THE PART PLAYED BY VASCULAR SPASM IN DISTURBING THE ANTICOAGULATING SYSTEM OF THE BLOOD

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Thrombosis and embolisms constitute one of the most important unsolved clinical problems. In spite of the efforts of clinicians, biochemists, pathologists, and physiologists, the cause of the formation of thrombi remains unknown. Suggestions have been made as to the possible significance of arrest of the blood flow in the greater or lesser circulation [5, 9], or of an increase in protein thrombogenic factors [7, 11, 13, 14], or of changes in the vascular wall [1, 2, 8]. However, all these ideas originate from clinical observations or from the findings of morbid anatomy and are not based on experiment.

The proposal put forward by B. A. Kudryashov and his coworkers that in man and animals there is a special physiological anticoagulating system appears to hold great promise. It was found that intravenous injection of even moderate doses of thrombin does not produce the normal reaction of forming thrombi, but as B. A. Kudryashov and P. D. Ulitinaya [4] have shown, on the contrary, the blood loses its ability to coagulate. The explanation that has been put forward is that the presence of excessive amounts of thrombin stimulates a reflex mechanism which has the effect of liberating into the blood stream humoral factors which eliminate the coagulating mechanism from the blood. It is not known in what way this system is brought into play nor on what substances its anticoagulating action depends. It is observed only that there is a fall in thromboplastic activity and fibrinogen content, and an increase in the amount of heparin-like substances. Kwann and his coworkers produced experimental thrombi in the limb vessels and observed that normally they were lysed in 9 — 32 hr; they ascribed this change to the secretion of cholinergic substances.

We have studied the anticoagulating system in several diseases to find what is the anticoagulating effect in vascular spasm. Clinically, it is thought that increased blood coagulation is an important factor in thrombus formation, and many consider it to be the principal cause of thromboembolic complication. If it is assumed that there is an anticoagulating system, then increasing coagulating power will bring about an opposite response from the organism and can therefore not by itself lead to the formation of thrombi. The object of the present investigation is to determine the nature of the accessory factors which, although not playing the main part, may, at any rate, be of critical importance in the formation of intravascular thrombi.

METHOD

The experiments were carried out on 29 Chinchilla rabbits weighing from 1.7 to 2.3 kg. Standard thrombin produced by the N. F. Gamalya Institute of Microbiology and Epidemiology was used. Before the experiment, 1.8 cc of dry thrombin from an ampoule was diluted in 10 g of physiological saline. The activity of the thrombin solution was measured by the time taken for 0.1 ml of the solution to coagulate 0.1 ml of oxalated blood at 37 deg. The activity was found to vary very little, and the coagulating time ranged from 10 to 12 sec.

First of all, the maximum dose of thrombin whose intravenous injection caused no thrombi to develop was determined; when injected, the blood actually lost its clotting power. The determination was made by injecting different amounts of thrombin solution into an ear vein. As can be seen from the table below, 4 ml of thrombin solution was the maximum dose which did not produce thrombi.

Number of Animals	Amount of thrombin solution (in g)	Effect of Injection
3	8	All animals died
4	6	Three rabbits died, one survived
4	4	All animals survived

The blood of the surviving animals failed to coagulate in 60 — 80 min. This confirms the existence in rabbits of the physiological anticoagulating system discovered by B. A. Kudryashov and P. D. Ulitina in rats.

We have tried to find whether this protective reaction is maintained in vascular spasm, which appears to be the principal factor in many pathological con-

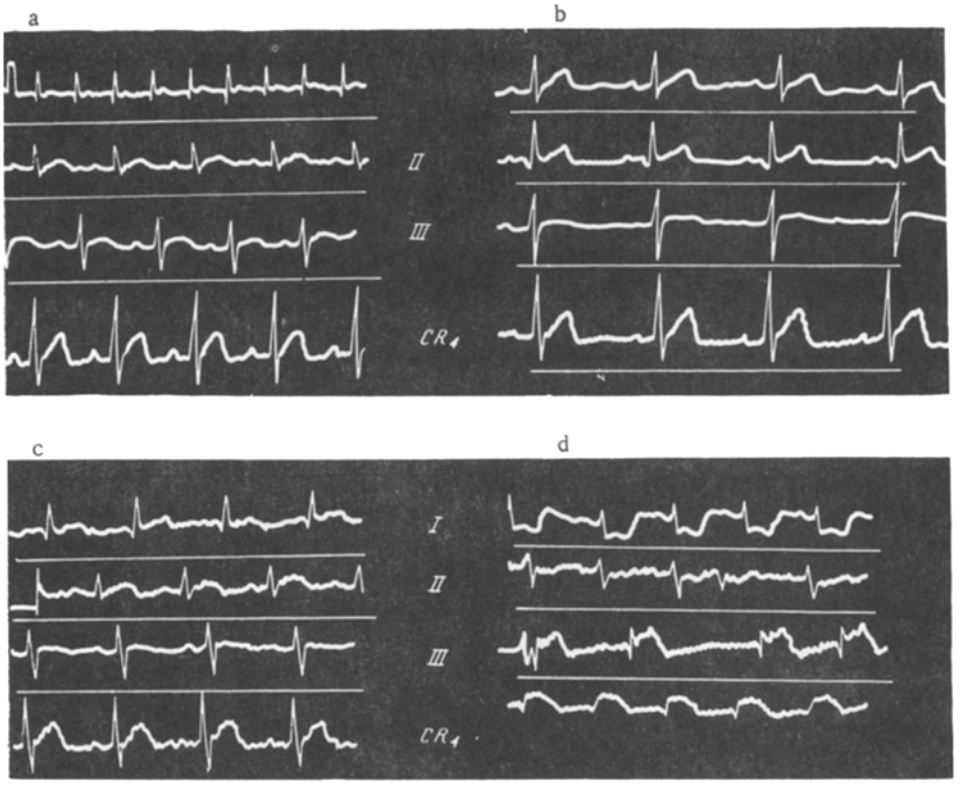

Fig. 1. Electrocardiograms after intravenous injection of (c) thrombin, (b) pituitrin, (d) simultaneous injection of thrombin and pituitrin; (a — normal). I, II, III — the three leads.

ditions. Pituitrin, whose vasoconstrictor effect has been known since the time of Krogh's classical work, was used to raise the blood pressure. Because pituitrin causes a pressor response in the coronary arteries [2, 15, 16], we decided to record the electrocardiogram so as to be able to detect the development of experimentally induced coronary thrombis and the resulting ischemia and myocardial infarction. Control observations on the ten rabbits showed that 0.5 cc of pituitrin injected intravenously caused no ischemia or cardiac infarction and that death did not ensue, so that there was no possibility of thrombi being formed in the vessels (Fig. 1). Here it can be seen that intravenous injection of 4 ml of a thrombin solution had little effect on the e.c.g.

Thus, neither the increased amount of thrombin nor pituitrin when given separately caused any thrombus formation. Immediately after the control experiments, the following procedure was carried out. A simultaneous injection of 4 ml of a thrombin solution and 0.4 cc of pituitrin was given into an ear vein. Four animals died immediately; post mortem examination revealed extensive thrombosis in different parts of the vascular system. In the remaining 17 animals, changes in the electrocardiogram typical of acute coronary damage and myocardial infarction were revealed (see Fig. 1). The e.c.g. changes indicated extensive myocardial damage associated with acute coronary thrombosis. Of the 21 animals used, seven died within 1 hr, six in the first 2 hr, three on the first day, and one on the second day. Coronary thromboses were found in all the animals post mortem and were confirmed microscopically. Figure 2 shows the thrombi formed directly at the origin of the aorta.

Histological investigation revealed typical acute coronary insufficiency and the onset of myocardial infarction. In seven cases only thrombosis of the coronary vessels was found, in eight cases there was also a thrombosis of the pulmonary artery, and in two animals thromboses were also found in the vessels of the abdominal cavity. It was found that small doses of heparin given after the development of the thrombus reduced subsequent intravascular thrombus formation. On this account, it was possible to enable four of the rabbits with signs of acute myocardial infarct to survive, though only for a short time, and to reduce the extent of the ischemic area. This method enables the damage to the myocardium to be limited.

The results obtained leave no doubt that vascular spasm prevents the development of the protective anticoagulating reaction, and allows intravascular thrombus formation to take place when the blood-thrombin content is increased.

The formation of thrombi in the coronary vessels shows that when the vessels are in spasm and clotting

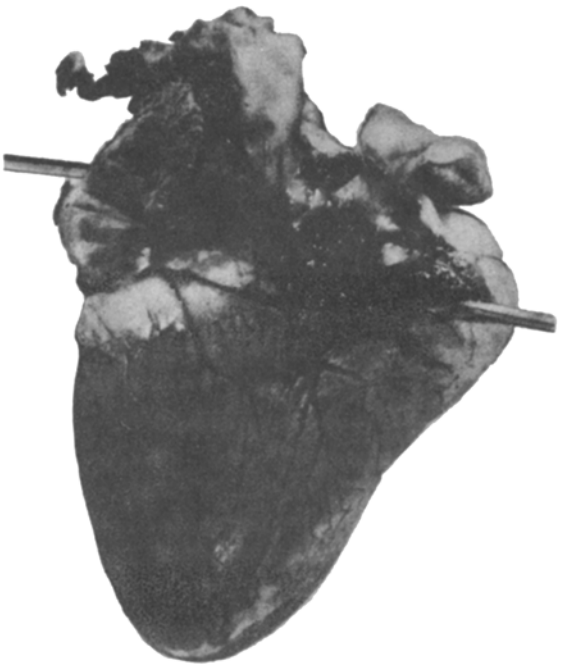

Fig. 2. Thrombosis of the coronary artery.

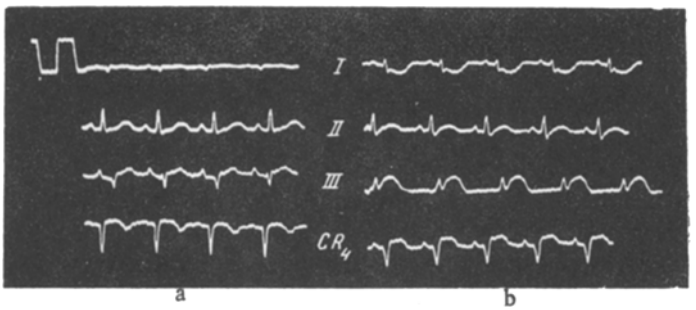

Fig. 3. E.c.g. of rabbit with 30 day myocardial infarct (a) before and (b) after intravenous thrombin injection.

power is raised, thrombi may develop independently of any changes in the walls. This conclusion is confirmed by other investigators [10] who found no changes in the vessel walls in a number of cases of myocardial infarction.

It has been shown [6] that in myocardial infarction, the coronary vessels are in a spastic condition which alters their response. In view of the high incidence of thromboembolic complications and repeated coronary thromboses, we investigated the anticoagulating reaction in myocardial infarction. We were especially interested in the period after the 30th day, when the e.c.g. returned to normal. The observations were made on nine rabbits in which myocardial infarction was induced by ligaturing the coronary artery.

As we had shown previously, injecting healthy rabbits with 4 ml thrombin solution causes no thrombus formation. In the experimental animals, in four cases the same thrombin injection produced electrocardiographic changes typical of repeated myocardial infarction. In five cases, 2 g of thrombin solution were sufficient to cause intravascular thrombus formation and coronary thrombosis (Fig. 3).

All nine rabbits died in the first 24 hr. Four received 2 g of thrombin solution, and in them the thrombus was found only in the coronary vessel; in the others they were found elsewhere in the vascular system as well; in one case, three hours after the development of myocardial infarction and marked physical signs, there was a split in the heart at the boundary of the scar tissue developed after the first infarction and the region affected by the coronary disturbance.

The results show that intravascular thrombus formation occurs more regularly after a myocardial infarction has developed. In such cases a second infarction and thromboembolic complications may be induced by increasing the clotting power of the blood. This fact confirms the clinical observations on the necessity for prolonged anticoagulation therapy extending into the post-infarction period.

Our conclusions are as follows: The development of vascular spasm interferes with the anticoagulating system and brings about intravascular thrombus formation; if spasm of the coronary arteries occurs when the blood-clotting power of the blood has been increased, myocardial infarction may develop without there being any changes in the walls of the coronary arteries; after the coronary infarction has developed, the altered condition of the anticoagulating system has the effect that increasing the coagulating power of the blood may now bring about thromboembolic complications and repeated coronary thrombosis.

SUMMARY

The effect of the vascular spasm on the function of the anticoagulating system of the blood was studied in experiments on rabbits. Intravenous injection of thrombin solution (4 g) into healthy animals did not provoke thrombosis; on the contrary, the blood lost its ability to coagulate. However the same dose of thrombin together with 0.5 ml of pituitrin resulted in the rapid formation of intravascular thrombi causing coronary thrombosis and myocardial infarction. A study was made of the extent of the possible action of the anticoagulation system in myocardial infarction which was induced by ligation of the coronary arteries. The administration of 4 g of thrombin induced a repeated infarction, and thrombosis in various parts of the vascular system. It was concluded that: a) The anticoagulation system of the blood becomes disturbed during vascular spasm, so that there is an increased tendency to intravascular thrombus formation; b) myocardial infarction may occur without changes in the walls of the coronary vessels only when there is spasm which causes an increase in the tendency of the blood to coagulate. Myocardial infarction itself will alter the anticoagulatory system of the blood, so that intravascular thrombus formation may be induced by small doses of thrombin administered alone.

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