p = 0.022$ and $\gamma = -0.59$, $p = 0.043$).

At the 2nd stage of observation, during the period of early convalescence, the relationship between the rate of erythrocyte aggregation and the concentration of fibrinogen ($\gamma = 0.41$, $p = 0.02$) was revealed, which indicates the continuing role of this protein in the formation of aggregates in the post-COVID period.

Correlation analysis was used to study the dependence of the rheological properties of erythrocytes on the presence/absence of comorbidities in patients and the severity of lung parenchyma damage according to chest CT. Single correlations were revealed: the degree of erythrocyte deformability

correlated with the presence of concomitant obesity ($\gamma = -0.76$, $p = 0.03$), disorders of erythrocyte disaggregation at a shear rate of 5 s^{-1} correlated with the severity of lung damage according to computed tomography ($\gamma = -0.45$, $p = 0.035$).

Discussion

According to published papers, hematological parameters of erythrocytes in patients with a new coronavirus infection aggravated by the development of pneumonia determine the severity of hypoxemia, and routine laboratory hematological parameters of erythrocytes can serve as indicators of the severity of the disease. Developing hypoxia, in turn, can affect the morphology, and functional activity of erythrocytes, including their rheological properties and life expectancy, contributing to the complex pathogenesis of COVID-19 (Foy *et al.*, 2020; Taj *et al.*, 2021; Russo *et al.*, 2022).

The ability of erythrocytes to deform is their most important property, which allows them to circulate in the microcirculation system efficiently and is crucial for tissue perfusion and delivery of substances necessary for metabolism to cells.

The factors that determine the erythrocyte deformability are the viscoelastic properties of the membrane and the viscosity of the intracellular contents, which depends on the concentration of hemoglobin in the cell (Muravyev *et al.*, 2013; Firsov *et al.*, 2016).

Among possible reasons for an increase in the rigidity of erythrocyte membranes are metabolic changes leading to an increase in the concentration of intracellular calcium, respiratory hypoxia resulting from the lung parenchyma damage, which creates conditions for the activation of free radical processes, structural damage to proteins and lipids that affect the viscoelastic properties of cell membranes (Glushkova *et al.*, 2016; Iddir *et al.*, 2020; Thomas *et al.*, 2020).

It can be assumed that the degree of influence of free radical processes on the erythrocyte membrane plasticity decreases in recovering patients, and then an increase in the hemoglobin concentration begins to play a role, which increases the intracellular viscosity and determines the degree of membrane plasticity (Borovskaya *et al.*, 2010), but complete recovery does not occur.

The revealed changes in disaggregation activity in group A may indicate the probability of conglomerate formation not only in capillaries but also in larger vessels, which increases the risk of venous and arterial thromboembolism (Weisel *et al.*, 2019).

Reduced aggregate strength in group B may be a restrictive mechanism for the formation of stasis in the area of microcirculation and vascular thrombosis.

Preservation of erythrocytes' rheological disorders during the period of early convalescence may be due to the life span of erythrocytes and serve as one of the causes of the consequences of COVID-19.

Hyperfibrinogenemia is one of the typical features of a new coronavirus infection, which indicates the development of hypercoagulable dysfunction (Pieters *et al.*, 2019). In the acute period of the disease, an increase in the content of this protein is associated with an increase in blood viscosity, which significantly disrupts its rheology.

The correlation between the indicators of erythrocyte aggregation and the level of acute-phase inflammatory proteins is explained by the «bridge» theory of the mechanism of erythrocyte aggregation, according to which high-molecular proteins, in particular fibrinogen, are absorbed on the cell membrane, enhancing erythrocyte aggregation (Brust *et al.*, 2014).

The hyperproduction of CRP observed in the acute period of the disease is due to the activation of its synthesis by cytokines, including IL-1 and IL-6, and is also a typical feature of COVID-19, reflecting the severity and outcome of the infection (Liu *et al.*, 2020; Stringer *et al.*, 2021; Smilowitz *et al.*, 2021).

The relationship between the level of C-reactive protein and the indicators of erythrocyte disaggregation indicates that the density of erythrocyte aggregates grows with increasing inflammation. A possible mechanism through which the relationship between CRP and the disaggregation properties of erythrocytes is realized is the stimulation of scrambling of erythrocyte membranes by this acute phase protein. Cell membrane modification and changes in its properties due to the translocation of phosphatidylserine may result in increased adhesion of erythrocytes to the vascular endothelium, activation of blood coagulation, and microcirculation disorders (Abed *et al.*, 2017; Soma *et al.*, 2022). In addition, a high level of CRP causes an increase in IgG on the cell surface, which can also increase the strength of erythrocyte aggregates (Ben-Ami *et al.*, 2003; Bouchla *et al.*, 2022).

The present study has limitations due to its pilot nature, the limited number of patients observed, and the possibility of the formation of erythrocyte rheological disorders against the background of comorbid pathology (Hazegh *et al.*, 2021; Moreno-Fernandez *et al.*, 2022). However, the known data on the severe course of COVID-19 in patients with a low comorbidity index do not exclude the role of new coronavirus infection in changing the functional properties of red blood cells.

Conclusion

Thus, in patients with a new coronavirus infection caused by SARS-CoV-2, pronounced disturbances in the rheological properties of erythrocytes were established, which largely persist in the early post-COVID period. The revealed critical changes in the deformability of erythrocytes can lead to a decrease in their passage through the capillary bed and aggravate impairment of the oxygen transport function of blood and tissue perfusion. Disturbance of erythrocyte aggregation, along with a significant change in the plasticity of their membrane, can serve as the basis for the formation of hemorheological disorders in the micro- and macrovasculature. Further studies are needed to clarify the mechanisms of hemorheological disorders in COVID-19, the degree of their contribution to the development of thrombosis, and to develop methods for appropriate correction.

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