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TRANSFER PROCESSES IN RHEOLOGICAL MEDIA

RHEOLOGICAL CHANGES IN THE BLOOD AND PLASMA OF PATIENTS WITH MYOCARDIAL ISCHEMIA AND DIABETES MELLITUS AND DYSFUNCTION OF THEIR ENDOTHELIUM

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The rheological properties of the whole blood and plasma of patients with myocardial ischemia and diabetes mellitus and of donors have been investigated using a Couette rotational viscosimeter at a temperature of 25°C in the range of rates of shear of 0.5–60 sec^{-1}. The rheological analysis was performed with the use of the Quemada relation. The functional state of the endothelium and some biochemical indices of the blood of these patients were investigated. It is shown that in patients with myocardial ischemia and diabetes mellitus, accompanied by dyslipemia and endocrine disturbances, rheological derangements and endothelial dysfunction develop.

There are a large number of publications indicating that, in patients with Type 2 diabetes mellitus, the viscosity of the blood and plasma are increased, the aggregation and deformability of erythrocytes are changed [1, 2], and hemorheological and circulatory disturbances develop. These works indicate that diabetes mellitus is one of the most important risk factors for myocardial ischemia. The risk of development of myocardial ischemia in patients with diabetes mellitus is two-to-three times higher than in persons free of it.

The development of efficient instrumental methods of early diagnosis of myocardial ischemia and estimation of the affections of the cardiovascular system and the state of the circulation bed and the peripheral hemodynamics in patients with Type 2 diabetes mellitus will make it possible to prescribe the necessary treatment of these patients in time and to obviate serious complications in them. Therefore, the study of the changes in the rheological characteristics of the whole blood in patients with myocardial ischemia and diabetes mellitus is of both scientific and clinical interest. Disturbances of the albuminous and lipid composition of the plasma of the indicated patients can also lead to changes in the rheological indices of their blood and the functional state of their endothelium.

A disturbance of the circulation processes in patients is caused mainly by changes in the rheological properties of their blood and plasma and points to deep ischemic affections of different organs and tissues in these patients. Thus, hemorheological changes represent a pathogenic feature of myocardial ischemia [3]. In the majority of cases, they lead to a disturbance of the local blood flow and, in the case of cardiovascular diseases, can be considered as an indication of an insufficiency of the peripheral blood flow and the circulation processes [4].

Endothelial dysfunction is a key manifestation of some forms of diabetes mellitus and the main reason for attendant vascular complications [5, 6]. In patients with diabetes mellitus, the endothelium cells of the vascular bed are damaged and do not protect vessels, which steps up the development of atherosclerosis in them. Moreover, hypergly-

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cemia (an increased content of sugar) enhances the oxidation processes leading to the appearance of thrombuses, inflammations, and metabolites. All of these pathological processes can damage vascular walls.

The aim of the present work is to determine the features of the disturbances of the blood-circulation processes in patients with myocardial ischemia combined with Type 2 diabetes mellitus, investigate the rheological properties of the blood and plasma in patients with these pathologies and in donors with the use of the rotational-viscosimetry method, and estimate the functional state of the endothelium and some biochemical and hormonal indices (total cholesterol, triacylglycerols, cholesterol of high-, low-, and very-low density lipoproteins, total protein, dehydroepiandrosterone, insulin). Of great importance is determination of a correlation relation between the rheological properties of the blood and plasma and the biochemical and hormonal indices of the indicated patients.

We investigated the above-indicated indices of 45 patients with myocardial ischemia and diabetes mellitus (MI + DM group), 35 patients with myocardial ischemia forming a comparison group (MI group), and 20 donors. All of the groups were identical in sex and age and obtained a standard therapy. Rheologic measurements were carried out with the use of a rotational viscosimeter realizing a Couette flow with rates of shear ranging from 0.5 to 60 sec^{-1} at a temperature of 25 $\pm$ 0.25°C. The blood for investigation was taken from the cubitus vein in amount of 8 ml and filled in a flask with heparin. The rheologic properties of the blood of patients (flow curve) were measured before and after the treatment procedure. We also measured the rheological indices of donors and then compared them with the analogous indices of patients. The packed-cell volume was also measured in all persons examined.

The accuracy of measuring the flow curve reached 10% for low rates of shear ($\sim$0.5 sec^{-1}) and 3% for high rates of shear (>20 sec^{-1}). The variation in the rheological data obtained for different patients was dependent on their individual features and was equal to $\sim$50% in the case where rheological measurements were carried out at low rates of shear and $\sim$15% in the case where measurements were carried out at high rates of shear. The accuracy of measuring the hematocrit was $\pm$1% and the variation in this index was equal to 18–58%.

The endothelium-dependent relaxation was investigated on a Phillips HDI-5000 apparatus with the use of a linear-movement pickup operating at a frequency of 5–12 MHz, and the diameter of the brachial artery and the rate of change in the arterial spectrum were determined in the process of running a test for reactive hyperemia. The total cholesterol and triacylglycerols were determined using a biochemical Hitachi-902 analyzer. The cholesterol of lipoproteins of high, low, and very low density was determined by the electrophoresis method with the use of a Sebia (France) set on a Solar apparatus. The dehydroepiandrosterone and the androgen synthesized in the adrenal cortex and sexual glands were measured by the immunofenzyme method, and the insulin was determined by the radioimmune method.

The indices of rheological properties of blood considered as a macroscopic continuum are being intensively used at present for diagnostic purposes because, as was noted above, hemorheological disturbances represent a pathogenic feature of myocardial ischemia. The rheological properties of this continuum are described mathematically with the use of the so-called constitutive relations (rheological models) characterizing the material properties of an elementary representative volume whose parameters can be used for rheological analysis of the initial data. Some of the rheological equations, such as equations for relaxation parameters of a five-parameter double exponential model [7], can be used for clinical purposes as equations with parameters carrying information on the stiffness of blood cells. These parameters are usually related to the aggregation ability and deformability of cells and, therefore, can be used for diagnostic purposes [8]. However, at present there is no reliable experimental and theoretical data on the functional interrelation between the parameters of the indicated rheological model and factors influencing the aggregation ability and deformability of erythrocytes. Therefore, this rheological analysis should be performed using constitutive relations with the minimum possible number of rheological parameters, which have already been approved in clinical practice. It is necessary that the relations be fairly simple for mathematical simulation of a flow in a blood vessel. Moreover, a model must satisfactorily approximate all experimental data throughout the range of change in the deformation rates with account for the conditions of an experiment. A large number of different hemorheological models (constitutive relations), which allow one to determine the curve of an actual blood flow with a different degree of accuracy, are presented in the literature [9].

One approach to the study of the above-described problem was proposed by Williams in 1929. He had developed a representation for describing the rheological properties of aggregated emulsions — close rheological analogs of blood. According to this representation [10, 11], a part of the shear forces of a pseudoplastic flow is expended for the destruction of erythrocyte aggregates and the other part gives rise to a viscous flow with high rates of shear. The total

resistance to the shear of this medium is the sum of the resistances set to the plastic and viscous flows. At small shear forces, solid elements of blood form aggregates that can be destroyed when these forces increase. A change in the sizes of the aggregates leads to a distortion of the streamlines passing near these aggregates and to an increase in the friction resistance between them. Therefore, at small shear forces, the erythrocyte aggregation increases the apparent viscosity of blood, whose behavior becomes non-Newtonian. It should be noted that changes in the hematocrit, the plasma viscosity, and the deformation and aggregation ability of erythrocytes can change the resistance to the blood flow in the vascular system and deteriorate the indices of this flow. Unfortunately, the interrelation between the rheological factors and the hemodynamic mechanisms is very complex, which makes the study of the rheology of pathophysiological processes difficult.

In [10], a rheological model for aggregated medium-concentration emulsions was constructed with the use of the momentum-transfer theory. Aggregates are bonded only in the process of their contact. When aggregates shear, these bonds extend, transform, and break, which leads to the transfer of the angular momentum from one motion layer to another. In an analogous rheological model, used by Sirs [11] for describing of the rheological behavior of a blood flow in narrow capillaries, the dependence of the blood viscosity on the rate of shear is described by the equation

$$\eta\,(\dot{\gamma}) = \eta_i + \frac{\tau_s}{\dot{\gamma}_*} + \dot{\gamma}\,. \tag{1}$$

Here, according to the Williams representation, η_i is the viscosity of a suspension of particles interacting only hydrodynamically, $\dot{\gamma}_*$ is the apparent kinetic rate of destruction of structural units (aggregates), and τ_s is the strength of an aggregate formed by solid blood elements. It should be noted that the strength of the aggregates increases with increase in τ_s.

Despite the fact that the simple rheological model (1) involves parameters having a clear physical sense, it allows one to obtain a fairly exact blood-flow curve only in a narrow range of rates of shear. The curve of a blood flow in a wide capillary determined with this model substantially differs from the actual one because the velocity of the flow is determined, in this case, with a large error. The aggregation of erythrocytes in the blood flowing in capillaries at low rates of shear gives rise to a two-phase flow and the appearance of a layer depleted in erythrocytes. The formation of this layer, as is known, is accompanied by a decrease in the hydrodynamic resistance and by a distortion of the flow-velocity profile.

The hydrodynamic resistance increases substantially at high hematocrit values. In an albumin-salt solution, where erythrocyte aggregation and two-phase flow are absent, the hydrodynamic resistance increases linearly with decrease in the mass flow rate. In [12], the blood flow in a capillary was calculated with the use of two rheological models: (a) a viscoplastic model in which the core of a flow is quasisolid and (b) a Quemada pseudoplastic model [13, 14] that gives a maximum exact velocity profile [15].

Investigation of the applicability of different constitutive relations for describing of a blood flow by fitting the experimental data on it, obtained on a coaxial-cylindrical rheometer, with the use of the least-squares technique have shown that equations of this type are best suited for simulation of the rheologic behavior of blood [16].

The Quemada rheological model constructed on the basis of comprehensive analysis of the Williams representation has the form

$$\eta\,(\dot{\gamma}) = \eta_i\,((1 + \lambda\dot{\gamma})/(\chi + \lambda\dot{\gamma}))^2\,. \tag{2}$$

According to the data of [16], this expression gives the curve of a blood flow with rates of shear ranging from 0.87 to 118 $\sec^{-1}$ with an accuracy of ~1.5%.

The parameters of rheological model (2) were determined by fitting the experimental data on a blood flow with the use of the least-squares technique. Then, correlation analysis of all the parameters determined was performed and the dependence of these parameters on the volume content of erythrocytes (hematocrit) and some biochemical indices was constructed.

TABLE 1. Rheological Indices of the Whole Blood and Plasma Viscosity

Indices		Donors	MI		MI + DM	
			before treatment	after treatment	before treatment	after treatment
Quemada model parameters	χ	0.43 ± 0.02	0.40 ± 0.01	0.40 ± 0.01	0.42 ± 0.01	0.40 ± 0.01
	η_i	4.7 ± 0.1	5.4 ± 0.1 [2)]	5.1 ± 0.1 [1)]	5.9 ± 0.1 [1)]	5.0 ± 0.1 [1)]
	λ	0.22 ± 0.02	0.15 ± 0.02 [1)]	0.12 ± 0.01 [2)]	0.12 ± 0.01 [2)]	0.12 ± 0.01 [2)]
Plasma viscosity	η_{pl}	1.56 ± 0.01	1.9 ± 0.01 [2)]	1.94 ± 0.01 [2)]	1.82 ± 0.01 [2)]	1.86 ± 0.01 [2)]

Note. Reliability of the differences between indices: [1)] $p < 0.05$; [2)] $p < 0.001$; in the other cases, $p < 0.01$.

As a result of the correlation analysis, the relation between the parameters of rheological model (2) and the hematocrit was determined. It has been established that only the parameter η_i is reliably dependent on it (for the other parameters, such a dependence was not revealed), and this dependence has the form

$$\eta_i = 0.05\mathrm{Hcr} + 1.6 \tag{3}$$

for the case where the correlation coefficient $r^2 = 0.78$, the confidence interval is 95%, and the hematocrit ranges from 18 to 60%. The other parameters of model (2) are related to the total-protein quotient (GP) by the following relation:

$$\eta_0 = 0.17 \ln (\mathrm{GP}) - 0.61 \tag{4}$$

for the case where the correlation coefficient $r^2 = 0.68$ and the confidence interval is 95%;

$$\lambda = -0.0002\mathrm{GP}^2 - 0.04\mathrm{GP} + 2 \tag{5}$$

for the case where the correlation coefficient $r^2 = 0.72$ and the confidence interval is 95%.

Because of the limited lifetime of blood samples, it is difficult to determine a single packed-cell volume for them; therefore, the parameters of the model were put mathematically into correspondence to the average packed-cell volume of a healthy man (45%) with the use of the correlation dependence obtained (see Eq. (3)). The data obtained are presented in Table 1. The rheological indices presented in this table were determined for a packed-cell volume of 45%.

It is seen from Table 1 that the parameter η_0, which is responsible for the aggregation of erythrocytes at low rates of shear or in the blood at rest, remains practically unchanged for all the groups investigated. The parameter λ, which is responsible for the destruction of aggregates by a shear flow, is reliably decreased for patients of both groups. A reliable difference between these parameters in the patents with myocardial ischemia and the patients with myocardial ischemia combined with diabetes mellitus was not revealed. The parameter η_i, which mainly determines the hydrodynamic resistance to a flow, was reliably smaller in the healthy donors than in the patients of both groups; this parameter decreased reliably in the patients with myocardial ischemia in the process of their treatment.

It is interesting to note that, in this case, the initial viscosity η_0 is independent of the hematocrit, even though this dependence is described in the literature [17]. This is evidently explained by the fact that the literature data were obtained for rates of shear much lower than the lower boundary of the measured rate of shear, equal to 0.5 sec^{-1}.

The parameters η_0 and λ are related to the total protein quotient. The first of them is proportional to the logarithm of the total protein quotient (4) and decreases to a negligibly small value with decrease in this quantity. When it tends to an infinitely small value, aggregates are absent in the blood, which is not surprising because the blood-protein components participate in the aggregation processes.

The parameter λ changed extremally with a change in the total-protein concentration (5); it increased when this concentration decreased or increased beginning with a minimum value at which, probably, the rate of destruction of aggregates by a shear flow is maximum and, consequently, the rheological indices of the blood can be somewhat corrected by drugs in the process of treatment with the purpose of changing the protein content of the blood plasma.

TABLE 2. Changes in the Diameter of the Brachial Artery before and after the Reactive Hyperemia in Patients with Myocardial Ischemia and in Patients with Myocardial Ischemia Combined with Diabetes Mellitus

Groups of patients	Initial size (mm)	After reactive hyperemia (mm)
MI	4.45 ± 0.19	5.18 ± 0.11[1)]
MI + DM	4.0 ± 0.25	4.34 ± 0.2

Note. Reliability of the differences between indices: [1)] $p < 0.05$; in the other cases, $p < 0.01$.

The total cholesterol of the patients with myocardial ischemia who did not undergo a medical treatment did not correlate with the parameters of the indicated rheological model. It has been established that, in these patients, the cholesterol of low-density lipoproteins is somewhat dependent on the hydrodynamic viscosity η_i (r = 0.41), the triacylglycerol level, and η_0 (r = −0.48). The level of dehydroepiandrosterone in the blood of the indicated patients correlated with λ (r = 0.61) and η_0 (r = −0.40). Correlation analysis of the rheological indices of the blood of the patients with myocardial ischemia who were subjected to a course of medical treatment has shown that, in them, the total cholesterol correlates with η_i and η_0 and the dehydroepiandrosterone level correlates with λ, which allowed us to suggest that androgen influences the rheological properties of blood. The correlation of the insulin content with the rheological indices points to the dependence of this hormonal index on λ (r = 0.630 in the patients with myocardial ischemia).

In the patients with myocardial ischemia and diabetes mellitus, only the glucose level was strongly dependent on λ (r = −0.49), which points to more complex disturbances of the rheological indices of the blood in these patients.

The viscosity of the plasma of patients of both groups differed reliably from that of donors, which is probably due to a disturbance of the protein and lipid metabolism in the patients; in this case, the plasma viscosity of the patients with myocardial ischemia was reliably higher than that of the patients with myocardial ischemia combined with diabetes mellitus before and after a course of their medical treatment. The coefficient of correlation between the total-protein quotient and the plasma viscosity in the patients with myocardial ischemia was 0.59.

Blood circulation in an organism depends not only on the rheological indices of the blood but also on the state of the vascular system. This is explained by the fact that, along with a change in the rheological indices, the lumen of a vessel changes because of the pathological processes that developed in the endothelium, which can significantly complicate the circulation problems because the heat and rate of a blood flow are proportional to the vessel diameter to the fourth power. Detailed investigation of the total action of these two factors on the circulation processes calls for a careful simulation of a blood flow.

In the group of patients with myocardial ischemia, 37.5% of the patients had a disturbed endothelium function, and, in the group of patients with myocardial ischemia combined with diabetes mellitus, 60% of the patients had this disturbance. Thus, 45.5% of the patients had a disturbed endothelium function. The patients with a change in the mean-square diameter of the brachial artery comprised 18% in the group of patients with myocardial ischemia and 9% in the group of patients with myocardial ischemia combined with diabetes mellitus (Table 2). It has been established that, in these patients, the endothelium-dependent relaxation depends on the cholesterol of low-density lipoproteins (r = −0.62) and the dehydroepiandrosterone level (r = 0.47). The data obtained indicate that the functional state of the endothelium in patients with myocardial ischemia and patients with myocardial ischemia combined with Type 2 diabetes mellitus is disturbed. In this case, the patients with myocardial ischemia and diabetes mellitus had a larger disturbance of the endothelium function. The data obtained point to the fact that one possible reason for the appearance of vascular complications in patients with myocardial ischemia combined with diabetes mellitus is a dysfunction of the endothelium, the functional state of which depends on the concentration of the low-density lipoprotein cholesterol.

In conclusion, it may be said that patients with myocardial ischemia combined with Type 2 diabetes mellitus have larger changes in the rheological parameters of the blood and a greater endothelial dysfunction than patients with myocardial ischemia only, which is probably one of the reasons for the appearance of marked vascular disturbances in the patients with the combined pathology. The rheological indices of the patients of both groups differed from the analogous indices of donors. The results obtained correlate with the changes in the total protein, the lipidogram, some hormonal indices, and the endothelium-dependent function of vessels in the patients of both groups. The results of the present work can be used for calculating the rate of blood flow or the pressure drop in a virtual vessel for the purpose

of determining the contribution of the rheological disturbances and the changes in the channel of this vessel to the head and the rate of the flow in it.

NOTATION

GP, total protein quotient, mg/liter; Hcr, packed-cell volume, %; $\dot{\gamma}$, rate of shear, 1/sec; $\dot{\gamma}_*$, constant of the apparent kinetic rate of destruction of structural units, 1/sec; η_i. hydrodynamic viscosity, mPa·sec; η, apparent viscosity, mPa·sec; η_0, initial viscosity, mPa·sec; λ, structure-sensitive parameter, sec; τ_s, strength of the structure, mPa; $\chi = (\eta_i/\eta_0)^2$. Subscripts: *i*, infinite rate of shear; pl, blood plasma; s, structure; 0, zero rate of shear.

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