THE MECHANISM OF PAPAVERINE'S EFFECT ON THE CORONARY CIRCULATION

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In a previous paper [4], we showed that papaverine, which increases the volumetric rate of the coronary blood flow, simultaneously increases the oxygen absorption of the heart. The ability of papaverine to increase the oxygen consumption of the myocardium under conditions of an intact organism has been confirmed in the work of E. P. Cheterikova [6]. The pronounced parallel between the changes which occur in the volumetric rate of the coronary blood flow and the oxygen absorption of the heart suggests aspecific relationship between the two processes. We wished to determine which was primary: the increase in the rate of the coronary blood flow or the increase in cardiac oxygen consumption.

Until recently, the vasodilative properties of papaverine were thought to be the sole cause of the increase in the volumetric rate of the coronary blood flow induced by the drug [10]. If this were true, it would seem that the increase in the oxygen absorption of the heart effected by papaverine is a consequence of the increase in the volumetric rate of the coronary blood flow. On the other hand, there are definite indications that the volumetric rate of the coronary blood flow depends directly on the oxygen consumption of the heart [8, 11]. On this basis, the reverse is possible, i.e. the increase effected by papaverine in the oxygen consumption of the heart is the primary process and the increase in the volumetric rate of the coronary blood flow, secondary. Therefore, both possibilities must be considered to obtain the answer to this question. In this connection, we thought it would be interesting to compare the action mechanisms of papaverine and euphylline, since the latter is believed to increase the volumetric rate of the coronary blood flow secondarily by primarily increasing the oxygen absorption of the heart [9].

EXPERIMENTAL METHODS

The investigations were performed with a preparation of the heart isolated in situ. For this purpose, cats anesthetized with urethan (0.6 g/kg) and chloralose (40 mg/kg) were used. Artificial respiration was employed, and blood clotting was prevented with heparin (1500 units per 1 kg).

The donor's blood was perfused through the aorta of the recipient. For this, the azygos vein and the venae cavae of the recipient were ligated. The pulmonary artery was ligated and transected, and a catheter was inserted in its central end. A ligature was placed on the ascending aorta, and the central section of the latter was connected to the perfusion pump by a catheter. From the carotid artery of the donor, blood entered the perfusion pump and flowed from the latter into the aorta of the recipient and thence into the right and left coronary arteries. The venous coronary blood collected in the right ventricle and flowed through the pulmonary artery to the pump—consumption meter [5], which measured the volumetric rate of the blood flow and returned the blood to the jugular vein of the donor. Perfusion was done with a pump with a constant perfusion ptessure. A second pump - consumption meter was used for this purpose.The perfusion pressure was kept at 90 mm of mercury. A pump of the type designed by V. M. Khayutin and co-authors [7] was used in a few experiments in which a constant perfusion volume was required. Because the aortic valves did not close completely during perfusion of the aorta, the left ventricle filled up with blood and, therefore, operated under a load which was greater than the perfusion pressure. The cardiac contractions under these conditions were rhythmic.

The preparation of the heart isolated in situ which we used made it possible to measure the whole volume of the coronary blood flow. Under these conditions, central regulation of the tonus of the coronary blood vessels was completely lacking.

An E. M. Krebs oxyhemograph, newly graded and fitted with a special cuvette, was used in all the experiments to record the oxyhemoglobin content of the venous coronary blood as it passed through the cuvette. Parallel determinations of the oxyhemoglobin content in the arterial blood entering the perfusion pump from the donor's carotid artery were made by the same method. In a number of cases, concurrent determinations of the hemoglobin content in the arterial blood were made. Myocardial oxygen absorption was determined from these data and the figures giving the volumetric rate of the coronary blood flow. A detailed description of this method can be found in one of our previous papers [3].

Intracoronary administration of papaverine was done in doses of 0.3, 0.5 and 1 mg. In a number of experiments, euphylline was administered for purposes of comparison in a dose of 1 mg after the papaverine. A total of 17 experiments were performed in which papaverine was administered 22 times, euphylline, 8 times.

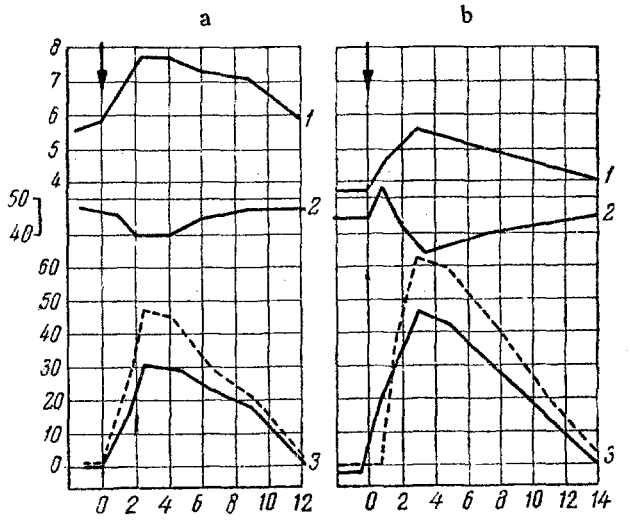

Fig. 1. Effect of papaverine on coronary circulation under conditions of an isolated heart in situ. Abscissa axis—time in minutes; ordinate axis: 1) volumetric rate of coronary blood flow in milliliters per minute; 2) oxygen content of venous coronary blood in percent of oxyhemoglobin; 3) volumetric rate of coronary blood flow in percent of original level—solid line; cardiac consumption of oxygen in percent of original level—dotted line. Arrows show time of intracoronary administration of 0.3 mg (a) and 1 mg (b) papaverine.

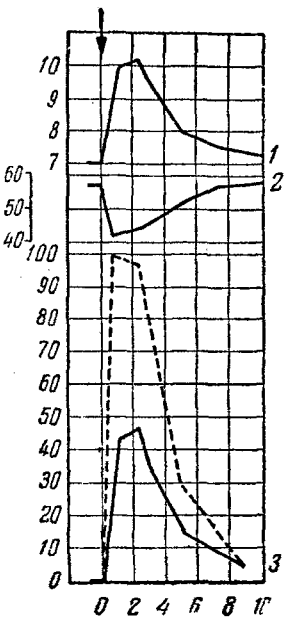

Fig. 2. Effect of euphylline (1 mg) on coronary circulation under conditions of an isolated heart. Symbols the same as in Fig. 1.

EXPERIMENTAL RESULTS

The following figures give the initial background of coronary circulation in our experiments with a perfusion pressure of 90 mm of mercury. The volumetric rate of the coronary blood flow was 8-13 ml/min. The oxygen absorption of the heart ranged between 0.9 and 0.6 ml/min. The oxygen content of the arterial blood constituted 90-95%, while the oxyhemoglobin content of the venous blood was 40-60%.

The oxyhemoglobin content of the venous coronary blood was considerably higher than that recorded for the blood issuing from the coronary sinus under conditions of an intact organism (20-35%). In our opinion, this fact excluded the possibility of cardiac hypoxia, since the reserve of unused oxygen was rather large.

When used in a dose of 0.3-0.5 mg, papaverine caused the volumetric rate of the coronary blood flow to increase 25-50% over the initial level. The increase in the oxygen absorption of the heart was considerably greater (40-80%). As a result, the oxygen content of the venous coronary blood as shown by the percent of oxyhemoglobin decreased by 5-10% for 5-10 minutes (Fig. 1, a). When papaverine was used in a dose of 1 mg, the cardiac consumption of oxygen showed no change or even slightly decreased during the first 1-2 minutes following administration of the preparation, while the volumetric rate of the coronary blood flow showed some increase. This caused

the oxyhemoglobin content of the venous coronary blood to increase 8-12% (Fig. 1,b). These changes were only observed during the first 1-2 minutes after the preparation was administered. Subsequently, the increase in the oxygen absorption of the heart considerably exceeded that of the volumetric rate of the coronary blood flow, and the oxyhemoglobin content of the venous coronary blood decreased.

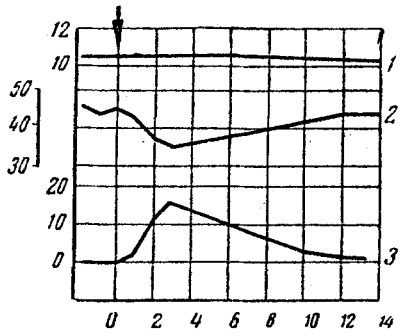

Fig. 3. Effect of papaverine on the oxygen absorption of the heart. Abscissa axis—time in minutes; ordinate axis: 1) volumetric rate of cornary blood flow in milliliters per minute (maintained at constant level); 2) oxygen content of venous coronary blood in percent of oxyhemoglobin; 3) cardiac consumption of oxygen in percent of original level. Arrow shows time of intracoronary papaverine administration (0.3 mg).

The use of euphylline increased the volumetric rate of the coronary blood flow 30-60% over the initial level. The increase in the oxygen absorption of the heart was even greater (60-120%). The oxygen content in the venous coronary blood decreased by 10-15% of oxyhemoglobin (Fig. 2). The changes in the blood supply of the heart lasted 5-10 minutes.

From the material cited, it is evident that papaverine showed a direct vasodilative effect when used in the larger dose (1 mg), increasing the coronary blood flow without changing the oxygen consumption. This effect is negligible and quickly superseded by one in which an increase in the oxygen absorption of the heart is predominant. The fact that papaverine causes a much greater increase in myocardial oxygen absorption than in the volumetric rate of the coronary blood flow gives reason to believe that it is the increase in the oxygen absorption of the heart muscle which is the primary effect of papaverine.

Comparison of the effects of papaverine and euphylline supported this conclusion. In fact, both euphylline and papaverine caused the oxyhemoglobin content of the venous coronary blood to decrease (10-15% and 5-10%, respectively). This indicates that both euphylline and papaverine increase myocardial oxygen consumption more than the volumetric rate of the coronary blood flow, the effect of papaverine being almost as strong as that of euphylline. Moreover, the dilatation of the coronary vessels effected by euphylline is known to be secondary—the result of increased cardiac consumption of oxygen [9].

To confirm the conclusion that papaverine affects the oxygen consumption of the heart primarily, we performed a few experiments in which papaverine was administered on a background of a constant volume of perfusion of the coronary vessels. Under these experimental conditions, papaverine caused cardiac consumption of oxygen to increase even though the volumetric rate of the coronary blood flow remained the same (Fig. 3). In this case, the increase in the cardiac consumption of oxygen was accomplished solely through a decrease in the oxyhemoglobin content of the venous coronary blood. We believe the data obtained to be sufficiently conclusive evidence to the effect that the vasodilative effect of papaverine is to a large extent indirect and is determined by the increase in the oxygen consumption of the heart.

The correlation of the changes induced by the experimental agents in the volumetric rate of the coronary blood flow and in the oxygen consumption of the heart differs somewhat when a preparation of a heart isolated in situ is used from that observed under conditions of an intact organism. Earlier [2], we demonstrated that, under conditions of the intact organism, there is either almost exactly the same degree of increase in the volumetric rate of the coronary blood flow as in the cardiac consumption of oxygen, or a slightly greater increase in the former under the influence of papaverine and euphylline. In the experiments performed on the isolated heart in situ, however, the volumetric rate of the coronary blood flow increases much less under the influence of the experimental drugs than the oxygen absorption of the heart does.

This difference evidently has to do with the fact that the mechanisms correlating the volumetric rate of the coronary blood flow with the oxygen absorption of the heart are disturbed under conditions of an isolated heart. It is also possible that the relatively high oxyhemoglobin content in the venous coronary blood of an isolated heart (40-60%) means that the heart's absorption of oxygen can be increased by greater extraction of the latter from the blood as well as by an increase in the volumetric rate of the coronary blood flow. Under conditions of an intact

organism, however, the oxygen content of the venous blood is negligible, and an increase in the heart's absorption of oxygen can only be provided for by a corresponding increase in the rate of the blood flow.

The fact that papaverine differs from euphylline in that it usually causes a greater increase in the volumetric rate of the coronary blood flow than in the cardiac consumption of oxygen under conditions of an intact organism [4] could be due to its spasmolytic properties. However, the direct vasodilative effect of papaverine on the coronary vessels is evidently not fundamental. The main reason for the increase caused by papaverine in the volumetric rate of the coronary blood flow is most probably the increase in the cardiac consumption of oxygen.

SUMMARY

Experiments were carried out on anesthetized cats (urethane with chloralose). A preparation of isolated heart in situ was used. The coronary arteries of the recipient cat were perfused with the blood of the donor. For this purpose two types of pumps were used: with a constant perfusion volume and with a constant perfusion pressure. The absorption of oxygen by the heart was measured simultaneously by the photometric method. The direct vasodilative effect of papaverine on the coronary vessels is not the main reason for increased volumetric rate of the coronary circulation provoked by papaverine. The main cause of this effect is augmented oxygen absorption by the heart under the influence of papaverine.

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