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STATE OF THE RHEOLOGICAL PROPERTIES OF BLOOD IN THE DYNAMICS OF DEVELOPMENT OF ACUTE DISTURBANCES OF CEREBRAL CIRCULATION IN ATHEROSCLEROSIS PATIENTS

V. G. Ionova

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The data on the state of the rheological properties of blood and the thrombocytic-vascular chain of hemostasis in the dynamics of development of transitional ischemic attacks and acute ischemic insult are presented and compared to the indices of healthy persons and patients with chronic cerebrovascular pathology. Throughout the period of observation, in the patients of all the groups examined we established changes in the increase in the blood viscosity, the aggregation of erythrocytes, and the content of fibrinogen (with decrease in the deformability of erythrocytes) and an increase in the activation of the function of thrombocytes against the background of the changed athrombogenic properties of the vascular system. It has been revealed that there is a close connection between the hemorheological disturbances and the heaviness of atherosclerotic affection of the main arteries of the heart.

Acute disturbances of cerebral circulation are widely encountered in people of developed countries and have the most serious consequences; therefore, they rank with the most important problems of contemporary medicine.

As is known, acute disturbances of cerebral circulation arise as a result of an insufficient inflow of blood to a certain region of the cerebrum; in this case, the deciding factor is the incompatibility between the demand for oxygen and its ingress to the cerebral tissue. In the majority of cases, ischemic acute disturbances of cerebral circulation develop in patients with atherosclerosis or with atherosclerosis in combination with arterial hypertension. The dimension and localization of cerebral infarcts depends not only on the severity of the atherosclerosis process leading to the development of a hemodynamically significant atherostenosis or to the complete occlusion of arteries as a result of the artheroobliteration, thrombogenesis, or embolism, but also on the position of these damages in the blood-supply system of the cerebrum and the structural features of its vascular system. A well-developed system of arterial anastomoses between the cerebral arteries of different levels and pools as well as with extracerebral vessels of the head and neck provides wide possibilities of functional adaptation of the hemodynamics to the demands of cerebral tissue [1]. However, compensatory blood flows in the connective arteries from one pool to another are accompanied by collisions and mixing of differently directed flows. In this case, fluctuation motions of blood are enhanced and there arise turbulent motions of blood, which substantially change the rheological behavior of the blood cells and their interaction with the endothelium of the vessels [2–4]. The changes in the hemorheological characteristics serve to activate the functions of thrombocytes and accordingly to enhance the local process of blood coagulation [5, 6] whose reversibility is provided first of all by the preservation of the athrombogenic potential of the endothelial lining of the vessels [7]. The development of an echeloned or tandem stenosis of the main arteries of the head (MAH) (extra- and intracerebral arteries) is a consequence of both the adaptation processes in response to the reduction of blood flow and the pathological changes in the vascular walls of small-diameter arteries, which can lead to the appearance of acute disturbances of cerebral circulation with irreversible and reversible neurological symptoms [8]. Many questions of interrelation between the pathogenic and compensatory mechanisms of development of disturbances of cerebral circulation and the part played in them by the changes in the rheology of blood are insufficiently understood.

Because of this, investigations aimed at interpreting the mechanisms responsible for the hemorheological disturbances and the factors determining the adaptability of the vascular system of atherosclerosis patients with cerebrovascular diseases seem to be urgent in both the scientific and practical aspects.

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The aim of the present work is comparative analysis of changes in the rheological properties of blood in the dynamics of development of acute ischemic insult (AII) with irreversible symptoms in the case of transitional ischemic attacks (TIA) in patients with atherosclerotic affection of the main arteries of the head.

To solve this problem, we investigated the examination data of 47 patients with acute ischemic insult on the 1st–3rd, 7th, and 21st days from the beginning of the disease and 33 patients with transitional ischemic attacks that were accompanied by the complete restoration of functions within 24 h. As the comparison groups, we examined 62 healthy males and 30 patients with atherosclerosis affection of the main arteries of the head, in which initial symptoms of chronic cerebrovascular pathology (CCVP) were clinically revealed.

Investigation Methods. The state of the main arteries of the head in the patients with chronic cerebrovascular pathology was documented by the data of ultrasonic dopplerography (USDG); for the patients with transitional ischemic attacks and acute ischemic insult, we additionally considered the results of cerebral panangiography. Local lesions of the cerebrum were visualized with the use of computer tomography.

The rheological properties of the blood were investigated immediately after it was taken from healthy persons on an empty stomach and on the 1st–3rd, 7th, and 21st days from the beginning of the disease in the patients with chronic cerebrovascular pathology. The blood taken for subsequent analyses was stabilized by a 3.8% solution of sodium citrate in a 9:1 ratio.

1. The viscosity of the blood was determined with the use of a homemade capillary viscometer. The blood was passed through the vertical spiral of a capillary which was sealed into a glass vessel filled with running water ($t = 37^{o}$C) coming from the outer circuit of a water thermostat; this made it possible to maintain a constant temperature of 37^{o}C in the viscometer. The index was calculated from the ratio K/B, where K is the time of passage of 2.0 ml of blood through the glass spiral tube, sec, and B is the time of passage of the same amount of distilled water, sec.

2. The hematocrit (Hct) value was determined on a hematocrit centrifuge with the use of heparinized capillaries.

3. The content of fibrinogen (FG) was determined by the dry-air method of R. A. Rutberg [9].

4. The aggregation ability of erythrocytes (AE) was analyzed on an aggregometer of the Chrono-Log Corp. (USA) by the method of K. M. Lakin et al. [10] in the process of inducing the kinetics of simultaneously added 10% solutions of fibrinogen and gammaglobulin.

5. The deformability of erythrocytes (DE) was investigated by the filtration method in our modification with estimation of the filtration time and the percentage of the filtrated cells of a 2% erythrocytic suspension. The index DE (filtr. time) sec was measured by the filtration time of erythrocytic-suspension samples and the index DE (Hb)% is the percentage of the filtrated cells. Based on the measurement of the hemoglobin concentration before and after the filtration, we calculated the ratio by the following formula: DE (Hb)% = $B \cdot 100/A$, where A is the hemoglobin content in the initial suspension and B is the hemoglobin content after the filtration.

6. The aggregation of thrombocytes (AT) was determined by the turbidimetric method on the aggregometer of the Chrono-Log Corp. (USA) according to the method of G. Born [11] with the use of adenosinediphosphoric acid (ADP) of concentration $1.2 \cdot 10^{-6}$ mole and adrenaline (Adr.) of concentration $6.2 \cdot 10^{-6}$ mole. The thrombocytic suspension was preliminarily incubated with prostacyclin (PGI_2) of concentration 100 nanomolee.

7. To estimate the athrombogenic potential of the vascular wall, we used a functional "cuff test" based on a short-term ischemia of the arm vessels [12]. In healthy persons, the compression caused by an increase of 10 mm Hg in the systolic-pressure values from its initial value with the help of a sphygmomanometer leads to the development of a short-term ischemia of the arm vessels in response to which there arises a protective reaction of the vessel endothelium. This reaction is expressed as the activation of the athrombogenic potential of vascular endothelium as a result of the formation of different biologically active substances in it, including substances with antiaggregation properties, and the release of them to the vascular channel. These effects manifest themselves as a decrease in the aggregation of thrombocytes and an activation of the fibrinolysis system.

The statistical processing of all the indices was done by the method of variation statistics. The reliability of the indices was estimated by Z, i.e., the Student criterion.

Investigation Results. It has been established on the basis of the data of clinical and instrumental examination methods that acute ischemic insult and transitional ischemic attacks develop in patients with a heavy atherosclerotic pathology of the arteries of the blood-supply system of the cerebrum. It has been revealed that in the case where there are different multilevel structural changes in the main arteries of the head as well as in the extra-

TABLE 1. Rheological Indices of Blood in Atherosclerosis Patients with Chronic Cerebrovascular Pathology ($M + m$)

Indices	Patients with CCVP, n = 30	Healthy persons, n = 62	p
BV, rel. units	5.3±0.1	3.8±0.1	< 0.001
Hct, %	43.9±0.4	40.9±0.3	< 0.001
FG, g/liter	3.17±0.6	2.7±0.5	< 0.001
AE, %	17.2±0.6	12.2±0.2	< 0.002
DE Hb, %	89.6±0.9	97.8±0.2	< 0.001
DE (filtr. time), sec	101.0±2.0	79.0±1.0	< 0.01
ADP-AT, %	52.9±4.6	40.3±2.6	ins.
Adr.-AT, %	52.8±4.6	40.3±2.7	< 0.05

Note: $p < 0.05$ is the reliability of distinction from the group of healthy persons.

and intracranial arteries, the occlusion of the carotid artery was 4.7 times more frequent in the patients with acute ischemic insult than in the patients with transitional ischemic attacks. It should be noted that in 40% of the patients with initial symptoms of chronic cerebrovascular pathology without acute cerebrovascular disturbances we also found indications of occlusion or stenosis of the main arteries of the head; in other patients, we found functional circulatory insufficiency in combination with a moderate stenosis of the arteries. Thus, in the examined groups of patients with a marked atherosclerotic pathology of the main arteries of the head and the extra- and intracerebral arteries we observed ischemic affections of the cerebrum, which were different in character and severity.

The data obtained in investigating the hemorheological characteristics of the atherosclerosis patients with clinical symptoms of the initial manifestations of chronic cerebrovascular pathology have shown that all the analyzed tests of these patients differ significantly from those of healthy persons. As is seen from the data presented in Table 1, the following indices are reliably higher in atherosclerosis patients with chronic cerebrovascular pathology than in healthy persons: blood viscosity, 5.3 ± 0.1 rel. units ($p < 0.01$); Hct, $43.9 \pm 0.4\%$ ($p < 0.003$); fibrinogen, 3.17 ± 0.61 g/liter ($p < 0.001$); aggregation ability of erythrocytes, $17.2 \pm 0.6\%$ ($p < 0.002$); deformability of erythrocytes (filtr. time), 101.6 ± 2.0 sec ($p < 0.01$). In this case, the filtration ability of erythrocytes decreased, amounting to $89.6 \pm 0.95\%$ in the patients as compared to $97.8 \pm 0.2\%$ in the healthy persons ($p < 0.001$). The functional activity of thrombocytes in the atherosclerosis patients with chronic cerebrovascular pathology was higher than the control values: the ADP-AT was $52.9 \pm 4.6\%$ ($42.8 \pm 2.6\%$ in the healthy persons) and the Adr.-AT was $52.8 \pm 4.6\%$ ($40.3 \pm 2.7\%$ in the healthy persons), $p < 0.050$. It should be noted that, when the functional "cuff test" was carried out, the ADP-AT of the patients did not decrease but had a tendency toward increasing in contrast to the healthy persons. For example, if in the healthy persons the ADP-AT decreased to $31 \pm 2.7\%$, i.e., by 28%, $p < 0.05$, in the patients with chronic cerebrovascular pathology it increased from 44.4 ± 4.0 to 48.5 ± 5.0, i.e., by 109%.

Analysis of the rheological data of the patients with chronic cerebrovascular pathology in the subgroups with or without symptoms of a disturbance of hemocirculation in the arterial blood-supply system of the cerebrum (ultrasonic-dopplerography data) has shown that there are no reliable differences between the values of the blood viscosity, fibrinogen, deformability of erythrocytes, and aggregation ability of erythrocytes. However, a more significant increase in Hct ($p < 0.01$) and in the aggregation activity of thrombocytes was observed in the subgroups with pathologic changes in the structure of the main arteries of the head as distinguished from the cases without symptoms of discirculation in them. Since the "cuff test" makes it possible to estimate the functional athrombogenic potential of the endothelial lining of the vessels, provided by the ejection of prostacycline and other substances with antithrombocyte activity, we estimated the effect of PGI_2 on the function of thrombocytes before and after the "cuff test." In the group of healthy persons, the ADP-AT decreased on the average by 28% after the "cuff test." Incubation of a thrombocyte-rich plasma carried out with PGI_2 before the "cuff test" decreased the ADP-AT by 43%. After the "cuff test," this effect was enhanced and the ADP-AT decreased by 60%.

In atherosclerosis patients with chronic cerebrovascular pathology, as distinguished from the healthy persons, the ADP-AT increased or remained at the initial level after the functional "cuff test," which manifested itself as a small increase in the average value of the ADP-AT from 44 ± 3.0 to $48.0 \pm 5.0\%$. This points to a decrease in the

TABLE 2. Rheological Indices of Blood in Patients with Transitional Ischemic Attacks and Chronic Cerebrovascular Pathology and in Healthy Persons

Indices	Examined groups				
	Phase of the TIA process		CCVP, n = 30	Healthy persons, n = 62	p
	TIA bout, n = 40	Interbout period, n = 39			
BV, rel. units	6.8±0.7***	5.8±0.3***	5.3±0.1***	3.8±0.1	< 0.001
Hct, %	45.6±2.8***	45.3±1.9***	43.9±0.4	40.4±0.3	< 0.01
AE, %	19.8±1.1*	16.4±1.5*	17.2±0.5*	12.2±0.2	< 0.05
DE Hb, %	82.9±10.3	82.9±10.3	89.6±0.9	97.8±0.2	ins.
ADP-AT, %	73.9±6.5***	50.0±10.0	52.9±4.6**	42.8±2.6	< 0.001
Adr.-AT, %	83.1±5.6***	47.5±8.8	52.8±4.6**	40.3±2.3	< 0.001
FG, g/liter	4.2±0.05*	3.9±0.1*	3.7±0.06*	2.4±0.05*	< 0.05

Note: $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.0001$ are the reliabilities of distinction of patients from healthy persons.

endogenous antiaggregation reserve of the vascular endothelium in the patients with chronic cerebrovascular pathology. In investigating the action of PGI_2 on the thrombocytes, it has been revealed that in this category of persons the sensitivity of thrombocytes to the antiaggregation action of PGI_2 is increased, which manifested itself as a more pronounced decrease in the ADP-AT relative to the initial value in comparison with the healthy persons. However, in the samples investigated after the "cuff test," the effect of prostacycline was somewhat lower than that in the initial samples. The absence of potentiation of the PGI_2 effect after the "cuff test" in the patients with chronic cerebrovascular pathology is, evidently, explained by the decreased antiaggregation reserve of the vascular system in them. Thus, the observed decrease in the antiaggregation potential of the vascular endothelium in the patients with chronic cerebrovascular pathology combined with a marked atherosclerotic affection of the main arteries of the head is apparently compensated for with the increased sensitivity of thrombocytes to the antiaggregation effect of prostacyclin.

Thus, in the case where in the atherosclerosis patients without acute cerebrovascular disturbances there is an atherosclerotic affection of the main arteries of the head at all the levels of the vascular system of the cerebrum, accompanied by the characteristic changes in the cerebral blood flow, there arise disturbances of the blood rheology as a result of the functional increase in the blood viscosity, Hct, fibrinogen, and aggregation ability of erythrocytes and the decrease in the deformability of erythrocytes.

The above-indicated structural and functional changes in the vascular system of the cerebrum in the atherosclerosis patients without acute ischemic insult and the significant shifts of the above-given hemorheological determinants are accompanied by the activation of the function of thrombocytes and their high sensitivity to both proaggregation and antiaggregation actions.

The rheological properties of the blood of patients with transitional ischemic attacks were investigated in the acute period, i.e., within 24 h after the beginning of a bout and in the interbout period within 2–5 days but no later than after 10 days from the beginning of the ischemic attack. The patients with an acute phase of the disease did not take thrombocyte-active preparations before the first taking of blood. It has been established that the investigated rheological indices in this category of patients differed most significantly from those of the healthy persons in an acute bout of transitional ischemic attack (Table 2). The index DE (Hb)% was quite variable and, on the average, it was practically the same at the instant of transitional ischemic attack and in the interbout period. The capacity of erythrocytes for aggregating was much higher than that in the norm in all the periods of observation, but it practically did not differ from that in the group of atherosclerosis patients without acute disturbances of cerebral circulation. High concentrations of fibrinogen ($p < 0.05$) were observed in both phases of the process of transitional ischemic attack. The increase in the average values of Hct was not reliable because of the intrarow variability of the indices.

The ADP- and adrenaline-induced aggregation of thrombocytes sharply increased at the instant a transitional ischemic attack began to develop. Its level reliably exceeded the normal value, on the average, by 173 and 206%, re-

TABLE 3. Dependence of the Changes in the Aggregation of Thrombocytes and in the Blood Viscosity on the Frequency of Transitional Ischemic Attacks

Frequency of bouts	ADP-AT, %	Adr.-AT, %	Blood viscosity
Rare attacks, n = 6	51.9±7.8	63.4±8.1	5.0±0.4
Frequent attacks, n = 21	62.9±8.8	72.5±7.8	6.4±0.6
Very frequent attacks, n = 13	73.8±9.6	90.6±5.3*	7.1±1.0*

Note: $^{*}p < 0.05$ is the reliability of distinction of the indices in patients with rare and very frequent bouts.

TABLE 4. Change in the Hemorheological Indices in the Dynamics of Acute Ischemic Insult

Indices	Time from the development of insult in patients (n = 44), day			Healthy persons
	1st	7th	21st	
BV, rel. units	5.70±0.40*	4.90±0.44*	4.44±0.14*	3.80±0.10
Hct, %	44.80±1.90	44.60±1.88	44.10±1.23	40.40±0.30
FG, g/liter	3.80±0.20*	4.32±0.17*	3.58±0.22*	2.60±0.50
AE, %	24.60±2.80*	14.20±1.22	10.92±1.04	12.20±0.20
ADP-AT, %	83.80±6.90*	50.30±4.86*	36.25±3.68	42.80±2.60
DE Hb, %	93.00±1.90*	–	92.78±2.73*	98.06±0.15
DE (filtr. time), sec	95.90±2.60*	–	98.37±5.09*	79.87±0.72

Note: $^{*}p < 0.05$ is the reliability of distinction of the indices of patients from the indices of the group of healthy persons.

spectively. In the interbout period, we observed a tendency toward a decrease in the functional activity of thrombocytes, but their number exceeded the control normal values.

The majority of patients with transitional ischemic attacks had frequent (n = 21) or very frequent (n = 13) bouts (Table 3). It has been established that the aggregation ability of thrombocytes and the blood viscosity increase more markedly with increase in the frequency of transitional ischemic attacks. It should be noted that when the frequency of bouts in the group of atherosclerosis patients with transitional ischemic attacks increased (by 32%), the increased values of both the blood viscosity and the aggregation of thrombocytes were retained in the interbout period. Thus, the phase of change in the function of thrombocytes is lost to a certain extent when the frequency of bouts of transitional ischemic attacks increases.

After the "cuff test," the decrease in the ADP-AT was different in different patients with transitional ischemic attacks. It amounted to 18% on the average in the group, which was much lower than the norm value. In 10% of the cases, we have revealed an inverted, proaggregation reaction in response to the "cuff test."

In the case of a combined action of the "cuff test" and PGI_2, the ADP-AT decreased relative to the initial value by 48%; the effect of PGI_2 was typical of healthy persons, i.e., there took place potentiation of the PGI_2 effect.

Thus, in the majority of cases, an antiaggregation effect of PGI_2 was observed in the patients with transitional ischemic attacks, but this effect was 3 times weaker than that in the healthy persons. It is characteristic that not only has the "cuff test" revealed the antiaggregation activity of the vessel wall but it has also revealed the enhancement of the antiaggregation action of PGI_2 on the thrombocytes.

An important aspect of the investigation is estimation of the effect of vasodilating medicinal preparations usually used in clinical practice. The patients with transitional ischemic attacks were examined against the background of the therapy with vasoactive and antiaggregation preparations (aspirin, Trental, Cavinton, and others). It has been established that preparations with vasoactive and antiaggregation action effectively decrease the aggregation of thrombocytes but have practically no influence on the blood viscosity. In the majority of cases, a pronounced antiaggregation therapeutic effect was accompanied by the clinical improvement and termination of transitional ischemic attacks. In a number of cases, the discontinuation of aspirin was accompanied by a rapid restoration of transitional ischemic attacks.

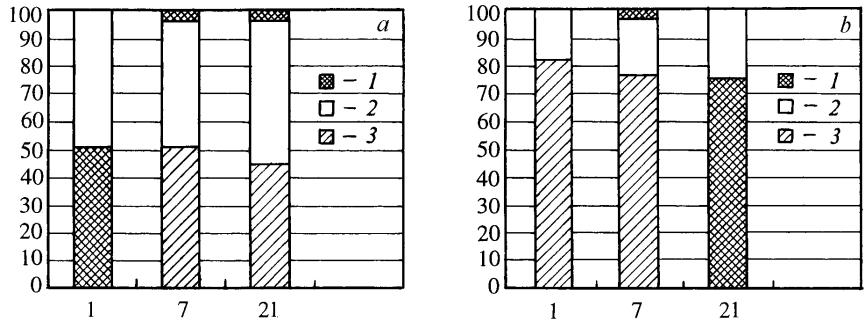

Fig. 1. Changes in the ADP-AT after the "cuff test" (a) and in the ADP–AT + PGI_2 (influence of PGI_2 on the ADP-AT) after the "cuff test" (b) in the patients with AII in the dynamics (the number of patients is indicated in percent on the vertical axis, the days of examination are indicated on the horizontal axis): 1) absence of differences from the values before the "cuff test", 2) excess over the values before the "cuff test", and 3) decrease in the values in comparison with those obtained before the "cuff test."

As has already been noted, the patients with acute ischemic insults were examined on the 1st, 7th, and 21st days of the disease. Into this group we included patients that did not take preparations with antiaggregation properties during 5–7 days before the insult. The data of studying the hemorheological indices, presented in Table 4, point to the fact that on the first day of the insult a significant change in the majority of the hemorheological indices takes place, except for Hct. The following indices reliably exceeded the normal values: blood viscosity, 5.7 ± 0.4 rel. units ($p < 0.01$); fibrinogen, 3.8 ± 0.16 g/liter ($p < 0.01$); aggregation ability of erythrocytes, $24.6 \pm 2.8\%$ ($p < 0.01$); DE (Hb), $93.04 \pm 1.9\%$ ($p < 0.01$); DE (filtr. time), 95.9 ± 2.6 sec ($p < 0.01$); ADP-AT, $83.8 \pm 6.9\%$ ($p < 0.01$). By the end of the most acute phase of the insult, on the 7th day the aggregation ability of erythrocytes and the ADP-AT decreased by a factor of 1.7 against the background of the therapy conducted, but it did not reach the normal values. The indices of the blood viscosity, Hct, and deformability of erythrocytes did not differ from the initial values. For example, the blood viscosity was reliably higher than the control value. It is significant that, according to both the data of the clinical estimation of the state of the patients and the values of the indices of the hemorheological characteristics, in the most acute phase of ischemic insult there are no significant differences between the bouts of transitional ischemic attacks and bouts of acute ischemic insult. As has already been noted, transitional ischemic attacks differ from acute ischemic insult in the character of affection of the cerebrum, the severity of the neurologic disturbances, and the dynamics of restoration of the lost neurologic functions. As is seen from the table, by the 7th day the aggregation ability of erythrocytes decreased to the normal values, while the other indices decreased in comparison with the initial ones but remained increased relative to the normal values. By the end of the acute period, the aggregation activity of the blood cells was normalized, but the blood viscosity, fibrinogen, and deformability of the erythrocytes differed from the normal values as before.

Estimation of the thrombocytic-vascular interactions with the use of the "cuff test," carried out in the patients with acute ischemic insult in dynamics, allowed the conclusion that in the group of patients as a whole, the average statistical values of the ADP-AT did not change significantly in response to the "cuff test." However, more detailed analysis of the data points to the fact that the response of thrombocytes to the "cuff test" was not unambiguous. For example, on the 1st day of the insult, the normal response to the short-term ischemia of the arm vessels — the aggregation of thrombocytes decreased by 33% — was observed in half the patients; however, in the other patients the ADP-AT increased by 49%, i.e., in half the patients there took place an unnatural response to the test stimulating the athrombogenic mechanisms of the vessel wall.

In the course of the "cuff test," on the 7th day of the disease a normal decrease in the ADP-AT of, on the average, 36% was observed in 51% of the patients, in 4% of the cases we revealed areactivity, i.e., the absence of a change in the ADP-AT, and in 45% of the patients there took place a paradoxical increase of 41% in the ADP-AT. The same differently directed reaction to the functional load was observed on the 21st day of development of the

acute ischemic insult. After the "cuff test" the ADP-AT decreased, on average, by 37% in 45% of the patients, in 51% of the patients it increased, on the average, by 46%, and in 4% of the patients changes in ADP-AT were absent.

Thus, throughout the acute period of insult, in half the patients with acute ischemic insult a significant decrease in the antiaggregation reserves of the vascular wall was observed.

Investigation of the sensitivity of thrombocytes to the action of prostacycline in the experiments *in vitro* has shown that throughout the acute period of the disease, in the samples taken before the "cuff test" the inhibiting effect of PGI_2 in the group was on the average practically normal and decreased the ADP-AT by 39–40%. A more detailed analysis has shown that on the 1st day after the "cuff test" a marked antiaggregation effect decreasing the ADP-AT by 51% was observed in the majority of cases (82%). However, in the other 18% of the cases, the proaggregation effect increasing the ADP-AT by 22% was observed.

On the 7th day, the individual reactions were more variable. For example, after the "cuff test", the antiaggregation effect of PGI_2 decreasing the ADP-AT by 47% was observed in 77% of the patients, the ADP-AT increased, on the average, by 25% in 19% of the cases, and changes were absent in 4% of the patients. The same differently directed reaction was observed on the 21st day. In the samples taken after the "cuff test," PGI_2 decreased the ADP-AT by 47% in 76% of the patients. The paradoxical proaggregation response to PGI_2 after the "cuff test," which manifested itself as an increase of 30% in the ADP-AT, has been revealed in 25% of the patients.

Thus, investigation of the action of one of the most powerful natural antiaggregating agents on the function of thrombocytes in the experiments *in vitro* has shown that in the majority of cases where an inverted reaction to the functional "cuff test" took place, addition of prostacycline to the samples of plasma restored its antiaggregation activity. However, paradoxical reactions to prostacycline, which manifested themselves as an increase in the ADP-AT and not as a decrease, were observed in a number of patients. They were revealed in both the initial samples and in the samples taken after the "cuff test." Moreover, the number of cases of inadequate response to the addition of PGI_2 increased after the "cuff test." It is significant that this tendency intensified in the dynamics of development of acute ischemic insult and reached the maximum by the end of the acute period.

Thus, in the residual period of acute ischemic insult the breakdown of the vascular-wall mechanisms generating prostacycline intensifies, which, evidently, is due to the pronounced negative influence of a local lesion of the cerebrum on the hemostatic potential of blood and the athrombogenic activity of the vascular system of the cerebrum.

Discussion. The data presented allow the conclusion that in all the considered cases of cerebrovascular pathology in atherosclerosis patients a change in the rheological properties of the blood takes place, which is accompanied by the activation of the function of thrombocytes. Of great importance is the fact that in atherosclerosis patients with chronic cerebrovascular pathology the entire complex of changes in the hemorheological and thrombocytic-vascular characteristics has a clear atherogenic trend compensated for with a certain preservation of the vascular-system mechanisms generating prostacycline. The results of examination of the patients with transitional ischemic attacks revealed significant changes in all the hemorheological and thrombocytic-vascular determinants, analogous to the changes in the group of atherosclerosis patients with chronic cerebrovascular pathology. At the same time, at the instant transitional ischemic attacks begin and, especially in the cases of a high frequency of these attacks, the changes in the rheology of the blood were most pronounced. It is significant that the high values of the blood viscosity were also preserved in the interbout period. Thus, a significant role in the development of transient cerebral ischemia in patients with an atherosclerotic affection of the main arteries of the head under hemodynamic disturbances is played by the disturbance of the blood rheology and the activation of its thrombogenic potential. The above-indicated processes can lead to the appearance of transitional ischemic attacks because of the transient cerebrovascular insufficiency by the mechanism of hemorheological microocclusion with the participation of the activation of the thrombocytic-vascular chain of hemostasis, or as a result of the arterioarterial embolism, in part by the aggregates of thrombocytes. A strong argument in favor of the above conclusion is the positive effect of antiaggregation therapy. As has been shown, in patients with frequent and very frequent bouts of transitional ischemic attacks, these attacks stopped after a long period of taking aspirin [13]. However, the increased values of the blood viscosity and the aggregation of erythrocytes and their poorer deformability even in the bout period were preserved in these patients, which can be due to the active atherogenesis in them.

In the dynamics of an acute process of cerebral insult, of particular importance is an increased level of fibrinogen, which being an acute-phase protein and a factor of coagulation of the hemostasis system, significantly affects

the viscosity characteristics of blood and influences not only the viscosity of plasma, but also participates in the process of aggregation of blood cells and favors the adhesion of thrombocytes to endothelium. These properties of fibrinogen made it possible to separate it as an independent risk factor of insult and a marker of atherosclerosis affection [14, 15]. The reliable increase in fibrinogen and the hyperaggregability of thrombocytes point to the fact that fibrinogen can be used as a molecular marker of atherosclerosis and a risk factor of development of an acute disturbance of cerebral circulation. An increase in the number of rigid erythrocytes under increased shear stress in the stenosed main arteries of the head can, on the one hand, serve to increase the ejection of the activator of thrombocytes — adenosinediphosphoric acid — from these cells and, on the other, exert a damaging effect on the endothelium of the arteries, especially in the microcirculatory bed. All these factors create conditions for enhancement of the processes of deposition of fibrin and adhesion of thrombocytes to the endothelium. Under these conditions, a decrease in the athrombogenic potential of the vessels favors thrombogenesis and atherogenesis. At the same time, atheromatous plaques are indicators of the thrombogenic potential of blood; it in turn intensifies the affection of the vascular wall. In this case, for example, in the region of the stenosed section of the carotid artery there can take place accumulation of thrombocytic aggregates that can move to the distal regions of the cerebrovascular system under certain conditions. It is precisely in this zone of the artery that highly active substances released in the reaction of liberation from thrombocytes can be concentrated, which can cause a local vasospasm of the affected section of the artery with increase in the degree of stenosis due to its functional components. In particular, the above-described mechanisms can lead to the development of hemorheological occlusion in small vessels of the cerebrum. The above-considered mechanisms of participation of hemorheological disturbances in the pathogenesis of cerebral ischemia can take place not only at the acute and residual stages of ischemic acute disturbance of cerebral circulation, but they also can develop at early stages of cerebrovascular pathology [16].

Evaluating the foregoing, it is well to bear in mind that the above-considered shifts in the state of the blood rheology and the enhanced thrombogenic activity of blood can exist latently for a fairly long time and be somewhat compensated for with the athrombogenic potential of the vascular system. Their realization in the form of thrombosis, thromboembolism, or rheological microocclusion require a certain "push" leading to a disbalance of thrombocytic-endothelial interactions. This proposition is clearly illustrated by the development of subjective complaints in patients with chronic cerebrovascular pathology under conditions of increased physical or emotional load and by an increase in the frequency of appearance of transitional ischemic attacks and acute ischemic insults after stress situations. Moreover, data on the state of the rheological properties of blood in the dynamics of development of acute disturbances of cerebral circulation show that the appearance of local lesions of cerebral tissue additionally affects the rheology of blood and increases the blood viscosity, fibrinogen, aggregation ability of erythrocytes, and Hct and deteriorates the deformability of erythrocytes, which intensifies the hemostatic activity both locally and in the entire system of blood supply, the process of breakdown of the antiaggregation potential of the vascular system, and accordingly the progress of atherosclerosis.

CONCLUSIONS

1. Different forms of ischemic disturbances of cerebral blood circulation, irrespective of the stage of their development, are characterized by significant unidirectional shifts of the hemorheological indices, intravascular activation of the hemostatic potential, and a change in the antiaggregation potential of the vascular system; these changes are closely related to the manifestation of an atherosclerosis affection of the main arteries of the head and the severity of an acute disturbance of cerebral circulation.

2. Analysis of the dynamics of change in the rheological properties of blood made it possible to establish that in patients with different forms of ischemic affections of the cerebrum, the unidirectional changes in the hemorheology and thrombocytic-vascular interactions are closely related to the process of atherogenesis and, apparently, are formed at the early subclinical stage of development of the vascular pathology of the cerebrum.

3. The results of the investigation carried out confirm the view that disturbances of the hemorheological status and thrombocytic-vascular interactions participate in the pathogenic mechanisms of thrombo- and atherogenesis and in the mechanisms responsible for the development of ischemic disturbances of cerebral circulation.

NOTATION

DCC, disturbance of cerebral circulation; MAH, main arteries of the head; AH, arterial hypertension; USDG, ultrasonic dopplerography; BV, whole-blood viscosity; Hct, hematocrit; Hb, hemoglobin; FG, fibrinogen; DE, deformability of erythrocytes; DE (filtr. time) sec, DE index determined from the time of filtration of an erythrocytic suspension; DE (Hb)%, DE index reflecting the percentage of filtrated erythrocytes; AT, aggregation of thrombocytes; ADP, adenosinediphosphoric acid; ADP-AT, aggregation of thrombocytes induced by ADP; Adr.-AT, aggregation of thrombocytes induced by adrenaline; PGI_2, prostacyclin; ADP-AT + PGI_2, aggregation of thrombocytes induced by ADP after incubation with PGI_2; p, reliability criterion; ins., difference between the groups is insignificant, i.e., $p < 0.5$.

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