THE EFFECT OF PAPAVERINE, EUPHYLLINE, AND DIBAZOL ON THE RATE OF THE CORONARY CIRCULATION, THE OXYGEN DEMAND OF THE HEART, AND THE WORK OF THE HEART

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In view of the widespread occurrence of diseases associated with disturbances of the coronary circulation, the experimental evaluation of drugs used in the treatment of coronary insufficiency is of great interest.

The literature contains a number of papers dealing with the study of the effect of papaverine, euphylline, and dibazol on the rate of the coronary blood flow [2, 5, 6, 8, 9, 10]. However, a sufficiently full idea of the character of the effect of these drugs on the blood supply of the heart can only be obtained if the oxygen demand of the heart and the work of the heart are studied at the same time as measurements are made of the rate of the coronary circulation.

The aim of the present research was to investigate the influence of papaverine, euphylline, and dibazol on the coronary circulation. As criteria of the state of the blood supply of the heart, we used the volume velocity of the coronary blood flow, the oxygen demand of the heart, and the work of the heart.

EXPERIMENTAL METHOD

Investigations were carried out on cats anesthetized with nembutal (40 mg/kg). While artificial respiration was applied to the animals, the chest was opened and a polyethylene catheter was introduced through the right auricle into the coronary sinus. Clotting of the blood was prevented by heparin (1500 units/kg). The rate of the coronary blood flow was judged by the volume of blood leaving the coronary sinus in a given interval of time. A detailed description of the method is given in the paper by N. V. Kaverina [1].

Concurrently with the determination of the volume velocity of the blood flow, the oxyhemoglobin concentration in the coronary venous blood flowing through the catheter was measured with an oxymeter. Parallel recordings were made of the oxyhemoglobin concentration in the arterial blood and of its hemoglobin content. The results obtained were used to determine the oxygen demand of the cardiac muscle. We described the method of measurement of the oxygen demand of the heart in our previous communication [3].

In a group of experiments the minute volume of the heart was also recorded along with measurements of the volume velocity of the flow of blood from the coronary sinus and of the oxygen demand of the heart. This was done by means of a special apparatus allowing the volume velocity of the blood flow in the pulmonary artery to be determined periodically [4].

The arterial pressure in the carotid artery was recorded with a mercury manometer. The figures obtained

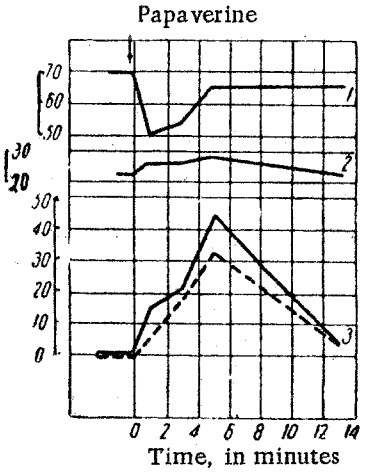

Fig. 1. The influence of papaverine on the blood supply of the heart. 1) Arterial pressure in mm Hg; 2) oxygen content in the blood of the coronary sinus in % of oxyhemoglobin; 3) outflow of blood from the coronary sinus as % of the initial level; ——) uptake of oxygen from the blood passing through the coronary sinus by the heart muscle, as % of the initial level - - - ; the arrow indicates the injection of papaverine in a dose of 1 mg/kg.

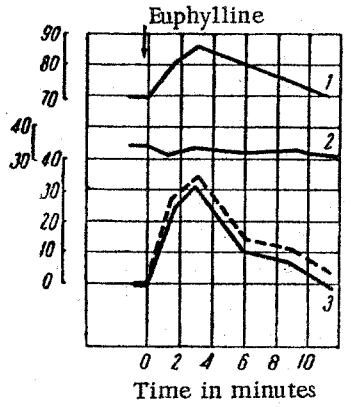

Fig. 2. The effect of euphylline (3 mg/kg) on the blood supply of the heart. Legend as in Fig. 1.

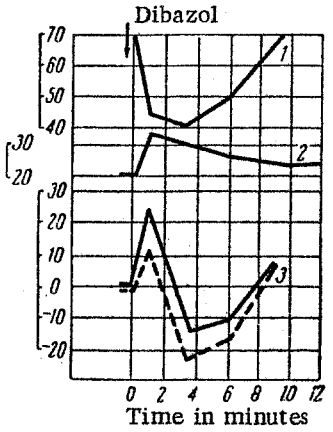

Fig. 3. The effect of dibazol (10 mg/kg) on the blood supply of the heart. Legend as in Fig. 1.

for the arterial pressure and the minute volume were used for calculation of the work of the left side of the heart. In view of the fact that the blood passing through the coronary sinus supplies mainly the left ventricle, we took into consideration only the work of the left side of the heart.

The drugs investigated were those most frequently used in the treatment of coronary insufficiency: papaverine (0.5, 1.0, and 2.0 mg/kg), euphylline (1, 3, 5, and 10 mg/kg) and dibazol (1, 3, 5, and 10 mg/kg). They were injected intravenously. Fifty experiments were carried out.

EXPERIMENTAL RESULTS

Experiments with papaverine. As a result of investigations it was shown that papaverine has the most pronounced influence on the rate of the coronary circulation. In a dose of 2 mg/kg, papaverine caused the volume velocity of the coronary blood flow to increase by an average of 70%, its duration of action being 45 minutes. Detailed information on the influence of papaverine on the rate of the coronary circulation has been given by us previously [2].

Measurements of the oxygen uptake of the heart showed that the increase in the volume velocity of the coronary blood flow was invariably accompanied by a corresponding increase in the oxygen demand of the cardiac muscle. As may be seen from Fig. 1, the curves of oxygen uptake and of the rate of flow of blood from the coronary sinus were almost parallel. The increase in the volume velocity of the coronary blood flow characteristically exceeded the increase in the oxygen demand of the heart to an insignificant degree. In the majority of experiments, papaverine caused an increase of 3-5% of oxyhemoglobin in the oxygen content of the blood of the coronary sinus (Fig. 1).

It must be pointed out that the curve of the oxyhemoglobin content of the blood in the coronary sinus reflects the correspondence between the rate of the coronary blood flow and the oxygen demand of the cardiac muscle. If the volume velocity of the coronary blood flow increased more than the oxygen uptake by the heart (see Fig. 1), the percentage of oxyhemoglobin in the blood of the coronary sinus rose. In cases when the increase

in the oxygen demand by the heart muscle preceded the increase in the rate of the coronary circulation, the percentage of oxyhemoglobin in the out-flowing blood was lowered. The character of the change in the oxyhemoglobin level in the blood of the coronary sinus in the papaverine experiments, showed that the increase in the rate of the coronary blood flow under the influence of papaverine slightly exceeded the uptake of oxygen by the cardiac muscle.

Since the ability of papaverine to increase the oxygen demand of the heart was unexpected, we conducted experiments to study the influence of papaverine on the oxygen demand of cardiac muscle by Warburg's method. For this purpose, in cats under artificial respiration the chest was opened and a strip of myocardium, weighing about 50 mg, was excised from the apex of the heart. Next, papaverine was injected intravenously in a dose of 1-3 mg/kg; 2-3 minutes later a second strip of myocardium was excised. Weighed samples of the two strips of myocardium were placed in a Warburg's apparatus*. The findings thus obtained confirmed the results of the experiments on the intact animal. The intensity of uptake of oxygen by the weighed samples of myocardium excised after the injection of papaverine was 21-41% greater, after incubation for 40 minutes, than the uptake of oxygen by the control samples.

It should be mentioned that the arterial pressure was lowered by the action of papaverine. The duration and magnitude of the depressor effect depended on the size of the dose of papaverine. In a dose of 0.5 mg/kg, papaverine lowered the arterial pressure by 15-30 mm Hg and its effect lasted from 3 to 10 minutes; in a dose of 2 mg/kg it lowered the arterial pressure by 25-45 mm for a period of 4-20 minutes. Very often, immediately after the depressor reaction an increase in the arterial pressure by 10-20 mm Hg above the initial level was observed. In some experiments, the increase in the rate of the coronary blood flow and in the oxygen demand of the heart under the influence of papaverine were maximal during the period of raised arterial pressure.

Measurements of the minute volume of the heart showed that this rose immediately after injection of papaverine, although the arterial pressure was lowered. In one of the experiments, for instance, 2 minutes after injection of a dose of 0.7 mg/kg of papaverine the arterial pressure fell from 90 to 70 mm Hg, but the minute volume rose from 133 to 166 ml. A similar relationship between the changes in the arterial pressure and minute volume was obtained in 5 of the 7 experiments. In 2 experiments the minute volume of the heart fell after injection of papaverine; the fall in the arterial pressure in these cases was sharp.

The work of the left heart, as a rule, was diminished after injection of papaverine. We were unable to detect any definite relationship between the changes in the work of the heart and the changes in the coronary circulation due to papaverine.

The influence of papaverine on the heart rate was insignificant. Immediately after injection of papaverine in a dose of 1.5-1.0 mg/kg, a slight fall in the heart rate was observed (by 5-6%), and 8-10 minutes later, this was replaced by a slight increase (by 3-4%). After injection of smaller doses of papaverine (0.5 mg/kg) a slight increase in the heart rate was observed (by 4-6%).

Experiments with euphylline. These experiments showed that euphylline had a marked effect on the volume velocity of the coronary blood flow. In a concentration of 10 mg/kg, for instance, euphylline caused the volume velocity of the coronary blood flow to rise on the average by 45% for a period of 30 minutes.

Measurements of the oxygen demand of the heart showed that euphylline, while increasing the rate of the coronary blood flow, increased the uptake of oxygen by the heart muscle (Fig. 2). The increase in oxygen consumption by the heart usually very slightly exceeded the increase in the volume velocity of the coronary blood flow. The oxyhemoglobin concentration in the blood of the coronary sinus usually fell by 1-3% under the influence of euphylline. In some experiments the oxyhemoglobin concentration was very slightly increased (by 1-2%). The increase in the rate of the coronary blood flow under the influence of euphylline in these experiments as a rule was very sharp.

Our findings of the fall in the oxyhemoglobin concentration in the blood of the coronary sinus under the influence of euphylline are in agreement with those of Foltz et al. [7]. According to these workers, euphylline caused an even more pronounced fall in the oxyhemoglobin content of the blood of the coronary sinus.

*These experiments were carried out by Candidate Biol. Sci. E. P. Chetverikova, to whom we extend our thanks.

Changes in the arterial pressure by the action of euphylline were insignificant. In small concentrations (1-3 mg/kg), euphylline as a rule caused the arterial pressure to rise by 5-10 mm Hg, and in large doses (5-10 mg/kg) it usually lowered the arterial pressure by 10-20 mm. However, the pressure level was quickly restored (in 2-3 minutes). We found no relationship between the changes in the rate of the coronary blood flow and the reaction of the arterial pressure to euphylline.

When the minute volume was measured, just as in the experiments with papaverine, some increase in the minute volume of the heart was observed to accompany the very slight reaction that followed immediately after injection of euphylline. In those experiments in which the initial level of the arterial pressure was low (60 mm), the depressor reaction to euphylline was accompanied by a fall in the minute volume.

The work of the heart was insignificantly affected by the action of euphylline.

Euphylline caused an increase in the heart rate. The maximum increase in the heart rate was observed 2-3 minutes after injection of the drug (5 mg/kg), and amounted to 7-15% by comparison with its initial level, and moreover the heart rate had not usually returned to its initial level at the moment when the rate of the coronary circulation was restored.

Experiments with dibazol. As we have previously shown [2], the action of dibazol on the rate of the coronary circulation is very transient. After injection of dibazol in a dose of 10 mg/kg, the volume velocity of the coronary circulation rose on the average by 40%. The increase in the rate of the blood flow, however, lasted only 2-3 minutes. The increase in the volume velocity of the coronary circulation was usually followed by a slight decrease in this velocity.

Comparison between the changes in the rate of outflow of blood from the coronary sinus under the influence of dibazol and the changes in the oxygen demand of the heart showed that these processes followed approximately the same course (Fig. 3). The curve of uptake of oxygen by the heart at first rose slightly and then fell below its initial level. So also did the curve of the change in the rate of the coronary circulation. It must be pointed out that dibazol caused a greater increase than did papaverine in the oxyhemoglobin concentration in the blood of the coronary sinus. The oxygen content of the blood of the coronary sinus rose by 7-12% of oxyhemoglobin under the influence of dibazol. In some experiments the oxyhemoglobin content was increased even more – by 15-20%. This usually occurred when the oxygen demand of the heart muscle was sharply reduced, but the outflow of blood from the coronary sinus was diminished to a far greater degree.

The fall in the arterial pressure under the influence of dibazol was of a marked character. In a dose of 3 mg/kg, dibazol caused the arterial pressure to fall by 12-20 mm for a period of 3-7 minutes, and in a dose of 10 mg/kg, by 30-40 mm for a period of action of 7-15 minutes. Just as in the experiments with papaverine, immediately after the depressor reaction, in some cases a slight increase in arterial pressure above initial level took place. The maximum increase in the rate of the coronary circulation under the influence of dibazol occurred during the period of the most marked fall in the arterial pressure.

The minute volume and the work of the left heart were diminished by the action of dibazol. Only in one of the experiments was an increase in the minute volume observed to accompany an insignificant fall in the arterial pressure.

Heart rate was decreased by from 5 to 15% after injection of dibazol. The changes in the heart rate lasted longer than the changes in the rate of the coronary blood flow.

SUMMARY

Experiments were performed on anesthetized cats. The author studied the effect of papaverine, euphylline, and dibazol on the volume velocity of the blood outflow from the coronary sinus, the oxygen uptake by the heart and the work of the heart. As shown by the experiments, the changes of arterial blood pressure, minute volume, the work of the heart, and the frequency of the heart beat do not play a decisive role in the increase of the volume velocity of the coronary blood flow under the effect of the drugs under investigation. The changes of the volume velocity of the coronary blood flow and the heart oxygen uptake under the effects of the above vasculo-dilating preparations are strikingly parallel.

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*See C. B. Translation.