THE EFFECT OF ADRENALIN, EPHEDRINE, AND AMPHETAMINE ON THE TONE OF THE CORONARY VESSELS AND THE OXYGEN ABSORPTION OF THE MYOCARDIUM IN THE HEART ISOLATED BY THE LANGENDORF PRINCIPLE

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In the intact animal, adrenalin, ephedrine, and amphetamine increase the volume velocity of the coronary blood flow and stimulate the absorption of oxygen by the heart [5]. The changes in these processes follow a distinctly parallel course, due primarily to the fact that the coronary vasodilator effect of these drugs is secondary and is related to the increased absorption of oxygen by the heart. Similar conclusions with regard to adrenalin have also been reported [4, 8, 13, 14].

The object of the present investigation was to analyze the effect of adrenalin, ephedrine, and amphetamine on the tone of the coronary vessels and on the absorption of oxygen by the myocardium in simpler experimental conditions, namely, on a heart preparation isolated by the Langendorf principle and perfused with Ringer-Locke solution. By means of this method hemodynamic influences can be excluded and the direct effect of drugs on the heart can thus be studied.

A series of investigations using adrenalin has been performed on the heart, isolated by the Langendorf principle and perfused with Ringer-Locke solution. The results proved contradictory. In some cases adrenalin caused dilation of the coronary vessels [7, 17, 19], and in others, constriction [2, 20]; sometimes the reaction of the coronary vessels to adrenalin occurred in two phases: constriction was followed by dilation [10, 15]. However, we found no report in the literature of investigations in which the effect of adrenalin on the coronary vessels of the heart isolated by the Langendorf principle was compared with its effect on the absorption of oxygen by the myocardium.

EXPERIMENTAL METHOD

We used cats' hearts, isolated by Langendorf's method. The coronary arteries were perfused through the aorta with oxygenated Ringer-Locke solution, warmed to 37°. The apparatus is shown schematically in Fig. 1. Ringer-Locke solution flowing through the coronary vessels was withdrawn by means of a catheter introduced through the pulmonary artery into the right ventricle, where fluid was collected from the coronary sinus and the other coronary veins. The openings of the superior and inferior venae cavae into the right atrium were ligated. Since, in the Langendorf method, part of the perfusion fluid enters the heart not through the coronary vessels, but through the incompletely closing aortic valves [20], this method of withdrawing the coronary fluid avoids introducing the error which unavoidably arises if the whole volume of the perfusion fluid flowing from the heart is measured.

To determine the oxygen absorbed by the heart from the perfusion fluid, we used Heyrovsky's method [3]. The principle of this method is that if two electrodes with a certain potential difference between them are placed in an aqueous solution of oxygen, a diffusion current develops as a result of the reduction of oxygen at the cathode. Under these circumstances the magnitude of the diffusion current is directly proportional to the oxygen concentration. As cathode we used a platinum wire 0.2 mm in diameter, insulated throughout its length except at the tip for a distance of 1 mm by being covered with glass. The anode was a silver chloride plate (0.5 × 0.5 cm). The two electrodes were mounted in a special cell D through which passed the Ringer-Locke solution, saturated with oxygen. The electrodes were supplied with current from a dry cell giving a voltage of 0.6 V. The magnitude of the diffusion current was

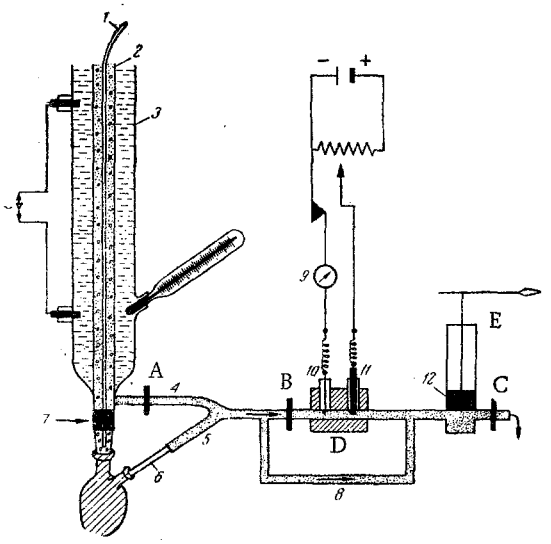

Fig. 1. Scheme of the apparatus for measuring the outflow of fluid from the coronary vessels and the absorption of oxygen by the heart isolated by Langendorf's method. A) Clamp; B and C) external electromagnetic valves; D) cell in which the cathode and anode are mounted; E) measuring cylinder. 1) Tube carrying oxygen supply; 2) buret containing Ringer-Locke solution; 3) glass container filled with water warmed to 37°; 4, 5) tubes; 6) catheter; 7) rubber tube for injection of the test drug; 8) shunt for outflow of fluid; 9) recording potentiometer; 10) cathode; 11) anode; 12) float.

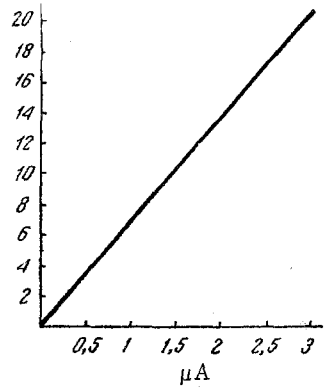

Fig. 2. Calibration curve of the polarographic apparatus. Along the axis of ordinates – O_2 in μg/ml.

recorded on paper by means of a somewhat modified recording potentiometer from a type OKO-19 oxyhemograph. The voltage was applied periodically to the electrodes for 30 sec every minute. Only the magnitude of the surging current was considered. In order to prevent the effect of changes in the velocity of flow of the Ringer-Locke solution through the cell on the readings of the polarographic apparatus, for the time during which the surging current was measured, the flow of fluid was halted by means of an external electromagnetic valve B. In this way the outflow of the fluid took place through a shunt. This halting of the flow of the Ringer-Locke solution through the cell was brought about automatically before each measurement of the surging current.

Experiments carried out to calibrate the polarographic apparatus showed that the relationship between the strength of the surging current and the oxygen concentration of the Ringer-Locke solution, determined by a chemical method [1], was rectilinear (Fig. 2). The oxygen absorbed by the heart was calculated by the following formula:

$$Q = (C_1 - C_2) \cdot V,$$

where Q is the oxygen absorbed by the heart (in μg/min); $C_1 - C_2$ is the difference between the oxygen concentrations of the Ringer-Locke solution entering and leaving the heart (in μg/ml); and V the volume velocity of the flow of fluid through the coronary vessels (in ml/min).

The oxygen concentration in the solution reaching the heart (C_1) remained constant when the oxygenation was carried out at maximal intensity (average 20 μg/ml). The values changing in the course of the experiment were thus the oxygen concentration in the fluid flowing from the heart (C_2) and the volume velocity of flow of the fluid (V). The latter was recorded as follows. The fluid flowing from the coronary vessels along the tube 5 (see Fig. 1) was directed into the measuring cylinder E. When valve C was closed, the fluid lifted the float (12) in the cylinder, and its movement was recorded mechanically on the drum of a kymograph. When valve C was opened, water ran out of the cylinder. The valve was closed periodically for definite time intervals. Knowing the volume of the cylinder and the time during which the valve was closed, the volume velocity of flow of the escaping fluid could be calculated from the height to which the float rose.

In all the experiments the strength of the myocardial contractions was measured by the method of Di Palma and Reiss [12], using a tensometric pick-up of variable resistance and an ink-recording potentiometer, thereby enabling the strength of the contraction of an area of myocardium measuring 1 cm^2 and also the rate of the cardiac contractions to be measured.

The drugs to be tested were injected into the rubber tube 7 (see Fig. 1), through which the Ringer-Locke solution entered the aorta of the isolated heart. Adrenalin was given in doses ranging from 1.0 to 0.005 μg, and ephedrine and amphetamine in doses of 10-100 μg. Altogether 25 experiments were performed.

EXPERIMENTAL RESULTS

The absorption of oxygen by the heart, isolated by Langendorf's method and perfused with oxygenated Ringer-Locke solution, was 0.8-1.1 ml/min/100 g weight of the heart when the volume velocity of outflow of the coronary fluid was 80-120 ml/min/100 g weight of the heart. It is interesting to note that in the intact animal, the absorption of oxygen by the cat's heart from blood draining into the coronary sinus (from 1/2 to 2/3 of the total coronary blood) was 3.5-5.5 ml/min/100 g weight of the heart when the velocity of outflow was 30-50 ml/min/100 g weight of the heart.

Hence, the heart isolated by the Langendorf principle absorbs only between one-sixth and one-ninth the volume of oxygen absorbed by the heart in the intact animal. This is not surprising if it is remembered that the isolated heart performs negligible work at a pressure close to zero. Moreover, the oxygen concentration in the oxygenated Ringer-Locke solution with which the heart was perfused was only from one-fifth to one-sixth the concentration found in the blood.

In our experiments adrenalin always caused a marked increase in the absorption of oxygen by the myocardium (by 50-200%), an effect lasting from 2 to 8 min depending on the dose of the drug (Fig. 3, A and B). Usually, under these circumstances, the volume velocity of outflow of coronary fluid also increased, although to a lesser degree than the absorption of oxygen by the heart, as a result of which the oxygen concentration in the outflowing fluid decreased. The effect of an increase in the outflow, followed by its restoration, usually appeared simultaneously with the increase in the absorption of oxygen by the heart and its restoration. In some experiments, notwithstanding the increase in the absorption of oxygen by the heart after injection of adrenalin, during the first minutes the coronary outflow fell, and then rose again (Fig. 3, D). In a few experiments adrenalin caused only a decrease in the volume velocity of the coronary outflow (Fig. 3, C). The oxygen consumption of the heart increased in these circumstances entirely as a result of an increase in its absorption from the coronary fluid.

The strength and frequency of the cardiac contractions were increased after injection of adrenalin. In large doses (1.0-0.1 μg), adrenalin caused a transient increase in the strength (two-fold, three-fold, or more) and frequency (by 50-70%) of the contractions, giving way after 2-3 min to a sharp decrease in both magnitudes. At the same time, arrhythmias developed. The absorption of oxygen by the heart and the volume velocity of the outflow of fluid from the coronary vessels nevertheless continued to increase (see Fig. 3, B).

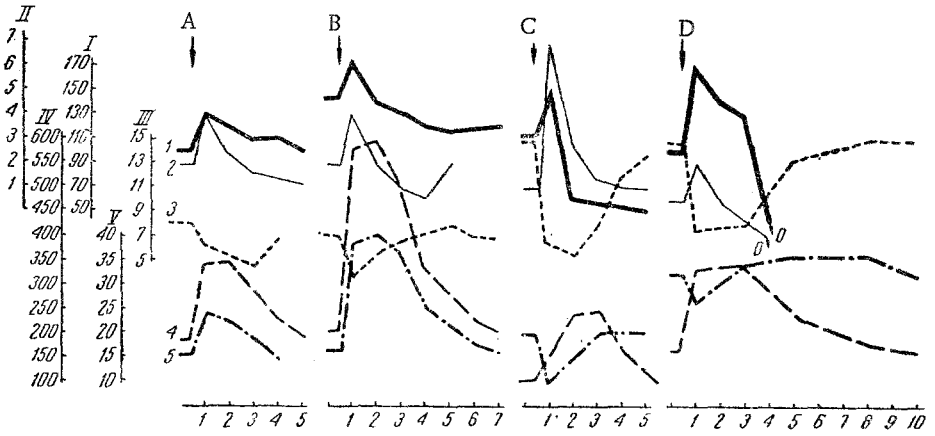

Fig. 3. Effect of adrenalin, injected in doses of 0.02 μg (A), 0.4 μg (B), 0.8 μg (C), and 1.0 μg (D) on the flow of fluid from the coronary sinuses and on the absorption of oxygen by the heart isolated by Langendorf's method. Along the axis of ordinates: I) heart rate in beats per minute; II) strength of contractions (in g) of an area of myocardium measuring 1 cm^2; III) oxygen concentration in outflowing coronary fluid (in μg/ml); IV) absorption of oxygen by the heart (in μg/min); V) volume velocity of outflow of fluid from coronary vessels (in ml/min).

After injection of small doses of adrenalin (0.05-0.01 μg), the frequency of the cardiac contractions increased by 30-50%, and this usually coincided with the period of increased oxygen absorption by the heart (see Fig. 3, A). The increase in the strength of the myocardial contractions was more marked, but sooner restored, than the increase in the absorption of oxygen by the heart.

The effect of ephedrine and amphetamine on the myocardium was similar. After injection of these drugs the absorption of oxygen by the heart increased by 50-200% and this action lasted for 8-15 min. The volume velocity of the coronary outflow was increased to a lesser degree than the absorption of oxygen by the heart, as a result of which the oxygen concentration in the outflowing fluid was decreased. The frequency and strength of the myocardial contractions increased by 30-50 and 50-100% respectively and this effect lasted for 8-15 min.

The increase in the volume velocity of the coronary outflow of the isolated heart following administration of adrenalin, ephedrine, and amphetamine was most probably the result of the increased absorption of oxygen by the heart. This was demonstrated by the parallel trend of the increase in these processes, and by the fact that the absorption of oxygen by the heart increased more than did the coronary outflow. The decrease in the volume velocity of the coronary outflow which was sometimes observed after administration of adrenalin was evidently the result, as also in the intact animal [4, 8, 9], of its direct vasoconstrictor action on the coronary vessels. After administration of adrenalin there is evidently a clash between its two opposite effects on the coronary vessels: an indirect (as a result of a change in metabolism) vasodilator action and a direct vasoconstrictor action. Dilatation of the coronary vessels usually prevails (see Fig. 3, A and B), but sometimes an initial vasoconstrictor phase of action is observed (see Fig. 3, D), and, in rare cases, purely constriction of the coronary vessels (see Fig. 3, C). In the intact animal, the detection of the direct vasoconstrictor effect of adrenalin on the coronary vessels is still more complicated. It may be observed only when special forms of perfusion apparatus are used [4, 8, 9].

We observed no precise correspondence between the increase in the frequency and strength of the myocardial contractions, on the one hand, and the increase in the absorption of oxygen by the heart following administration of adrenalin, ephedrine, and amphetamine, on the other. This was especially so in respect of the experiments in which large doses of adrenalin were given (see Fig. 3, B). After injection of small doses of adrenalin, this correlation was more applicable to the frequency than to the strength of the contractions (see Fig. 3, A).

Adrenalin does not increase the absorption of oxygen by the non-contracting tissue of the heart [6, 11, 16], but nevertheless does cause a parallel increase in the strength of the contractions and in the absorption of oxygen by the isolated papillary muscle of the heart [18]. Hence, it may be assumed that the increase in the absorption of oxygen by the heart after administration of adrenalin is associated with changes in the activity of the cardiac muscle fibers.

The effect of adrenalin, ephedrine, and amphetamine on the coronary vessels and on the absorption of oxygen by the myocardium, when investigated on the isolated heart, is thus analogous to their effect in the intact animal.

SUMMARY

Experiments were carried out on cat hearts, isolated after Langendorf and perfused with Ringer-Locke solution. Cardiac oxygen uptake was determined by the difference in the oxygen content in the fluid flowing in and out of the heart, measured polarographically, as well as by estimating, the volume velocity of the coronary outflow. As established, adrenalin, ephedrine and amphetamine caused a marked rise of the cardiac oxygen uptake. The volume velocity of the fluid outflow from the coronary blood vessels increased to a lesser degree than the cardiac oxygen uptake. Notwithstanding the rise of the oxygen uptake by the heart after use of adrenalin there was at times a reduction of the volume velocity of the coronary outflow. It is assumed that in using adrenalin there occurs a clash between two of its antagonistic effects on the coronary vessels: of an indirect one (due to the change of metabolism) – the vasodilating, and a direct one – the vasoconstricting. Usually dilation of the coronary vessels prevails, but sometimes there occurs a vasoconstricting reaction.

There is no precise conformity between the rise of frequency and strength of myocardial contractions, on the one hand, and the rise of the cardiac oxygen uptake under the effect of adrenalin, ephedrine and amphetamine, on the other hand.

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