ON THE SIGNIFICANCE OF THE FIBRINOLYTIC SYSTEM OF THE BLOOD

I. A. Oivin and V. P. Baluda

From the Department of Pathological Physiology (Head, Prof. I. A. Oivin) of the Kuban Medical Institute (Krasnodar)

(Presented by Active Member of the AMN SSSR A. V. Lebedinskii)
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At the beginning of our century, it was postulated that there was a dynamic equilibrium in the organism between the deposition of fibrin and its removal from the vascular bed [12]. In the last few years it has been established that fibrinolytic activity is an inherent property of normal blood [18]. Hypotheses have been advanced that fibrin is constantly formed in the organism, lining the internal surface of the vessels and facilitating blood flow. The formation of fibrin occurs simultaneously with fibrinolysis [5, 7]. Along with this, there are indications that activation of the fibrinolytic system of the blood leads, not only to fibrinolysis, but to fibrinogenolysis as well. It is reasoned that the afibrinogenemia developing in healthy animals subsequent to the intravenous injection of thrombin or thromboplastin is caused by fibrinogenolysis, developing as a result of activation of the fibrinolytic system [4]. The proponents of this theory point to the presence of an inverse relationship between the fibrinolytic activity of the blood and its concentration of fibrinogen [10]. However, it is difficult to accept the premise that, under the conditions of the organism, the activation of the fibrinolytic system leads to fibrinogenolysis, since an increase in the activity of this system is observed under any conditions of stress, while the concentration of fibrinogen in the blood is characteristically relatively constant. We attempted to elucidate these debatable questions.

EXPERIMENTAL METHOD

We investigated the bloods of both healthy and ill human subjects, as well as dogs. Venous blood, drawn in silicon coated syringes (dichlorodimethylsilane) was quickly transferred to three centrifuge tubes. In the first tube, placed in a water bath at 37°, we added 1 ml of blood for determination of the coagulation time [11]; in the second tube, containing 0.5 ml of a 1.34% solution of sodium oxalate, we added 4.5 ml of blood; in the third tube, containing 4 units of heparin, we added 2 ml of blood. In the second and third tubes, the blood was mixed with the anticoagulants and quickly centrifuged for 5 minutes at 1000 revolutions per minute. The plasma was drawn off, and the tubes containing the plasma were placed in an ice bath. In the oxalated plasma, we determined the concentration of fibrinogen [2] and the fibrinolytic activity by the degree to which fibrin was lysed [6] and by the time of fibrin lysis of the euglobulin fraction (euglobulin time) [10]. We determined the fibrinogenolytic activity in the heparinized plasma. For this purpose, the plasma was incubated for 3 hours in a water bath at 37°, and then thrombin was added to it. On the basis of the difference in fibrin content in the clots obtained from the plasma before and after its incubation, we were able to appraise the fibrinogenolytic activity of the blood.

EXPERIMENTAL RESULTS

In the healthy subjects (30 humans) we succeeded in demonstrating fibrinolytic activity in the blood; it was equal to an average of 17, $\sigma \pm 4\%$. In the healthy dogs [21] the fibrinolytic activity of the blood averaged 18, $\sigma \pm 4\%$. We were unable to demonstrate fibrinogenolytic activity in the blood of the dogs or human subjects.

In order to increase the fibrinolytic activity of the blood, the dogs were injected intravenously with nicotinic acid, using a dosage of 1 mg per kg of body weight. The experiments were carried out on 21 dogs. As can be seen from Table 1, blood coagulation was accelerated in the dogs, and fibrinolysis markedly intensified [standard deviation (D) was calculated with reference to the original data].

Despite this, no fibrinogenolytic activity appeared in the plasma, and the concentration of fibrinogen did not change. In the following experiments, thromboplastin (a product of the Leningrad Institute of Blood Transfusion, series 5, activity of 20 seconds) was continuously injected into the femoral vein (8 dogs) for 20 minutes, using a dose of 10 mg per kg of body weight.

Table 2 shows that within a minute after initiation of the infusion of thromboplastin solution blood coagulation was accelerated, the concentration of fibrinogen was reduced, and fibrinolytic activity increased. In this case,

TABLE 1. The Effect of Nicotinic Acid on the Coagulation and Fibrinolytic and Fibrinogenolytic Activity of the Blood of Dogs

Indices	Statistical indices	Before the injection	Following the injection by			
			5 min	15 min	30 min	60 min
Coagulation time (in seconds)	M	336	266	216	234	300=0.2
	D		< 0.01	< 0.001	< 0.001	
Euglobulin time (in seconds)	M	322	295	170	179	312=0.2
	D		< 0.05	< 0.001	< 0.001	
Degree of fibrin lysis (in %)	M	18	30	44	41	25=0.1
	D		< 0.001	< 0.001	< 0.001	
Fibrinogenolysis (in %)	M	0	0	0	0	0
	D					
Fibrinogen (in mg%)	M	349	343=0.5	341=0.5	335=0.5	317=0.2
	D					

both before the experiment and during it we did not demonstrate any fibrinogenolytic activity in the blood. After 15-30 minutes, coagulation of the blood was markedly slowed, the concentration of fibrinogen was reduced, and fibrinolysis sharply intensified; fibrinogenolytic activity was noted in the blood. After 60 minutes, fibrinogenolytic activity was no longer demonstrable in the blood, while fibrinolysis was still markedly intensified, coagulation slowed, and the concentration of fibrinogen decreased. All the dogs survived.

TABLE 2. The Effect of Slow Injection of Thromboplastin on the Coagulation, and Fibrinolytic and Fibrinogenolytic Activity of the Blood of Dogs

Indices	Statistical indices	Before the injection	Following the injection by			
			1 min	15 min	30 min	60 min
Coagulation time (in seconds)	M	320	210	520	760	480
	D		< 0.001	< 0.01	< 0.001	< 0.001
Degree of fibrin lysis (in %)	M	20	27	57	52	33
	D		< 0.01	< 0.001	< 0.001	< 0.01
Fibrinogenolysis (in %)	M	0	0	24	18	0
	D			< 0.001	< 0.001	
Fibrinogen (in mg %)	M	290	215	156	131	153
	D		< 0.001	< 0.001	< 0.001	< 0.001

In experiments on 8 dogs, we observed that acute blood loss (40%) causes an acceleration in blood coagulation, which corresponds to the numerous data in the literature and, in particular, to the investigations of V. P. Baluda and N. A. Gorbunova [1]. In this case, the fibrinolytic activity rose sharply (by two times), and the concentration of fibrinogen decreased ($D < 0.001$).

In investigations on 30 sick human subjects, one of us (V. P. Baluda, together with V. V. Chernaya and A. I. Slavovii) showed that operative procedures on the organs of the peritoneal cavity are accompanied by an acceleration of blood coagulation by an average of $1\frac{1}{2}$ times, by an intensification of fibrinolytic activity by 2 times, and by an increase in the concentration of fibrinogen by $1\frac{1}{2}$ times ($D < 0.001$). In 25 patients with thromboembolic complications, blood coagulation was elevated by an average of 25%, the concentration of fibrinogen was increased by 20%, and fibrinolytic activity was markedly reduced (up to 4%); there was no fibrinogenolytic activity in the blood.

In patients with atherocardiosclerosis (V. P. Baluda and A. I. Paritskaya) the blood coagulation was accelerated by an average of 20%, while the fibrinolytic activity of the blood was reduced. In patients with myocardial infarcts, we observed an acceleration in blood coagulation, marked weakening of its fibrinolytic activity, and a considerable increase in the concentration of fibrinogen.

Coworkers of our laboratory [3] showed that with Botkin's disease the concentration of fibrinogen and the fibrinolytic activity are elevated, while with primary cirrhoses of the liver the fibrinolytic activity of the blood is intensified and the concentration of fibrinogen reduced; with cardiac cirrhoses, the concentration of fibrinogen is increased, while the fibrinolytic activity of the blood is unchanged.

In the organism of healthy human and animal subjects, there exists a dynamic equilibrium between the coagulatory system of the blood (procoagulants-anticoagulants and inhibitors of the anticoagulants) and the fibrinolytic system, which enables the maintenance of the blood in a fluid state and the process of hemostasis in case of injury to the vessels. Under conditions of stress (pain, blood loss, operative procedures, the injection of nicotinic acid, adrenalin, etc.), as is also known from the literature, blood coagulation is accelerated. This makes possible the cessation of blood flow out of injured vessels. Under such conditions, the fibrinolytic activity of the blood always increases, which inhibits propagation of the thrombus, from the site of its initial formation, throughout the vascular system, and permits the lysis of clots formed at sites distant from the place of injury of the vascular wall. Increase in the fibrinolytic activity of the blood appears to be a normal defense reaction of the organism associated with acceleration of blood coagulation.

As the presented results of the experiments showed, slow intravenous injection of thromboplastin leads to a deceleration in blood coagulation, and to a intensification in the blood's fibrinolytic activity. Thromboplastin causes the deposition of fibrin, which leads to activation of the fibrinolytic system of the blood. The reduced coagulation rate of the blood basically appears to be a result of a marked hypofibrinogenemia. With atherosclerosis and thromboembolic disease, the increased coagulability of the blood is accompanied by a decrease in its fibrinolytic activity, which is one of the principal reasons for the development of thromboses in these diseases, particularly in the coronary vessels. In primary cirrhoses of the liver, blood coagulation is slowed and the fibrinolytic activity is increased, explaining the relative rarity with which thromboses of the coronary vessels develop in such patients [9].

As can be seen from the data presented, a direct relationship does not exist between the fibrinolytic activity of the blood and its concentration of fibrinogen. Thus, with injections of nicotinic acid, the concentration of fibrinogen does not change, while fibrinolysis is intensified markedly. With cardiac cirrhoses of the liver, fibrinolysis remains unchanged, and the concentration of fibrinogen in the blood increases. With operative procedures and other stress situations, the concentration of fibrinogen and the fibrinolytic activity of the blood increase simultaneously. In studying the daily fluctuations in the concentration of fibrinogen and fibrinolytic activity, using both healthy and ill human subjects, we found no correlation between these indices [9].

Thus, an elevation in the fibrinolytic activity of the blood is not accompanied by a mandatory decrease in the fibrinogen concentration, and vice versa. Explanation lies in the fact that intensification of the fibrinolytic activity of the blood can develop without an increase in its fibrinogenolytic capacity. This is attested to by the investigative results presented above (the effects of nicotinic acid, blood loss, etc.). Apparently, in pure systems fibrinolysin can bring about the lysis of both fibrin and fibrinogen. However, under conditions found in the organisms the fibrinogenolytic activity of fibrinolysin is impeded by inhibitors which do not affect its fibrinolytic properties [13]. This offers an explanation for the physiologically expeditious selectivity in the functioning of the fibrinolytic system, directed toward the dissolution of fibrin, i.e., of thrombi, but, as a rule, not affecting the fibrinogen circulating in the blood. Hypofibrinogenemia that is not due to disruptions in the synthesis of fibrinogen, basically develops as a result of the primary formation of fibrin (fibrination) with its subsequent lysis, the latter arising as a result of activation of the fibrinolytic system.

SUMMARY

Subject to a study in experiments on dogs (involving intravenous administration of nicotinic acid and thromboplastin, blood loss) and in observations of patients (operative interventions, atherosclerosis, thromboembolic disease, etc.) were interrelationships between the blood coagulation, fibrinogen concentration, fibrinolytic and fibrinogenolytic activity. The blood of healthy individuals and dogs showed fibrinolytic activity to be present regularly. Fibrinogenolytic activity, on the other hand, was absent. In stress conditions (surgical intervention, blood loss, nicotinic acid administration) the blood coagulation was accelerated with blood fibrinolytic activity increasing at the same time (no fibrinogenolysis was present). Intensified fibrinolytic activity of the blood is a normal protective body reaction, occurring with acceleration of blood coagulation. This regularity is disturbed in pathological conditions. Association of accelerated blood coagulation with diminished fibrinolysis (atherosclerosis, thromboembolic disease) creates favorable conditions for thrombosis. There is no direct relationship between blood fibrinogen concentration and its fibrinolytic activity. This is explained by the fact that, as a rule, activation of fibrinolytic system in the body leads to the intensification of its fibrinolytic properties, but not of fibrinogenolytic ones.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.
