EFFECT OF CHLORACYZINE, PAPAVERINE, AMINOPHYLLINE, AND ADRENALIN ON MYOCARDIAL OXYGEN TENSION IN ACUTE LOCAL CARDIAC ISCHEMIA

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The purpose of the present work was to investigate the effect of chloracyzine*, papaverine, aminophylline, and adrenalin on myocardial oxygen tension in regional disorders of the coronary circulation caused by ligation of the descending branch of the left coronary artery.

EXPERIMENTAL METHOD

The experiments were carried out on cats anesthesized with urethane (0.05 g/kg) and chloralose (30 mg/kg). During the experiment the animals were injected intravenously with ditiline in a concentration of 1:1000 at a rate of 5-8 drops per min. The oxygen tension in the heart was determined polarographically by Épshtein's method [6]. A special switching device made it possible to alternately feed the current to one and the same galvanometer from 2 electrodes situated in different sections of the myocardium. While measuring the current in the circuit of one cathode, the current continued to flow in the circuit of the other. Thus, we measured not surging, but diffusion currents established in two sections of the myocardium. The indications of the galvanometer were recorded every 15 or 30 sec alternately from both electrodes.

Simultaneously with determining the oxygen tension in the myocardium, the arterial pressure was measured by a mercury manometer. All the investigated substances were injected intravenously in doses causing an evident increase in the volume of coronary circulation [2]: chloracyzine, in a dose of 3-5 mg/kg; papaverine, 1-2 mg/kg; aminophylline, 5-10 mg/kg; adrenalin, 5-20 μg/kg.

The coronary circulation was disrupted by ligation of the descending branch of the left coronary artery at the boundary between its middle and distal third. Prior to ligation of the coronary artery, one of the active electrodes was inserted into the supposed zone of ischemia and the other into a section of the myocardium which was known to be supplied with blood not from the ligated artery. The coronary artery was ligated 10-15 min after insertion of the electrodes, when the diffusion current ceased to decrease and was stabilized at a definite level. The established magnitude of the current which reflected the oxygen tension in the heart was taken as 100%.

There was a total of 25 experiments in which 45 injections of the investigated substances were made.

EXPERIMENTAL RESULTS

Ligation of the descending branch of the left coronary artery caused a 30-90% drop of current strength in the ischemic zone in comparison with the initial level. If the electrode was in the center of the ischemic zone, the drop of oxygen tension was usually more evident than when it was near its edge. This fact corresponds to experimental data obtained by other authors [5, 11, 12].

* Publisher's Note: Chloracyzine is 2-chloro-10-(3-dimethylaminopropionyl) phenothiazine.

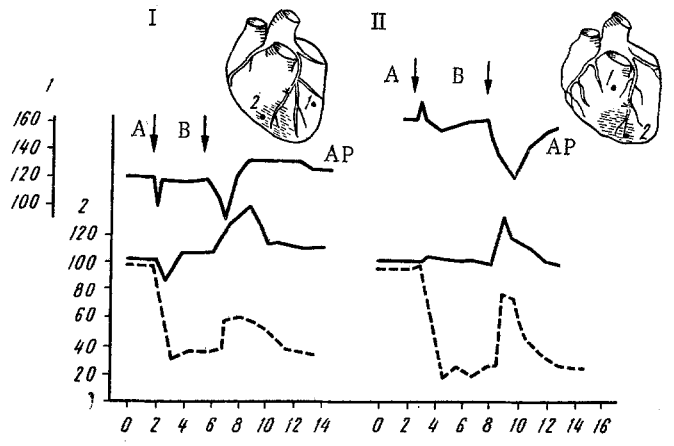

Fig. 1. Effect of chloracyzine and papaverine on oxygen tension in the myocardium. Along the abscissa is the time (min); along the ordinate 1) Arterial pressure, AP (mm Hg); 2) current strength reflecting oxygen tension (in percent of initial level) in myocardial zone far from ischemic area (solid line) and in the ischemic zone (dashed line); A) Ligation of descending branch of left coronary artery; B) injection of substance; I) Experiment with use of chloracyzine in dose of 5 mg/kg; II) experiment with use of papaverine in dose of 2 mg/kg. Hatching on diagram of heart designates area of ischemia, points 1 and 2 indicates position of electrodes.

The experiments demonstrated that chloracyzine causes an evident increase of oxygen tension in the cardiac muscle: the increase of current strength under the effect of chloracyzine varied from 20 to 100%. in comparison with the initial level when the effect lasted 4-8 min. An increase of oxygen tension occurred not only in inactive sections of the heart, but also in the ischemic zone of the myocardium (Fig. 1I).

Further observations revealed that papaverine also has the ability to increase oxygen tension in the myocardium. This effect can be observed in experiments with ligation of the coronary artery and without it. An increase of current strength under the effect of papaverine outside the ischemic zone was 20-50% with the effect lasting 4-6 min; in the ischemic zone the current strength increased more appreciably, by 30-70% (Fig. 1II). This was especially evident when the electrode determining the oxygen tension in the ischemic zone was near its edge.

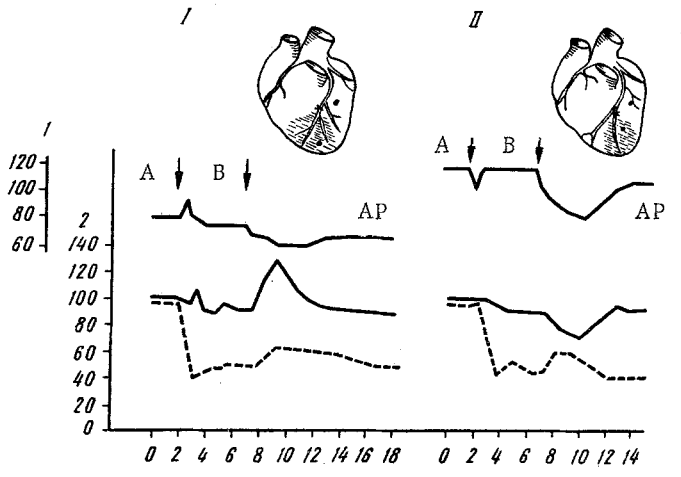

Fig. 2. Effect of aminophylline on myocardial oxygen tension. Designations are the same as in Fig. 1. I and II) Two experiments with use of aminophylline in a dose of 10 mg/kg.

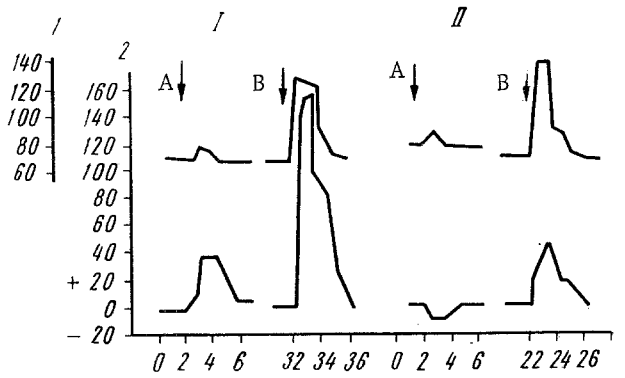

Fig. 3. Effect of adrenalin on myocardial oxygen tension. Along abscissa is time (min); along ordinate: 1) Arterial pressure (in mm Hg); 2) current strength reflecting oxygen tension in heart (in percent of initial level); A) Injection of adrenalin (20 μg/kg) with stabilization of arterial pressure; B) injection of adrenalin in the same dose without stabilization of arterial pressure; I and II) Two experiments with the use of adrenalin.

Unlike chloracyzine, papaverine does not always increase oxygen tension in the myocardium. In 3 out 13 experiments it, conversely, lowered the oxygen tension (the current strength dropped by 5-20%). In our opinion the fact is quite important that in these experiments a distinct increase of oxygen tension (an increase of current strength by 30-70%) was noted in the ischemic zone despite the drop of oxygen tension in the intact sections of the heart. In the experiments with aminophylline the indicated phenomenon was observed constantly.

The oxygen tension in the heart outside the ischemic zone increased under the effect of aminophylline only in some of the experiments (in 4 out of 11) and then gradually only to a small degree: the current strength increased 10-30% and the effect lasted 2-4 min (Fig. 2I). Most frequently (in 7 of 11 experiments) aminophylline lowered the oxygen tension in the myocardium outside the ischemic zone (current strength dropped by 10-30%). In spite of this, the oxygen tension almost always increased (increase of current strength by 5-30%) in the ischemic zone, just as in the experiments with papaverine (Fig. 2II).

Adrenalin in doses of 5-20 μg/kg induced a pronounced increase of oxygen tension in the heart, which corresponds to previously obtained data [10]. This increase of oxygen tension occurred simultaneously with an increase of arterial pressure. With a 50-80 mm Hg rise of arterial pressure the current strength increased 40-80%, whereas with a rise of pressure by 80-130 mm it increased by 100-200% in comparison with the initial level (Fig. 3).

In our previous work it was demonstrated that an appreciable increase of the oxygen content in the venous coronary blood under the effect of adrenalin in large doses is associated with a rise of arterial pressure, which forces through the coronary vessels a greater quantity of blood than is necessary to satisfy the energy requirements of the heart [3]. It seems probable to us that the increase of oxygen tension in the heart under the effect of adrenalin has the same origin.

To check this assumption, experiments were carried out in which the arterial pressure was stabilized at a definite level. This was achieved by connecting the abdominal aorta of the cat with a constant-pressure reservoir. It turned out that with stabilization of pressure, adrenalin did not cause a marked increase of the oxygen tension in the myocardium (see Fig. 3I); sometimes it was even possible to note a slight decrease of oxygen tension under the effect of adrenalin (see Fig. 3II). Thus, the pronounced increased of myocardial oxygen tension induced by adrenalin in large doses is evidently caused to an appreciable degree by an increase of arterial pressure.

The oxygen tension in the ischemic zone under the effect of adrenalin, just as with the use of other investigated substances, usually increased to a greater degree than in the intact areas of the myocardium.

The increase of myocardial oxygen tension under the effect of the indicated coronary-dilators indicates that the delivery of oxygen increases the heart's need for it. A decrease of oxygen tension indicates that its consumption under the effect of these substances increases to a greater degree than the coronary circulation supplying the heart with oxygen.

The fact that papaverine and aminophylline in a number of cases lowered the oxygen tension in the myocardium confirms our previous conclusions that the coronary-dilating effect of these substances to a considerable extent is determined by their ability to increase the energy requirements of the heart for oxygen [4]. At the same time chloracyzine, which does not stimulate an increase of oxygen uptake by the heart [1], never lowers the oxygen tension in the myocardium, unlike the other substances we investigated.

An increase of oxygen tension in the ischemic zone under the effect of the indicated substances is evidently a consequence of the increase of oxygen delivery by the blood. It is natural that upon ligation of the coronary artery

such an increase can occur apparently only as the result of dilation of the vessels surrounding the ischemic zone and of the improvement of collateral circulation in it. This is indicated by the fact that papaverine and aminophylline upon ligation of the coronary artery reduce the size of the infarcts [8, 9] and also improves the electrocardiographic indexes attesting to myocardial ischemia [7, 13].

An increase of oxygen tension in the ischemic zone under the effect of papaverine and aminophylline occurred despite the fact that these substances increase oxyten uptake by the heart. They increase the oxygen tension in the ischemic zone even when it diminishes in the other myocardial areas. This fact evidently indicates that dilatation of the cardiac vessels, caused by an increase of the myocardial requirement for oxygen, leads to an enhancement of the flow of arterial blood along the collaterals to the ischemic zone and thus improves its oxygen balance. This occurs even in those cases where oxygen uptake outside the ischemic zone increases to a greater degree than the coronary circulation. Apparently if there is a marked shortage of oxygen, the additional increase of the requirement for it under the effect of papaverine and aminophylline in the ischemic zone is not substantial in comparison with the increase of the oxygen flow along the collaterals.

This phenomenon explains to a certain extent why papaverine and aminophylline have an effect in coronary disease, by dilating the coronary vessels owing to an increase of the heart's requiremnt for oxygen.

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