Platelet Aggregation and Endothelial Function in Patients with Complicated Essential Hypertension (Ischemic Stroke) and Coronary Heart Disease

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In patients with complicated essential hypertension (ischemic stroke) and coronary heart disease, inductors of platelet aggregation in various doses induced "paradoxical" changes in platelet aggregation activity reflecting the degree of decompensation under conditions of persistent endothelial dysfunction. Aggregation inductors in low doses were shown to have a greater diagnostic significance. The content of endothelial dysfunction markers in the blood was persistently elevated under these conditions.

Key Words: *platelet aggregation; endothelial dysfunction*

In Russia, approximately 400,000 people are annually diagnosed with stroke. The mortality rate in the acute period of stroke reaches 35%. By the end of the 1st year after stroke, the mortality rate increases by 12-15%. Essential hypertension (EH), atherosclerosis, and coronary heart disease (CHD) are the major risk factors for stroke. Hemostasis disorders play the key role in the pathogenesis of these diseases. They contribute to the development of thrombotic complications and endothelial dysfunction [2,4,5].

The vein occlusion test (*e.g.*, cuff test with short-term ischemia of shoulder tissues) is extensively used in medical practice for evaluation of endothelium state. This test is characterized by thrombin formation and cascade of reactions to restore the hemostatic balance. Blood samples from the cubital vein are examined for evaluation of the endothelial function [4].

In this work, aggregation activity of platelets was studied using high and low doses of aggregation inductors. The cuff test was performed to evaluate the degree of endothelial dysfunction in patients with complicated EH (ischemic stroke) and CHD.

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MATERIALS AND METHODS

Fifty-seven patients were examined in the acute period of ischemic stroke (35 men and 22 women, average age 56.3±0.9 years). The patients received no disaggregant therapy before hospitalization. All patients had concomitant cardiovascular diseases: 47 patients (82.5%) had stage III EH (100% patients) and stable angina pectoris (functional class I-II); 14 patients (24.6%) had postinfarction cardiosclerosis, 5 patients (8.8%) had persistent atrial fibrillation, and 3 patients (5.3%) had paroxysmal fibrillation. The study of the hemostatic system was performed 24 h after disease onset and on day 14 of aspirin therapy (daily dose 75 mg). Twenty-three patients (40.3%) were examined 3 months after stroke. The control group included 22 sex- and age-matched individuals (average age 52.4±1.0 years) without history of cardiac or cerebral diseases.

The diagnosis of ischemic stroke and cardiovascular disorders was made after standard clinical examination and confirmed by the results of computed tomography, ultrasonography of neck vessels, transthoracic echocardiography, and 24-h ECG monitoring.

Vascular and platelet hemostasis was studied. Spontaneous and induced platelet aggregation (PA) was

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assayed on a LA230-2 BIOLA aggregometer using ADP (0.1 and 5 mM) and epinephrine (10 μg/ml) as inductors.

The concentration of von Willebrand factor (vWF) in blood plasma from patients was measured in the acute period of ischemic stroke and 3 months after disease onset. These measurements were performed before and after the cuff test.

The samples were described by median (Me) and interquartile range (25 and 75 percentiles, C_{25} and C_{75}). The significance of differences between independent samples was evaluated by nonparametric Mann–Whitney test. The statistical analysis was performed by means of Statistica 7.0 software (StatSoft Inc., 2004).

RESULTS

A statistically significant increase in spontaneous PA was observed only in patients with complicated EH and CHT by the 3rd month after ischemic stroke. PA induced by 5 mM ADP and epinephrine was shown to decrease significantly on day 14 of standard antithrombotic therapy with acetylsalicylic acid in a daily dose of 75 mg (p=0.03 and p=0.02, respectively).

We performed a detailed study of PA induced by ADP in low (0.1 mM) and high doses (5 mM). The patients were divided into the following two groups: group 1, normal and high PA induced by 0.1 mM ADP; and group 2, low and high PA induced by 5 mM ADP.

TABLE 1. PA Induced by 0.1 mM ADP (Mean Radius of Aggregates) in Patients with Complicated EH (Ischemic Stroke) and CHD (Me; C25-C75)

Parameter	Normal aggregation (n=36)	High aggregation (n=21)
Before therapy	1.36; 1.2-1.6	2.51; 2.1-3.2
After therapy	1.49; 1.4-1.9*	2.13; 1.7-2.7

Note. *p=0.007 compared to the pretreatment parameter.

TABLE 2. PA Induced by 5 mM ADP (Light Transmission, %) in Patients with Complicated EH (Ischemic Stroke) and CHD (Me; C_{25}-C_{75})

Parameter	Low aggregation (n=32)	Normal and high aggregation (n=25)
Before therapy	21.6; 6.0-27.0	44.2; 40-61
After therapy	17.2; 12.5-29.0	32.6; 23.5-42.0*

Note. *p=0.003 compared to the pretreatment parameter.

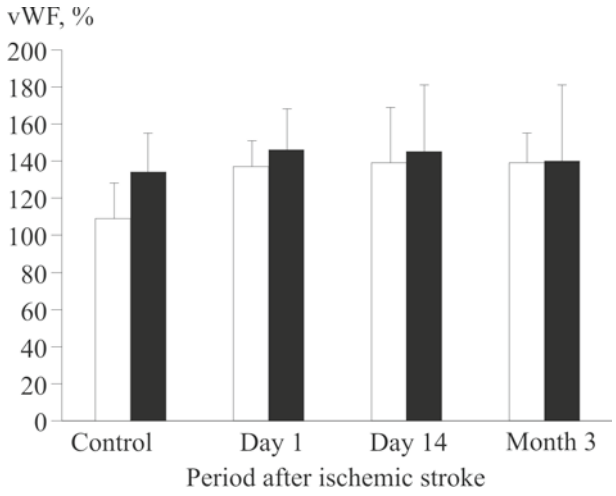

Fig. 1. Concentration of vWF in patients with complicated EH (ischemic stroke) and CHD (Me; C_{25}-C_{75}) before (light bars) and after the cuff test (dark bars).

In 21 of 57 patients with complicated EH (ischemic stroke) and CHD (36.8%), PA induced by 0.1 mM ADP surpassed the normal (Table 1). The opposite results were obtained in the study of PA induced by 5 mM ADP. PA was elevated in only 5 patients (23.8%). PA was below the lower limit of normal in 9 patients (42.8%). Our results are consistent with published data [1,12]. It can be suggested that patients with complicated EH and CHD are characterized by increased formation of small platelet aggregates. These changes serve as a criterion for the prethrombotic state.

Antithrombotic therapy in patients with normal or increased formation of large platelet aggregates was accompanied by a decrease in PA induced by 5 mM ADP (p=0.003). These changes were observed on day 14 after ischemic stroke (Table 2). However, the same therapy in patients with normal aggregation response was followed by a statistically significant increase in PA induced by ADP in low dose (p=0.007).

PA in 23 patients with EH and CHD was also studied 3 months after ischemic stroke. Disaggregant therapy (aspirin, daily dose 75 mg) was followed by an increase in the number of patients with high PA in response to 0.1 mM ADP (up to 47.8%).

On day 1 after ischemic stroke, the content of vWF in patients with complicated EH and CHD surpassed the control by 31.7% (Fig. 1). The therapy had no effect on vWF concentration. vWF concentration on the 3rd month after ischemic stroke remained above the control level (by 21.3%).

The cuff test revealed a statistically significant increase in the concentration of vWF in patients with complicated EH and CHD (Fig. 1). The concentration of vWF in healthy donors was elevated by 30% in

response to venous occlusion (p=0.0006). The concentration of vWF in patients with EH and CHF increased by 6.5 (p=0.0001) and 4.3% (p=0.00001) over the first 24 h and on day 14 after ischemic stroke, respectively. The cuff test showed that vWF concentration in patients with EH and CHD increases less significantly 3 months after stroke (by 0.7%, p=0.003).

Published data show that EH and CHD are accompanied by an increase in the concentration of vWF in blood plasma [6,7]. The interaction between platelets and vascular wall is a key event in the pathogenesis of disturbances in regional blood flow (*i.e.*, strokes) [8,11].

Ischemic stroke is accompanied by an increase in the content of endothelial dysfunction markers in the blood [9,10,13]. Reactivity of the endothelium decreases significantly under these conditions. These changes modulate platelet component of hemostasis and, probably, play a role in the development of "paradoxical" PA. It is manifested in variations of the platelet response to inducing agents in low and high doses [1,3].

Our results suggest that evaluation of endothelial decompensation and selection of disaggregant therapy in patients with complicated EH (ischemic stroke) and CHD should be performed by using the aggregation-inducing agents in specified doses.

RESULTS

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