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INFLUENCE OF THE TEMPERATURE AND OVERSOURING OF BLOOD ON ITS HEMORHEOLOGICAL PROPERTIES

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The influence of the change in the temperature and the acidity of blood on its hemorheological properties has been analyzed. It is shown that, at temperatures lower than 45°C, the temperature dependence of the apparent viscosity of blood at a rate of shear ranging from 0.3 to 50 sec^{-1} is adequately defined by the Arrhenius model with a viscous-flow activation energy of 13–17 kJ/mole. In the range of pH 6.3–7.6, the oversouring of blood mainly influences the critical shear stress, and the Caisson viscosity depends only weakly on the acid-base equilibrium.

Introduction. Certain therapeutic procedures lead to changes in the local and total temperatures of a human body and in the intensity of the blood flow in heated and cooled biotissues. The temperature can increase as a result, e.g., of a local or a total hyperthermia and a photodynamic therapy of tumors. The use of heat for treatment of oncologic patients is often accompanied by a hyperglycemia caused by artificial means for the purpose of oversouring of a tumor biotissue by intensification of the metabolic processes in it. A temperature higher than 42°C and a decreased acid-base equilibrium are factors damaging the neoplastic tissue and influencing the hemorheological properties of the blood in the process of a therapeutic action. The aim of the present work is to quantitatively estimate this influence on the basis of available literature data and results of hemorheological investigations carried out by the REOMED scientific group in the period from 1995 to 1997 within the framework of project B94-009 of the Belarusian Republic Basic Research Foundation "Rheophysics and processes of heat transfer in living systems as a problem of total hyperthermia" (manager of the project Prof. Z. P. Shul'man).

Influence of the temperature on the Hemorheological Properties of Blood. It is known that the viscosity of blood decreases with increase in its temperature. This dependence is defined mathematically by the Arrhenius equation of chemical kinetics [1]:

$$\eta = \eta_A \exp\left[\frac{E}{R\,(T+273)}\right]. \tag{1}$$

The measurements carried out in [1] have shown that the difference between the activation energies of the blood and plasma flows $\Delta E = E_b - E_{pl}$ is equal to 5.15 kJ/mole, i.e., the relative viscosity of blood η/η_{pl} is proportional to exp ($\Delta E/RT$); however, the temperatures and the rates of shear at which this value of ΔE was determined were not indicated in this work. By contrast, it has been established in [2] that the relative viscosity of blood in the range of rates of shear 1–100 sec^{-1} is independent of the temperature, which points to the fact that the temperature dependence of the blood viscosity is determined by the properties of the plasma and not the bonds between the erythrocytes. According to [1], the activation energy of a viscous plasma flow and of the blood serum in norm and in the case of certain diseases depends only slightly on the rate of shear. For the plasma and blood serum at $\dot{\gamma}$ = 0.223–3.48 sec^{-1}, it takes, respectively, the values 14.6–15.8 kJ/mole and 17.2–16.5 kJ/mole.

It is known that the temperature dependence of the viscosity of the plasma in norm is analogous to that of water [3]:

$$\eta = \eta_0 \exp\left[-\frac{g\,(T-T_0)}{(T+h)\,(T+T_0)}\right]. \tag{2}$$

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TABLE 1. Change in the Shear Stress (τ, mPa) and Dynamic Viscosity (μ, mPa·sec) of the Blood of a Healthy Patient with Increase in Its Temperature

$\dot{\gamma}$, sec^{-1}	Parameters	Temperature, ^oC				
		25.4	30.0	35.1	40.2	45.2
0.365	τ	28.13	27.27	25.70	21.69	18.11
	μ	77.07	74.77	70.41	59.42	49.62
0.595	τ	31.08	31.08	27.85	25.70	22.35
	μ	52.24	52.24	46.81	43.19	37.56
1.602	τ	54.42	49.24	46.84	43.67	38.35
	μ	33.97	30.74	29.24	27.26	23.94
2.641	τ	69.87	60.74	56.64	54.42	48.75
	μ	26.46	23.0	21.45	20.61	18.46
7.109	τ	124.8	106.3	97.19	92.45	86.20
	μ	17.56	14.95	13.67	13.00	12.13
11.49	τ	135.1	140.7	128.6	122.3	112.9
	μ	14.37	12.25	11.19	10.65	9.83
30.92	τ	360.2	313.1	280.5	264.2	246.3
	μ	11.65	10.13	9.07	8.55	7.97
57.97	τ	521.5	371.2	335.9	390.2	363.8
	μ	10.23	9.35	8.46	7.66	7.14

Here η_0 = 173 mPa·sec is the viscosity of the plasma at a temperature of T_0 = 23°C, h = 111°C, and g = 420°C.

In [4], the influence of the temperature on the relative viscosity of the human blood at T = 23 and 37°C was investigated using capillary, cylindrical, and "cone-plate" viscosimeters. The relative viscosity determined in these viscosimeters was independent of the temperature at rates of shear changing in the range 1–800 sec^{-1}. However, the viscosity of the blood with low (less than 1 sec^{-1}) rates of shear, determined in the capillary viscosimeter, was temperature-dependent.

Table 1* presents the initial data used in our analysis — results of rheological experimental investigations of the whole blood stabilized with heparin, performed using a VIR-78 coaxial-cylindrical viscosimeter; the blood samples were thermostated at a temperature of 25–45°C. The packed cell volume of the blood samples was brought to 45% by addition of an erythrocyte mass. Figure 1 shows these data in graphic form (Fig. 1a) and the results of their processing in Arrhenius coordinates (Fig. 1b and c) for the purpose of determining the activation energy of a viscous blood flow. It is evident from Fig. 1b and c that the temperature dependence of the apparent viscosity of blood is well defined by the Arrhenius law in the temperature range 25.5–45.2°C. The parallelism of the straight lines indicates that the activation energy of a blood flow is independent of the rate of shear. Note that the relation between the parameter η_A of model (1) and $\dot{\gamma}$ of blood is approximately defined by the power function (see Fig. 1b)

$$\eta_A = (380\dot{\gamma})^{-0.65}, \tag{3}$$

and the activation energy of a viscous flow E = 14.3 ± 1.8 kJ/mole is close to that of the blood plasma.

Figure 2 presents data of Table 1 in Caisson coordinates and the temperature dependence (obtained by us) of the parameters τ_0 and μ_p of the Caisson model:

$$\tau^{1/2}(T, \dot{\gamma}) = \tau_0^{1/2}(T) + [\mu_p(T)\,\dot{\gamma}]^{1/2}. \tag{4}$$

*Measurements are made by O. B. Gorodkina, a worker of the Scientific-Research Institute of Hematology and Hemotransfusion of the Ministry of Public Health of the Rebublic of Belarus.

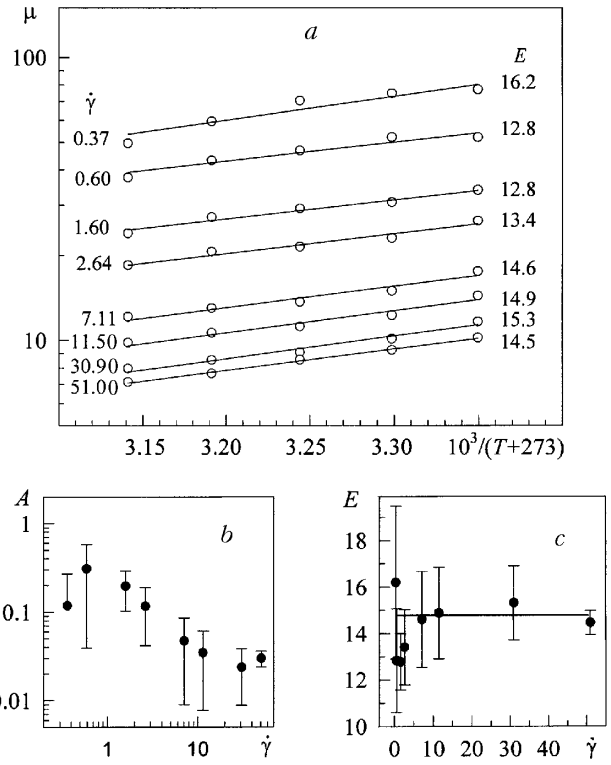

Fig. 1. Influence of temperature on the viscosity of the blood at different rates of shear (a) and dependence of the parameters of Arrhenius model (1) on the rate of shear (b and c). μ, mPa·sec; T, °C; A, mPa·sec; E, kJ/mole; $\dot{\gamma}$, $\sec^{-1}$.

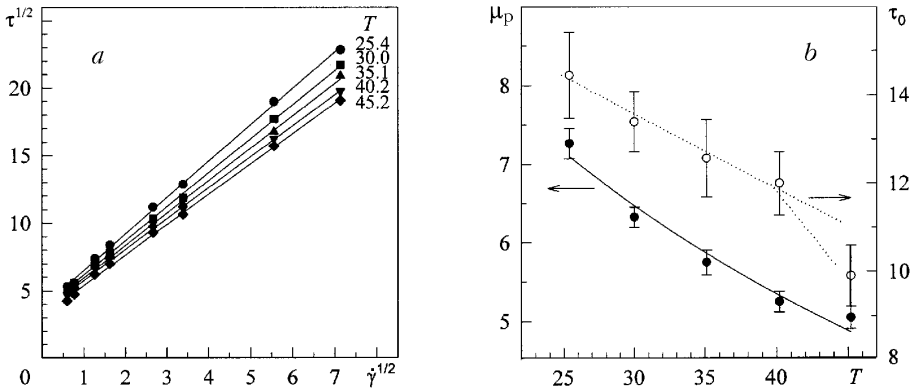

Fig. 2. Temperature dependence of the rheological properties of the blood (obtained on the basis of the data from Table 1): a) blood flow curves in Caisson coordinates at different temperatures; b) dependence of the Caisson model parameters on the temperature. τ, mPa; μ_p, mPa·sec; τ_0, mPa; T, °C; $\dot{\gamma}$, $\sec^{-1}$.

It is seen from Fig. 2b that, in the wide temperature range 25–40°C, the critical Caisson shear stress decreases linearly with increase in the temperature, and only in the range of hyperthermal temperatures does there arise a marked deviation from this tendency toward smaller values that exceeds the error in determining the parameter considered. The change in the Caisson viscosity at $T > 37$°C relative to the value of this parameter at $T = 37$°C is well approximated by the relation

$$\mu_p(T)/\mu_p(37) \approx 1 - 4(T-37)/(T+273). \quad (5)$$

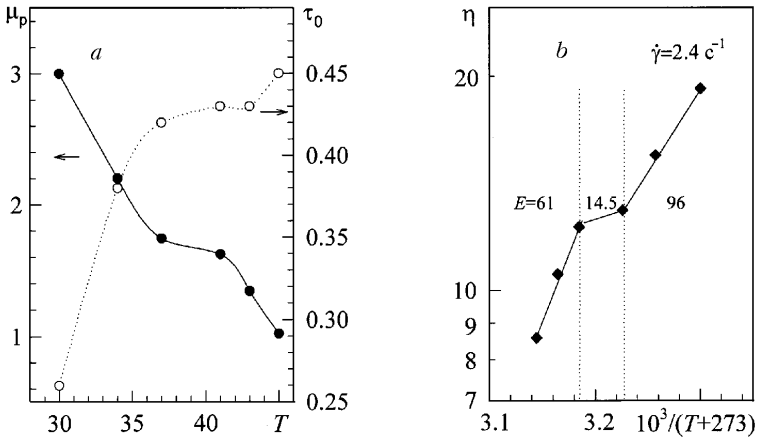

Fig. 3. Temperature dependence of the rheological properties of the blood (obtained on the basis of the data from [6, 7]): a) blood-flow curves in Caisson coordinates at different temperatures; b) apparent viscosity of the blood in Arrhenius coordinates. μ_p, mPa·sec; τ_0, mPa; T, ^oC; η, mPa·sec; E, kJ/mole.

An increase in the temperature to $T = 45^oC$ leads to a decrease in τ_0 and μ_p by 20.6 and 14.6% as compared to the values of these parameters at 37^oC. The large values of τ_0 and μ_p, which are not contradictory to the literature data, have engaged our attention.

Let us consider, for comparison, the data of other authors. According to the data of [5], the critical shear stress in 90% of healthy people is independent of the temperature in the range 15–37^oC; however this parameter increases substantially at temperatures lower than 15^oC, which can be very significant for simulation of the hemodynamics and the heat exchange in the process of hypothermia. These dependences differ quantitatively and, for the critical shear stress, qualitatively from those obtained in [6, 7]. The experimental data obtained in the indicated works are shown by points in Fig. 3, and the solid curves were obtained as a result of the processing of these data (for the plasticity in the Caisson model) in accordance with the Arrhenius model (1) in the three temperature ranges 30–37^oC, 37–41^oC, and 41–45^oC. The rheological measurements were carried out in [6, 7] with the use of an RM-10 coaxial-cylindrical rotational viscosimeter operating in the regime of push deformation of the medium investigated. Note that the calculated values of τ_0 were small as compared to the yield stress (see Fig. 2b) estimated by the data presented in Table 1. It is possible that this dependence $\tau_0(T)$ is due to the push regime of operation of the RM-10 viscosimeter and the absence of equilibrium between the processes of aggregation–disaggregation after the change from the high rate of shear (of the order of 500–1000 sec^{-1}) to a lower definite rate of shear. The temperature dependence of the viscosity, presented in Fig. 3b, shows that the activation energy of a viscous blood flow significantly exceeds its characteristic values, equal to 14–16 kJ/mole, beyond the temperature range 37–41^oC.

Change in the Hemorheological Properties of Blood with Decrease in Its pH. The temperature of a living organism influences the hemorheological properties of the blood not only directly, which was detected in rheometric experiments, but also indirectly: it enhances the metabolic activity of cells and increases the concentration of the products of their vital activity, with the result that the chemical and gas composition of the blood changes and the acid-base equilibrium shifts toward an oversouring of the blood. For example, in the case of local hyperthermia, the pH level of the blood at a site of heating can decrease to 5.6. The hemorheological shifts are increased when a large amount of glucose, which, in addition, changes (increases) the viscosity of the blood, is introduced into a tumor. High temperatures increase the penetrability of the walls of the exchange capillaries for water and high-molecular proteins. When a tumor is heated, the content of fibrinogen and albumins in it [8] as well as the hematocrit increase, which should increase the viscosity of the blood flowing through it. A complete model of the influence of these changes in the composition of the blood *in vitro* on its hemorheological properties has not yet been constructed. Only the influence of the combined action of the pH level and the temperature on the viscosity of the blood *in vitro* was investigated [9]. The data of this work, presented in Table 2, shows how the apparent viscosity of the blood changes with increase in its temperature to 43^oC at pH 7.4 and 6.4. These values of the blood viscosity, obtained in [9] with the

TABLE 2. Influence of the Temperature and Acidity on the Viscosity of the Blood

Patient	Viscosity, mPa·sec	pH	Relative change in the viscosity, %		E, kJ/mole
			T = 37°C	T = 43°C	
F30	5.73	7.4	100.0	93.7	8.8
		6.4	108.6	94.2	8.1
F25	5.53	7.4	100.0	86.1	20.3
		6.4	108.1	91.9	22.1
F58	7.07	7.4	100.0	84.0	23.6
		6.4	112.9	98.2	18.9
M55	6.43	7.4	100.0	91.0	12.8
		6.4	104.7	99.1	7.5
M68	6.22	7.4	100.0	89.1	15.7
		6.4	112.1	108.5	4.4
Average	6.20	7.4	100.0	88.5	16.5
		6.4	109.4	100.0	12.1
Rats (healthy)	9.65	7.4	100.0	85.0	22.1
		6.4	109.9	108.5	1.8
Rats (with a tumor)	10.40	7.4	100.0	81.4	27.9
		6.4	103.9	104.9	–1.3

use of a capillary viscosimeter, correspond to the average rates of shear exceeding 100 $\sec^{-1}$. As is seen from the table, the blood viscosity decreases with increase in the temperature and increases with decrease in pH. On the average, these factors compensate each other, and so the blood viscosity at T = 43°C and pH 6.4 is equal to that at T = 37°C and pH 7.4. Since, in the case of local hyperthermia, pH in a tumor can be much lower, the viscosity of the blood in the tumor can be markedly increased as compared to its value in a normal tissue. Of course, the corresponding proportions will depend on the degree of oversouring of the blood in the tumor and the excess of its temperature over the temperature of the healthy tissue. Approximation of the data presented in Table 2 gives a near linear dependence of the blood viscosity on pH

$$\eta_{43^\circ C}(\mathrm{pH})/\eta_{43^\circ C}(7.4) \approx 1.96 - 0.13\mathrm{pH}\,. \tag{6}$$

If pH decreases under the combined action of a hyperglycemia and a local hyperthermia, e.g., to 5.6, this model suggests an increase in the blood viscosity by 23% as compared to that at pH 7.4.

The estimates of the activation energy of a viscous blood flow, presented in the last column of Table 2, are very different for different patients. It is seen that the activation energy of a viscous blood flow decreases with decreases in pH. The data obtained for rats indicate that the Arrhenius dependence of the viscosity of their blood on the temperature breaks down at pH lower than 7.4. This is supported by some data on E, obtained for the blood of patients at pH 6.4, even though the activation energy of the blood flow is, on average, close to the literature data (and, at pH 7.4, it is close to that of water — 16.5 kJ/mole [1]).

Experimental data presented in [9] reflect the combined action of a hyperthermia temperature and an increased acidity on the whole-blood flow curves and the influence of a superlethal temperature ($T > 45^\circ$C) on the apparent viscosity. They are shown graphically in Fig. 4 (points) along with our data obtained on their basis (solid lines). Analysis of Fig. 4 shows that the dependence of $\tau^{1/2}$ on $\dot{\gamma}^{1/2}$ is linear, i.e., the Caisson model is roughly true at the rates of shear ranging from 22.5 to 450 $\sec^{-1}$ (Fig. 4a), and the temperature dependence of the apparent viscosity at $T > 45^\circ$C (Fig. 4b) differs substantially from the Arrhenius dependence. The solid curve in this figure is our approximation of experimental points with the use of the model

$$\eta = A\,(1 + \exp[-(T-B)/(T-C)])\exp[E/R\,(T+273)]\,, \tag{7}$$

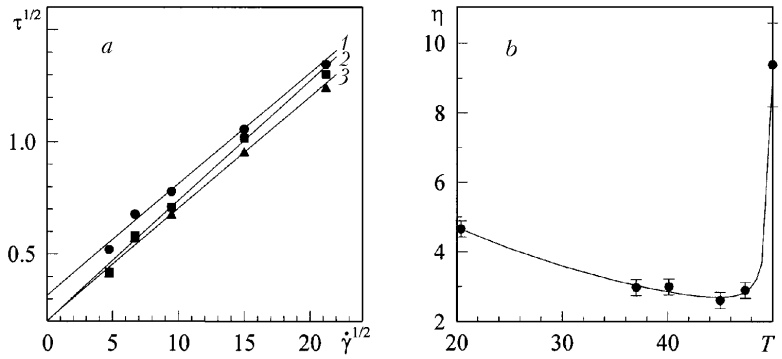

Fig. 4. Temperature dependence of the rheological properties of the blood (obtained on the basis of the data from [9]): a) whole-blood-flow curves in Caisson coordinates (T = 37°C and pH 6.3 (1), 37°C and 7.3 (2), 43°C and 6.3 (3); b) apparent viscosity of the blood at different temperatures and a shear stress of 1.63 Pa at the wall of the capillary viscosimeter. τ, mPa; $\dot{\gamma}$, sec^{-1}; η, mPa·sec; T, °C.

in which $A = (6.78 \pm 5.87)\cdot 10^{-4}$ mPa·sec, B = 48.4 ± 0.7°C, C = 51.0 ± 0.4°C, E = 20.7 ± 2.1 kJ/mole. It is seen that the calculated and experimental data are in good agreement; however, the error in estimating the parameter A is very large because of the small number of the data used.

Processing of the results (Fig. 4a) has given the following values of the Caisson parameters: curve 1) τ_0 = 100. 6 ± 15.8 mPa, μ_p = 2.39 ± 0.19 MPa·sec; curve 2) τ_0 = 41.4 ± 11.5 mPa, μ_p = 2.78 ± 0.23 mPa·sec; curve 3) τ_0 = 42.1 ± 10.3 mPa, μ_p = 2.41 ± 0.19 mPa·sec. Consequently, a decrease in pH mainly influences the critical shear stress, and the action of this decrease on the plastic viscosity is weaker.

Conclusions. In the range of therapeutic temperatures, the dependence of the apparent viscosity of blood on the temperature is well described by the Arrhenius model with a viscous-flow activation energy of 13–17 kJ/mole at rates of shear changing in a wide range. An increase in the temperature and a decrease in pH of the blood act differently on its viscosity so that, at T = 43°C and pH 6.3, the viscosity of the blood *in vitro* remains practically equal to that before heating (at T = 37°C and pH 7.6). It may be suggested that the viscosity of the blood with an acidity of up to pH 5.6 (possible in the case of combined action of a hyperthermia and a hyperglycemia) will be larger by 23% as compared to the initial one.

An oversouring of blood mainly influences the critical shear stress, and the Caisson viscosity at pH 6.3–7.6 depends only slightly on the acid-base equilibrium.

NOTATION

A, parameter of model (7), Pa·sec; B, C, model parameters (7), °C; E, activation energy of a viscous flow, J/mole; g, h, parameters of model (2), °C; R, gas constant, J/(mole·°C); T, temperature of a liquid (blood or blood plasma), °C; T_0, characteristic temperature, °C; $\dot{\gamma}$, rate of shear, sec^{-1}; η, apparent viscosity of blood, Pa·sec; η_A, characteristic viscosity of blood, Pa·sec; μ_p, plastic viscosity (parameter of the Caisson model), Pa·sec; τ_0, critical shear stress (Caisson model parameter), Pa; τ, shear stress, Pa. Subscripts: b, blood; pl, plasma; p, plastic; A, Arrhenius model parameter; 0, zero rate of shear or characteristic temperature.

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