THE CORRELATION OF CHANGES IN THE VOLUMETRIC RATE OF CORONARY BLOOD FLOW AND CARDIAC OXYGEN CONSUMPTION UNDER THE INFLUENCE OF ADRENALINE, NORADRENALINE, EPHEDRINE, AND PHENAMINE.

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Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 52, No. 10, pp. 67-71, October, 1961.
Original Article submitted November 9, 1960

A great deal of work has been devoted to the study of the effect of adrenaline on the coronary vessels. However, only in recent years, in investigations of the influence of adrenaline on the volumetric rate of coronary blood flow, has this work begun to take into account the metabolic side of its action. Some authors [12], feel that the ability of catechol amines to increase the consumption of oxygen by the heart is the leading pathogenetic mechanism in the evocation of an attack of stenocardia.

In connection with the importance of the problem indicated, we undertook an investigation of the influence of a series of phenylalkylamines – adrenaline, noradrenaline, ephedrine and phenamine – on the volumetric rate of coronary blood flow, and the consumption of oxygen by the heart.

Reports in the literature indicate that, under the conditions of an intact organism, adrenaline and noradrenaline, which raise the consumption of oxygen by the heart, increase the volumetric rate of coronary blood flow [8,9]. Several authors who employed perfusion apparatus in their experiments, found a transitory contraction in the coronary vessels prior to their clearly-expressed dilation [2, 6, 7]. A few articles [10, 11] report that ephedrine stimulates an increase in the volumetric rate of coronary blood flow. We did not find any reports in the literature available to us on the effect of phenamine on the supply of blood to the heart.

EXPERIMENTAL METHOD

We carried out our experiments on 38 cats which had been narcotized with urethane (0.6 g/kg) or chloralose (40 mg/kg). The outflow of blood from the coronary sinus of the heart served as an index of the volumetric rate of the venous blood circulation. For this purpose, we opened the animals' chest cavity, using artificial respiration, and we inserted a polythylene catheter via the right auricle of the heart into the cornary sinus. A detailed description of the operation is presented in an article by N. V. Kaverina [1]. We measured the blood flowing from the coronary sinus with the aid of a special pump [5]. This instrument automatically registered the volumetric rate of the blood flow and returned the blood into the jugular vein of the cat. Coagulation of the blood was prevented with heparin (1500 units/kg). Simultaneously with the determination of the rate of blood flow, we carried out photometric assay of the oxyhemoglobin content of the venous coronary blood flowing through the catheter. Parallel to this we recorded the content of oxyhemoglobin in the arterial blood (femoral artery) and its content of hemoglobin. The results obtained were used to determine the consumption of oxygen by the cardiac muscle. The method indicated for the measurement of the consumption of oxygen by the heart has been previously described by us [3]. All substances tested were introduced intravenously in the following doses: adrenaline – 1, 2, 5, 20, 30 γ/kg; noradrenaline – 1, 2, 5, 20 γ/kg; ephedrine – 0.1, 0.2, 0.5, 1 mg/kg; phenamine – 0.1, 0.5, 1 mg/kg.

EXPERIMENTAL RESULTS

Adrenaline in small doses (1-2 γ/kg) produced an increase in the volumetric rate of coronary blood flow by 40-60% in comparison to the original level, with a duration of effect of 2-4 minutes. The consumption of oxygen by the heart during this time also increased (Fig. 1).

Usually, the increase in the volumetric rate of coronary blood flow exceeded, by a little, the rise in the intake of oxygen by the cardiac muscle, a consequence of which was an increase in the content of oxygen in the blood of the coronary sinus by 2-4% oxyhemoglobin. However, in some tests, the quantity of oxyhemoglobin in the venous coronary blood was lowered slightly (1-3% oxyhemoglobin). The arterial pressure under the influence of adrenaline

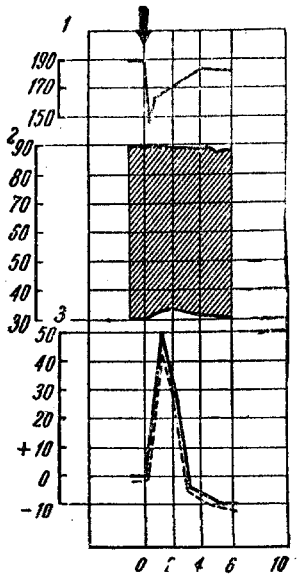

Fig. 1. The effect of adrenaline on the cardiac blood supply. Abscissas – time in minutes; ordinates – 1) arterial pressure in millimeters of Hg; 2) content of oxygen in arterial blood and blood of the coronary sinus in % of oxyhemoglobin; 3) outflow of blood from the coronary sinus in % of the original level (solid line) and consumption of oxygen by the heart from the blood draining from the coronary sinus, in percents of the original level (dotted line). Administration of adrenaline in a dose of 2 γ/kg is indicated by the arrow.

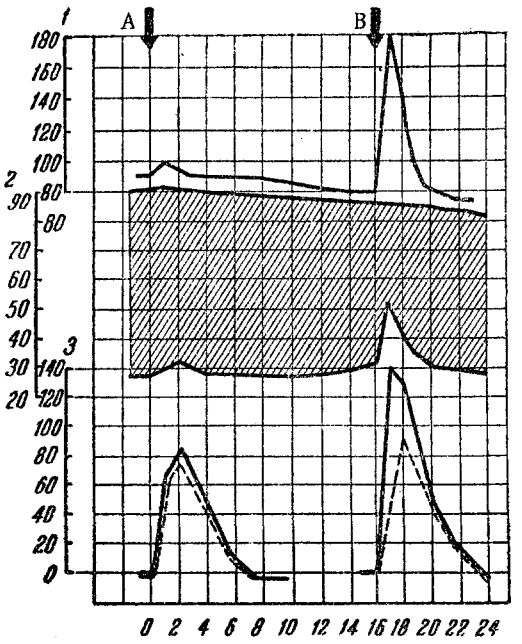

Fig. 2. The effect of adrenaline on the cardiac blood supply under the conditions of stabilization of arterial pressure. a) Administration of adrenaline (indicated by the arrow) in a dose of 20 γ/kg with stabilization of the arterial pressure; b) administration of adrenaline (indicated by the arrow) in the same dose without stabilization of the arterial pressure. The remaining designations are the same as in Fig. 1.

in doses of 1 - 2 γ/kg was raised in some tests and lowered in others. The extent of the changes in the arterial pressure in these cases was 10-30%. The contraction rate of the heart was also altered slightly (by 10-15%) both in terms of an increase and a decrease. The degree of increase in the rate of the cornary blood flow and the consumption of oxygen by the heart under the influence of adrenaline (1-2 γ/kg) did not depend essentially on the trend of the changes in the arterial pressure and the rate of the heart beat.

Adrenaline in a dose of 5 γ/kg produced a rather sharply expressed rise in the volumetric rate of coronary blood flow — 70-100 % with a duration effect of 3-5 minutes. The intake of oxygen by the heart rose approximately to the same extent as the rate of blood flow.

The rise in the volumetric rate of the coronary blood flow to a significantly higher degree than the consumption of oxygen by the heart was observed only under the influence of adrenaline in large doses (20-30 γ/kg). Adrenaline in these doses increased the arterial pressure 2-3 times in comparison to the original level. The volumetric rate of coronary blood flow rose to approximately the same extent. The consumption of oxygen by the heart was raised under these conditions to a significantly lesser degree, as a result of which the content of oxygen in the venous coronary blood rose sharply (by 15-25% oxyhemoglobin). The duration of the changes in the arterial pressure, in the rate of coronary blood flow and in the quantity of oxyhemoglobin was approximately the same and was 5-8 minutes.

It seemed to us that the described significant rise in the content of oxygen in the blood of the coronary sinus was associated with the fact that the arterial pressure rise after administration of adrenaline "forces" a larger amount

of blood through the coronary vessels than is necessary for the satisfaction of the energy requirements of the heart. In order to check this assumption, we carried out tests in which the arterial pressure was stabilized at a determined level. This was achieved by the use of a reservoir, connected to the abdominal aorta of the cat and raised to the determined level. It was found that when the pressure was stabilized the adrenaline raised the volumetric rate of the coronary blood flow to a significantly lesser degree and did not produce abrupt shifts in the oxyhemoglobin content of the venous coronary blood (Fig. 2). This indicated that in the absence of a clearly expressed rise in the arterial pressure, a parallelism is recorded between the changes in the volumetric rate of coronary blood flow and the intake of oxygen by the heart under the influence of adrenaline in large doses.

In the experiments in which noradrenaline was used, the change in the rate of coronary blood flow and consumption of oxygen by the heart were analogous to that observed in the adrenaline tests. Therefore, we were unable to confirm the findings of Gollwitzer-Meier [9] on the significantly stronger effect of adrenaline, in comparison to noradrenaline, on the consumption of oxygen by the heart.

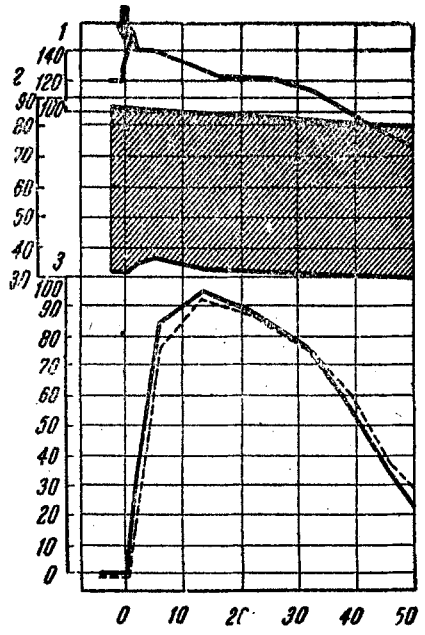

Fig. 3. The effect of ephedrine on the cardiac blood supply. The administration of a 0.5 mg/kg dose of ephedrine is indicated by the arrow. The remaining designations are the same as in Fig. 1.

The effect of ephedrine on coronary blood circulation manifested itself even at a dose of 0.1 mg/kg. At this dose, ephedrine almost did not change the arterial pressure, but the volumetric rate of the coronary blood flow increased by 30-50 % in comparison with the original level, with a duration of effect of 10-15 minutes. At a dose of 0.5 mg/kg, ephedrine produced an expressed and protracted rise in the coronary blood flow (by 70-120% in the course of 1-1½ hours). The intake of oxygen by the heart muscle under these conditions was raised (Fig. 3). The rise in the volumetric rate of the coronary blood flow under the effect of ephedrine corresponded so exactly with the rise in the intake of oxygen by the heart that the content of the oxyhemoglobin in the blood of the coronary sinus was changed by only 2-4 %, usually in the form of an increase. Under the effect of a 0.5 mg/kg. dose of ephedrine, the arterial pressure was raised by 20-30%. The original level of the arterial pressure was restored within 10-15 minutes after the administration of the substance in the presence of a marked increase in the coronary blood flow.

In our tests, phenamine showed almost the same effect as ephedrine on the cardiac blood supply. At a dose of 0.5-1 mg/kg, it produced an expressed and protracted increase in the coronary blood flow (70-140 %, duration 1-1½ hours and more). The arterial pressure under these conditions was raised by only 10-20% with a duration of effect of 10-20 minutes. The intake of oxygen by the heart muscle was increased to almost the same extent as the rate of blood flow. Consequently, the content of oxygen in the venous coronary blood was raised by only 2-5% oxyhemoglobin.

Therefore, judging by our experiments, adrenaline and noradrenaline produce a sharp, but brief rise in the rate of the coronary blood flow. The effect of ephedrine and phenamine on the cardiac blood supply is inferior in strength to that of adrenaline or noradrenaline, but it is distinguished by its duration.

The rise in the volumetric rate of coronary blood flow and the intake of oxygen by the heart, under the influence of the substances tested, proceeds in a parallel manner. The parallelism in the changes of the processes indicated is only briefly disturbed by the administration of adrenaline and noradrenaline in large doses. This is conditioned by the sharp rise in the arterial pressure which plays the role of a mechanical factor determining the blood flow.

The increase in the work of the heart under the influence of adrenaline and noradrenaline in small doses, or better, of ephedrine and phenamine, also, is not the decisive condition for the increase in the intake of oxygen by the heart. Testifying to this is the circumstance that two basis factors, which determine the energy output of the heart – the rate of the heart beat and the arterial pressure – may, under the effect of adrenaline and noradrenaline (1-2γ/kg), be both elevated and lowered, while the intake of oxygen by the heart under these conditions is insignificantly raised. Speaking in behalf of the assumption indicated is the fact that a maximum increase in the intake of

oxygen by the heart under the effect of ephedrine and phenamine is observed at a time when the arterial pressure is already lowered to the original level.

Large doses of adrenaline and noradrenaline produce such an expressed rise in the load of the heart that it must of necessity lead to an increase in the intake of oxygen by the heart. However, an increase in the work of the heart even under the effect of large doses of adrenaline and noradrenaline does not completely explain the rise in the intake of oxygen by the heart muscle. In support of what has been said, tests can be presented where large doses of adrenaline (see Fig. 2), under stabilized arterial pressure, produced an expressed rise in the intake of oxygen by the heart. In the case where large doses of adrenaline and noradrenaline were used, a rise in the intake of oxygen by the myocardium evidently takes place, and also, a subsequent increase in the work of the heart, thanks to the direct effect of phenylalkylamines on the metabolism of the myocardium.

The significant increase in the volumetric rate of coronary blood flow under the administration of small doses of adrenaline and noradrenaline, and, better, of ephedrine and phenamine, results, secondarily, in a rise in the energy requirement of the heart for oxygen. The fact that a rise in the volumetric rate of the coronary blood flow slightly exceeds an increase in the intake of oxygen by the heart under the effect of phenylalkylamines does not contradict the above-stated assumption. It is possible to draw an analogy with dinitrophenol. This substance initially increases the intake of oxygen by the heart, which proceeds to an expressed increase in the volumetric rate of coronary blood flow. Nevertheless, the increase in the volumetric rate of blood flow under the effect of dinitrophenol exceeds, by a little, the rise in the intake of oxygen by the myocardium, as a result of which the content of oxyhemoglobin in the blood of the coronary sinus is insignificantly raised [4]. Testimony in support of the assumption that phenylalkylamines do not have a direct vasodilating effect on the coronary vessels, is available in the research of N. V. Kaverina [2] and Berne [6]. These authors showed that in a large mass of work on the perfusion of coronary vessels, adrenaline does not cause them to dilate, since the demand of the heart for oxygen is supplied in excess.

It is interesting that the authors named [2, 6], who employed perfusion apparatus in their work, discovered a brief vasoconstricting phase in the adrenaline effect, and this preceded the dilation of the coronary vessels. They consider this phase to be the result of a direct effect of adrenaline on the heart vessels. At the same time, the brief vasoconstricting phase does not appear in the recording of the outflow of blood from the coronary sinus. It is best masked, under these experimental conditions, by the hemodynamic changes.

SUMMARY

Investigations were carried out on anesthetized cats. The blood outflow volume velocity from the coronary sinus was registered. Simultaneously a photometric recording was made of the cardiac oxygen intake. As shown, adrenaline and noradrenaline caused a marked but brief increase of the coronary blood flow velocity. The effect of ephedrine and phenamine (benzedrine) on the cardiac blood supply was less pronounced than that of adrenaline and noradrenaline but more lasting. The rise of the coronary blood flow volume velocity under the effect of the substances investigated parallels the intensified oxygen absorption by the heart. A rise of cardiac loading under the effect of phenylalkylamines is not completely attributable to the increased oxygen absorption by the heart.

LITERATURE CITED

1. N. V. Kaverina, Farmakol. i Toksikol., No. 1 (1958), p. 39.
2. N. V. Kaverina, and G. F. Kareva, Farmakol. i Toksikol., No. 6 (1960), p. 516.
3. I. Ye. Kisin, Byull. Éksper., Biol. i Med., No. 3 (1959), p. 117.
4. I. Ye. Kisin, Farmakol. i Toksikol., No. 3 (1961), p. 297.
5. I. Ye. Kisin, and V. L. Tsaturov, Byull. Éksper. Biol. i Med., No. 8 (1960), p. 118.
6. R. Berne, Circulat. Res., 6 (1958), p. 644.
7. L. Binet, and M. Burstein, Presse Méd., 61 (1953), p. 1703.
8. H. Feinberg, and L. N. Katz, Am. J. Physiol., 193 (1958), p. 151.
9. Kl. Gollwitzer-Meier, and E. Witzleb, Pflüg. Arch. Ges. Physiol., No. 255 (1952), p. 469.
10. E. J. Leyko, Pharmacol. Exp. Ther., 38 (1930), p. 31.
11. B. Narayana, C. R. Soc. Biol., 114 (1933), p. 550.
12. W. Raab, Ann. N. Y. Acad. Sci., 64 (1956), p. 528.