CHARACTERISTICS OF THE ACTION OF STROPHANTHIN ON THE COLLATERAL CORONARY CIRCULATION

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Because strophanthin is widely used in the treatment of acute cardiac failure, often developing as a result of a disturbance of the nutrition of the myocardium, the study of its action on the collateral circulation in the heart is of interest.

EXPERIMENTAL METHOD

Experiments were carried out on dogs weighing from 10 to 21 kg, anesthetized with thecodine (dihydrohydroxycodeinone) and pentobarbital sodium (5 mg/kg thecodine subcutaneously and 35 mg/kg pentobarbital sodium intraperitoneally). The state of the collateral coronary circulation was judged from the dynamics of the retrograde blood flow in the system of the descending branch of the left coronary artery. For this purpose the descending branch of the left coronary artery, preliminarily isolated in its middle third, was ligated and a cannula introduced into its peripheral end. The retrograde blood flow was recorded by means of a photometric droplet counter on the drum of a kymograph. The outflowing blood was reinfused with heparin solution (1000-1500 units/kg) into the right femoral vein. The arterial pressure and the amplitude of the cardiac contractions were recorded simultaneously by means of a mercury and elastic manometer. The ECG was recorded in chest leads V_4–V_5 and an epicardial lead (the electrode was applied to the margin of the zone of ischemia).

Strophanthin was injected in doses of 0.2 cat units (16 experiments) and 0.5 cat units (12 experiments) per kilogram body weight. The first dose was conventionally described as therapeutic, the second as the minimal toxic dose. To study the action of strophanthin in toxic doses, in some experiments strophanthin was injected again in a dose of 0.5 cat unit/kg 30 min after its first injection in a dose of 0.2 cat unit/kg. To determine the relationship between the pressure level in the descending branch of the left coronary artery and the retrograde blood flow, in a series of experiments the pressure in the peripheral segment of the descending branch and the retrograde blood flow were recorded consecutively.

To analyze the mechanism of the changes in the collateral coronary blood flow developing under the influence of strophanthin, eight experiments were performed in which the arterial pressure was stabilized and nine experiments in which the cholinergic innervation of the heart was blocked by atropine.

Altogether 58 experiments were conducted on 48 animals.

EXPERIMENTAL RESULTS

Strophanthin, in a dose of 0.2 cat unit/kg, caused a marked and statistically significant increase in the arterial pressure with a simultaneous increase in the retrograde outflow. By the 3rd min, as is clear from Fig. 1A, the arterial pressure had risen by 12.9±4.7% ($P < 0.02$) and the retrograde blood flow had increased by 13.2±1.9% ($P < 0.01$). With slight fluctuations both indices remained at this level until the 10th min of observation. Next followed a fall of arterial pressure and a decrease in the retrograde blood flow, although not reaching the initial values during the whole period of observation.

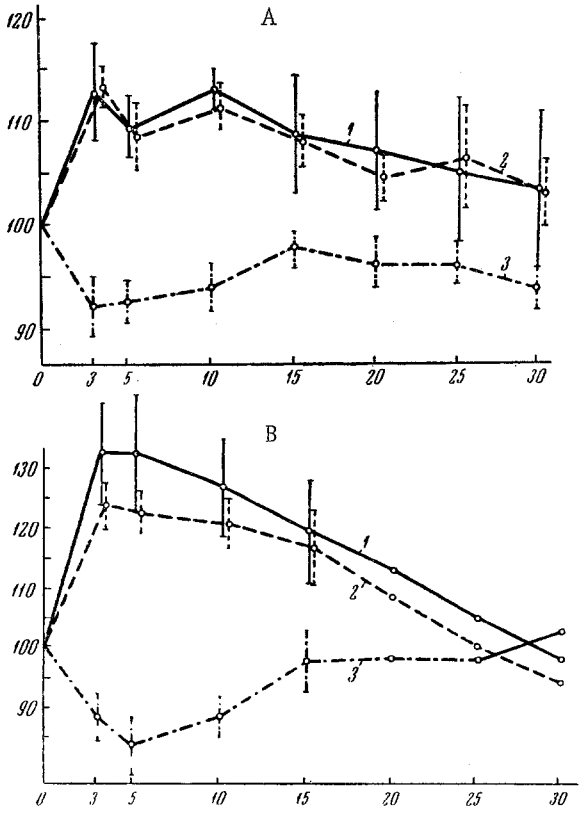

Fig. 1. Dynamics of the retrograde blood flow, the systemic arterial pressure, and the heart rate during the action of strophanthin in a dose of 0.2 cat unit/kg (A) and 0.5 cat unit/kg (B). Here and in Fig. 2, along the axis of ordinates—changes in retrograde outflow (1), arterial pressure (2), and heart rate (3) (in % of initial values); along the axis of abscissas—time in min.

When the relationship between the arterial pressure and the retrograde outflow of blood was expressed by the coefficient K (the ratio between the maximal changes in the retrograde flow, expressed as a percentage of the initial value, and the changes in arterial pressure, also expressed as a percentage of its initial value, in the same time interval), it was noted that the relative changes of the two indices when strophanthin was injected in a dose of 0.2 cat unit/kg were very slight ($K = 1.159$).

The greatest slowing of the heart rate was found at the 3rd min ($-7.9 \pm 3\%$, $P < 0.02$) after injection of the glucoside. Later a tendency was noted for the heart rate to return to normal, although the weak negative chronotropic action of strophanthin persisted until the end of the observation—until the 30th min ($-5.9 \pm 2.7\%$, $P < 0.05$).

The electrocardiographic signs of acute local ischemia of the myocardium after ligation of the descending branch of the left coronary artery took the form of a considerable elevation of the S—T interval and of disturbances in the rhythmic activity of the heart. The changes in the ECG as a result of the action of strophanthin in a dose of 0.2 cat unit/kg consisted of prolongation of the P—Q interval (slowing of conduction), a very slight increase in the voltage of the R wave in some experiments, and depression of the S—T interval.

In the experiments in which the retrograde outflow and the pressure in the descending branch of the left coronary artery were recorded, a direct relationship was found between these values.

For instance, when the rate of the retrograde flow was 0.84 ml/min a pressure of 24 mm Hg was recorded, and when the retrograde flow was 3.04 ml/min the pressure was 34 mm Hg. The rapid (3-5 sec) stabilization of the retrograde outflow when the change was made from measuring the retrograde pressure to measuring the magnitude of the outflow from the peripheral end of the descending branch of the left coronary artery indicates that an adequate pressure gradient was present in the field of distribution of the left descending artery.

As a result of the study of the action of strophanthin in a dose of 0.5 cat unit/kg, a slight but definite predominance of the relative changes in the retrograde outflow over those in the arterial pressure was found. The sharp increase in the retrograde outflow towards the 3rd min after injection of the glucoside ($+ 32.5 \pm 8.5\%$, $P < 0.01$), was replaced by a gradual decrease towards the initial values at the 30th min. The changes in the retrograde outflow repeated the picture of the changes in the systemic arterial pressure (Fig. 1B).

To describe the characteristics of the changes in the arterial pressure and retrograde outflow in this series of experiments, the close values of the coefficient K are demonstrative: 3rd min—1.365, 5th—1.433, 10th—1.300, 15th—1.160, 20th min—1.490, demonstrating a slight but constant predominance of the relative changes in the retrograde outflow by comparison with the intensity of the pressor reaction.

The most intensive negative chronotropic action of strophanthin in a dose of 0.5 cat unit/kg developed at the 5th min ($-16.2 \pm 4.7\%$, $P < 0.01$).

The increase in the heart rate at the 30th min, together with the more marked disturbances of excitability in the form of mainly monomorphic grouped extrasystoles (8 experiments), and also the instability of the arterial pressure were evidence of the toxic action of strophanthin in a dose of 0.5 cat unit/kg.

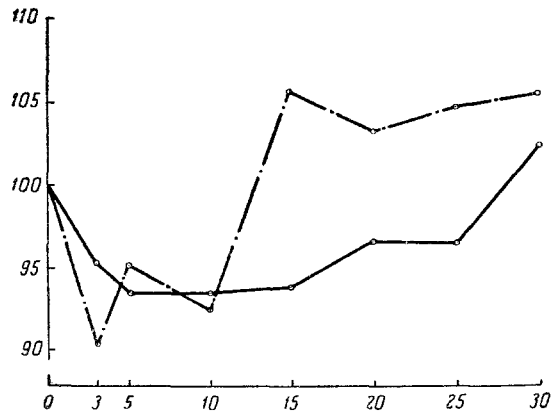

Fig. 2. Changes in retrograde blood flow and heart rate under the action of strophanthin in a dose of 0.5 cat unit/kg with stabilization of the arterial pressure.

The investigation of the effect of strophanthin in a dose of 0.5 cat unit/kg (10 experiments) against the background of a previous injection of the drug in a dose of 0.2 cat unit/kg revealed almost total areactivity of the animals. The toxic action of the preparation in the experiments of this series was manifested in a severe disturbance of the rhythmic activity of the heart, developing at the 5th-10th min of the experiment and continuing until the end of the observations. As a rule, the extrasystoles were grouped and monomorphic in character, and in four cases the heart stopped beating at the 15th-20th min.

A pressor reaction (to + 8.3%) with an increase in the retrograde flow of + 19.9± 6.4% ($P < 0.02$) were found at the 3rd min. The sharp fall in the arterial pressure and the retrograde blood flow after the 3rd min continued until the end of the observation—until the 30th min (arterial pressure 42.6 ±8%, $P < 0.01$).

The above-mentioned changes in the retrograde blood flow were evidently associated to a considerable degree with the increase in the volume velocity of the total coronary blood flow under the influence of strophanthin.

In experiments in which small doses of strophanthin were used, the changes in the retrograde blood flow were close to the changes in the total coronary blood flow [1].

Analysis of the relationship between the changes in the collateral coronary blood flow and the systemic arterial pressure shows that the main factor determining the changes in the collateral blood flow was the level of the arterial pressure. In a special series of experiments in which the action of strophanthin was studied in conditions of stabilization of the systemic arterial pressure, it was discovered that strophanthin, in a dose of 0.5 cat unit/kg, causes a moderate, yet adequately constant decrease in the retrograde blood flow in the first 5 min after administration of the drug—by 4.8% at the 3rd min and by 6.5% at the 5th (Fig. 2). This effect persisted to a lesser degree until the end of the observation—until the 30th min (2.2%). The decrease in the blood flow in the initial phase after injection of the preparation was also observed in experiments in which strophanthin was injected in a dose of 0.2 cat unit/kg. The fact that no parallel was found between the changes in the retrograde blood flow and the heart rate gives no grounds for connecting these changes in the collateral coronary circulation with the changes in the rhythm.

It may be supposed that the decrease in the retrograde blood flow was due to the cholinergic type of action of strophanthin on metabolism in the myocardium and on the tone of the coronary vessels. This suggestion is supported by the results of experiments on the isolated heart [2], in which a decrease in the retrograde outflow of perfusion fluid was found as a result of the action of strophanthin in a dilution of 1:10,000,000.

Exclusion of the cholinergic innervation led to a reduction in the negative chronotropic action on strophanthin. The changes in the retrograde outflow under these circumstances were very small and inconstant.

Hence, the increase in the retrograde blood flow from the peripheral segment of the descending branch of the left coronary artery under the action of strophanthin was due to the increase in the general arterial pressure caused by the drug. When the arterial pressure was stabilized, strophanthin actually gave rise to a slight fall in the collateral retrograde blood flow.

LITERATURE CITED

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