

EXPERIMENTAL DATA CONCERNING THE EFFECT OF FIBRINOLYSIN ON THE CORONARY BLOOD FLOW

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During recent years a new thrombolytic preparation — fibrinolysin — has been used in the treatment of thrombosis and embolism. Clinical observations [1, 3-5] have indicated the beneficial effect of fibrinolysin on the coronary circulation in patients with myocardial infarction. In this connection it is interesting and important to make an experimental study of the influence of fibrinolysin on the coronary blood flow, in particular because no report of any such investigation could be found in the Soviet or non-Soviet literature.

To avoid a reflex increase in the coagulation of the blood, fibrinolysin is used only in conjunction with heparin. It was therefore important to examine the effect of fibrinolysin and heparin on the coronary circulation both separately and together. It was also regarded as desirable to study the combined action of trypsin and heparin on the coronary blood flow, for a certain quantity of trypsin is used to activate fibrinolysin in the course of its preparation.

EXPERIMENTAL METHOD

To study the volume velocity of the coronary blood flow the method of Morawitz and Zahn was used in N. V. Kaverina's modification [2]. Dogs were anesthetized with intravenous hexobarbital and, under controlled respiration, the thorax was opened through a right-sided incision and the pericardium was divided. A polyvinyl chloride catheter was introduced into the coronary sinus through the right auricle and the cavity of the right atrium. The catheter was connected by a system of tubes with the jugular vein and a graduated manometer. In the initial state blood from the coronary sinus entered the jugular vein and during this time the manometer recorded the pressure in the coronary sinus. To measure the volume velocity of the coronary blood flow the tube conveying blood to the jugular vein was temporarily compressed and all the blood was directed to the manometer. Heparinization, as described by N. V. Kaverina, was not used, and the whole system of tubes and the manometer were silicone-treated.

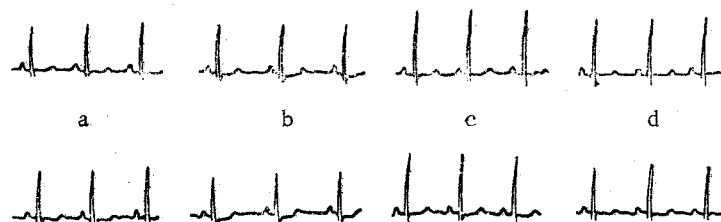
Besides the investigation of the volume velocity of the blood flow, the arterial pressure and ECG were recorded.

Altogether 18 experiments were carried out on 10 dogs.

Observations were made after the coronary blood flow had been kept at a constant level for 10-15 min. The effect of fibrinolysin and heparin on the coronary circulation was studied in dogs in the initial state and after the production of pituitrin spasm of the coronary vessels. Pituitrin (1.5-2.0 units/kg) was chosen as vasoconstrictor because, although causing obvious spasm of the coronary vessels lasting for 25-30 min, it does not affect the coagulation of the blood. Fibrinolysin, issued by the Gor'kii Institute of Epidemiology and Microbiology, was injected intravenously in a dose of 5000-8000 units in 10 ml of physiological saline. The dose of heparin was 5000 units.

RESULTS

The preparations investigated caused a considerable increase in the volume velocity of the coronary blood flow, and the difference between the experimental and control values was significant.



Improvement in the coronary circulation under the influence of fibrinolysin after spasm of the coronary vessels produced by pituitrin: a) ECG before injection of pituitrin; b) 4 min after injection of pituitrin; c) ECG 2 min after; d) 4 min after injection of fibrinolysin.

Injection of fibrinolysin was accompanied by an increase of 15 ml/min (33%) in the volume velocity of the coronary blood flow. A more marked increase in the blood flow — by 22 ml/min (50%) — took place in response to the combined administration of fibrinolysin and heparin. Trypsin with heparin increased the coronary blood flow by 9 ml (24%), and heparin alone by 4 ml/min (10%). The injection of physiological saline caused variations in the blood flow within limits of 1 ml/min (2.7%).

After preliminary pituitrin spasm, which led to a reduction of 13.5 ± 4 ml/min ($33 \pm 8\%$) in the volume velocity of the coronary blood flow, the preparations tested not only restored the level of the blood flow depressed by pituitrin, but increased it to approximately the same indices as in the experiments without spasm produced by pituitrin. In these experiments the largest increase in the coronary blood flow (by $140 \pm 20\%$) was also observed after injection of fibrinolysin with heparin. Fibrinolysin alone gave a somewhat less marked coronary dilator effect (by $92 \pm 14\%$). The increase in the volume velocity of the coronary blood flow following the administration of trypsin with heparin was smaller still ($61 \pm 12\%$), but more marked than after injection of heparin alone (by $38 \pm 7\%$). Physiological saline had no appreciable effect on the blood flow at the height of pituitrin spasm.

The increase in the blood flow, both with or without the preceding injection of pituitrin, began after the 1st minute, reached its maximum at the 4th-7th minute, and after 20-30 min the level of the blood flow was back to its original value.

Most spasmolytic preparations are known to dilate not only the coronary, but also the peripheral vessels. In this connection it was important to investigate the dynamics of the changes in the arterial pressure.

A clear hypotensive action of these preparations was discovered. It was manifested both when the initial pressure had been established and after pituitary spasm. Injection of pituitrin raised the arterial pressure by 43 ± 12 mm; it then returned to its original level after 15-20 min. The fall in arterial pressure was greatest after injection of fibrinolysin with heparin (by $66 \pm 8\%$). Fibrinolysin in the pure form, and trypsin with heparin also lowered the arterial pressure, but to a lesser degree (by $42 \pm 2\%$ and $36 \pm 6\%$ respectively). In all the experiments the arterial pressure fell from the 1st minute, although it quickly (after 10-18 min) returned to its original level. Under the influence of heparin little change took place in the arterial pressure. In control experiments with physiological saline no essential changes were observed in the arterial pressure.

In experiments in which the ECG was recorded in three standard leads on a "Galileo" electrocardiograph the administration of pituitrin caused changes in the curves, most often in the form of a rise or fall of the ST-interval, less often elevation of the T-wave. The ECG was studied periodically after administration of fibrinolysin alone, fibrinolysin with heparin, trypsin with heparin, and heparin alone. In every case positive changes were found in the ECG: the ST-interval moved closer to the isoelectric line, the shape of the T-wave became more pronounced. The change in the ECG were especially marked after administration of fibrinolysin and of fibrinolysin with heparin: in some experiments the normal ECG was fully restored after considerable coronary disturbances caused by pituitrin (see figure).

As an additional measure, in two experiments pituitrin was injected against the background of the action of fibrinolysin. Judging from the level of the arterial pressure and the magnitude of the volume velocity of the coronary blood flow, the pituitrin spasm was less marked and developed later than without the parenteral injection of fibrinolysin, and the typical pituitrin changes did not appear on the ECG.

Bearing in mind that the coronary blood flow increases with a decrease in the blood oxygen concentration, the level of the oxygen saturation of the blood in the coronary sinus was investigated (using an oxyhemometer manufactured at the "Krasnogvardeets" factory). These investigations showed that during the period of administration of fibrinolysin the oxygen concentration was unchanged. These results demonstrate that the increase in the volume velocity of the coronary blood flow under the influence of fibrinolysin is independent of changes in the oxygen concentration in the blood.

SUMMARY

It was found in experiments on dogs that fibrinolysin, fibrinolysin with heparin, trypsin with heparin, and heparin alone caused a considerable increase in the volume speed of the coronary blood flow. It was revealed that the preparations under study not only restored the level of the blood flow decreased due to pituitrin but also raised it approximately to the same indices as in the experiments without a pituitrin-induced spasm. The largest increase in the blood flow was noted upon a combined administration of fibrinolysin and heparin. At the same time, one could also note a distinct hypotensive effect of the investigated preparations. Fibrinolysin eliminated the spasm of the coronary vessels caused by pituitrin and improved the ECG. The vasodilating action of fibrinolysin discovered in the experiment in addition to its principal thrombolytic activity makes it especially valuable for patients with thrombosis of the peripheral vessels, coronary thrombosis, and for those threatened by these diseases.

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