ANALYSIS OF THE ACTION OF STROPHANTHIN-LIKE GLUCOSIDES ON THE COLLATERAL CIRCULATION IN THE MYOCARDIUM

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Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 55, No. 3, pp. 52-55, March 1963
Original article submitted April 28, 1962

As a result of the use of cardiac glucosides in myocardial infarction, the investigation of their action on the collateral circulation in the heart is of great interest. One of the important indices of the level of the collateral circulation is the magnitude of the retrograde blood flow from the peripheral segment of the ligated or thrombosed vessel. The retrograde blood flow from the coronary vessels, the presence of which was first noted by A. Tal'yantseva [2], immediately after ligation amounts to 4.0-4.5% of the total volume of blood flowing through the artery before ligation [7]. These values of the blood flow along the collaterals naturally cannot prevent the development of necrosis of the heart muscle. There is no doubt, however, that the inflow of blood along the collaterals ameliorates the ischemia in the marginal zones of necrosis, thereby reducing the area of the myocardial infarct.

Hence we can understand the role of drugs favoring the development of the collateral circulation in the treatment of myocardial infarction in the acute stage. The inflow of blood along the collaterals, like the coronary blood flow in general, depends on a series of factors of which the most important are the level of the arterial pressure, the contractile activity of the heart, and direct and indirect influences acting on the tone of the coronary vessels.

In the present investigation we studied the direct myotropic action of homphothin, erysimin, and strophanthin on the tone of the coronary vessels.

EXPERIMENTAL METHOD

Experiments were carried out on isolated cats' hearts. The criterion used to determine the state of the collateral circulation was the retrograde flow of perfusion fluid from the peripheral cut end of the ligated descending branch of the left coronary artery. The descending branch was ligated at the level of the lower border of the auricle of the left atrium. The general coronary outflow and the retrograde flow of perfusion fluid were recorded simultaneously during equal intervals of time and then expressed in milliliters per minute.

The action of homphothin on the tone of the coronary vessels was investigated in concentrations of 1:2,500,000 (5 experiments), 1:5,000,000 (13 experiments), 1:10,000,000 (18 experiments), and 1:20,000,000 (17 experiments); the action of erysimin and strophanthin in concentrations of 1:5,000,000 and 1:10,000,000 (72 experiments).

EXPERIMENTAL RESULTS

In no case was perfusion of the vessels of the isolated cat's heart with solutions of homphothin* in all the concentrations tested, followed by a decrease in the outflow of perfusion fluid outside the limits of spontaneous variation during prolonged perfusion. When homphothin was perfused in a dilution of 1:2,500,000 the changes in the total and retrograde outflow were not uniform, were slight in degree, and did not extend beyond the limits of the background variations. In this series of experiments, however, there was a tendency for the retrograde flow of perfusion fluid to show an increase.

In 11 of 13 experiments, homphothin in a dilution of 1:5,000,000 caused an increase in the retrograde and total outflow of perfusion fluid. The increase in the coronary outflow was most marked during the first perfusion of the glucoside. The changes in the outflow of perfusion fluid were usually biphasic in character: at the beginning of perfusion of the glucoside a decrease in the outflow was observed, followed by an increase. Subsequent perfusion of nutrient medium constantly led to a decrease in both the total and the retrograde flow of perfusion fluid.

*Name not verified—Publisher's note.

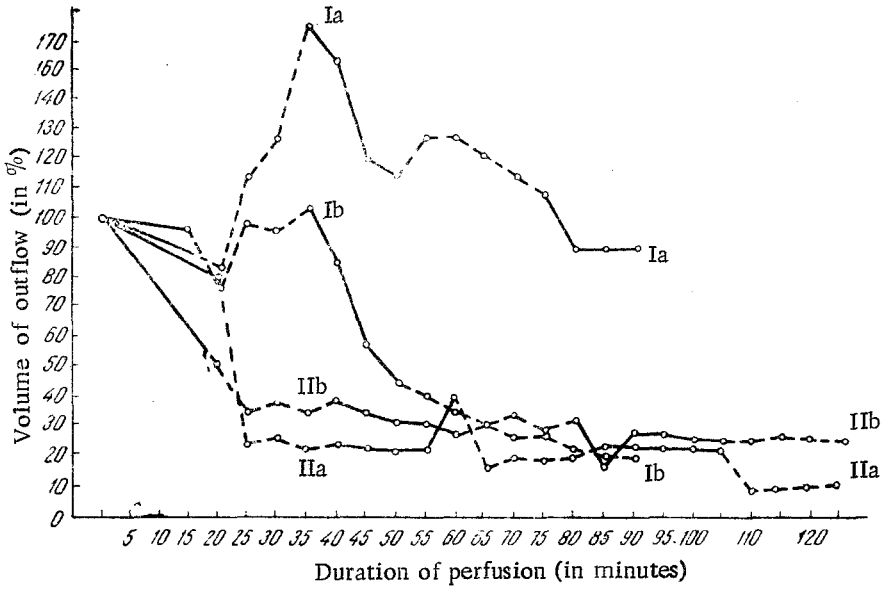

Fig. 1. Effect of homphothin (I) and strophanthin (II) in a dilution of 1:10,000,000 on the total coronary (a) and retrograde (b) flow of perfusion fluid. The changes in the total and retrograde outflow of perfusion fluid at the moment of perfusion of glucosides are shown by broken lines

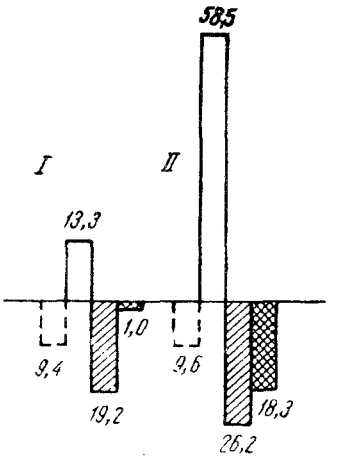

Fig. 2. Effect of homphothin (unshaded columns), strophanthin (obliquely shaded columns) and erysimin (cross-hatched columns) in a dilution of 1:10,000,000 on the total (I) and retrograde (II) flow of perfusion fluid (as percentages of the initial value of the outflow). The broken line denoted the spontaneous changes during perfusion.

Similar but more marked changes were also observed when homphothin was perfused in a dilution of 1:10,000,000 (Fig. 1). Perfusion of homphothin in a concentration of 1:20,000,000 led to a tendency for the retrograde and total outflow of perfusion fluid to increase within the upper limits of the background variations.

Strophanthin, in dilutions of 1:5,000,000 and 1:10,000,000, caused no significant increase in the retrograde and total outflow of perfusion fluid, and no decrease in the outflow of perfusion fluid outside the limits of the changes associated with the long duration of perfusion.

Perfusion with erysimin in a dilution of 1:5,000,000 led in all the experiments to a decrease in the total (by 25%) and retrograde (by 24.2%) outflow of perfusion fluid. In a dilution of 1:10,000,000, on the other hand, erysimin caused very slight changes (either in increase or a decrease) in the total coronary outflow. Bearing in mind the spontaneous decrease in the outflow of perfusion fluid during perfusion with erysimin, it may be considered that this alkaloid generally leads to dilatation of the coronary vessels without thereby increasing the volume of the retrograde blood flow (Fig. 2).

These experimental findings characterizing the effect of cardiac glucosides on the coronary vessels are largely in agreement with the data in the literature (see Table). The experiments showed that homphothin had the most marked coronary vasodilator action and strophanthin the weakest; erysimin occupied an intermediate position in this respect. This statement applies mainly to the effect of glucosides in a dilution of 1:10,000,000; in higher concentrations (1:5,000,000; 1:2,500,000) of the drug this action became weaker and a tendency towards constriction of the coronary vessels became apparent. The action of the cardiac glucosides during the first perfusion was accompanied by a more marked decrease in the total outflow than during perfusion with nutrient fluid. The more marked decrease in the

Effect of Cardiac Glucosides on the Tone of the Coronary Vessels and the Coronary Blood Flow (from the data in the literature)

Author	Preparation	Dose or concentration	Technique and test object	Effect
Quettel, Schimert [8]	Strophanthin K	0.005 mg/kg	Dog's heart. Measurement of the coronary blood flow with a Rein's stromuhr.	No effect.
I. A. Chuevskii [5]	Strophanthin	1:1,000,000–1:10,000,000	Arrested isolated cat's heart.	Increased outflow preceded by a transient decrease.
Yu. S. Chechulin [4]	Strophanthin K	1:1,000,000–1:8,000,000	Isolated human heart (after infarction and angina pectoris).	In 50% of cases – dilation, in 50% of cases – constriction.
A. D. Turova [3]	Erysimin	1:1,000,000–1:500,000	Arrested isolated cat's heart.	Constriction.
A. D. Turova [3]		1:10,000,000–1:50,000,000	Arrested isolated cat's heart.	No effect.
M. A. Angarskaya, et al. [1]	Homphothin		Isolated heart.	Marked dilation.
M. A. Angarskaya, et al. [1]	Gofruzid		Isolated heart.	Dilatation.
Gessner [6]	Usaron–alcoholic extract of Radix homphocarpi	In the presence of inactive doses of suprarenin	Isolated calf's heart	Dilatation.

total coronary outflow was associated with an increase in the tone of the heart muscle during perfusion with glucosides.

When perfusion was repeated the changes in the total outflow were, as a rule, very small. In these cases too, however, the experimental results were very clear, for in the overwhelming majority of cases the perfusion of nutrient fluid directly after perfusion of glucosides caused a more marked fall in the volume of the outflow of perfusion fluid. The coronary vasodilator action of the test glucosides was observed in all the experiments only during the period of perfusion of glucoside solutions, probably because of their rapid reabsorption and clearance during perfusion of nutrient fluid.

The positive effect of homphotin and, to a lesser degree, of erysimin and strophanthin on the retrograde outflow was determined mainly by the vasodilator action of the glucosides on the arterioles and capillaries, for in our experimental conditions (with a stable pressure of the nutrient fluid, absence of contractions of the left ventricle, and free outflow of perfusion fluid from the veins), the main factor influencing the retrograde flow was the dilatation of the interarterial anastomoses. The coronary dilator action of homphothin also revealed by the experiments of M. A. Angarskaya and co-workers [1], is probably due to the distinctive structure of this glucoside. Homphothin contains a genin, closely related in its structure to the genins of the little studied species of Strophanthus – emicymarin and sarmentogenin, and in contrast to strophanthin and erysimin, has no aldehyde group at C_{10}. A role of some importance may also belong to the specific features of the glucone, which in homphothin consists of methylreductinic acid.

SUMMARY

Experiments were staged on isolated cat hearts. Under study was the effect produced by homphothin, strophanthin and erysimin on the general coronary outflow and the retrograde flow of the perfusate from the anterior descending branch of the left coronary artery. Homphothin produces the greatest coronary dilatating effect. Erysimin and strophanthin had no significant effect on the retrograde flow of the perfusate. The vasodilating effect of homphothin on the coronary vessels is connected with the peculiarities of its chemical structure.

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