EFFECTS OF EPINEPHRINE, ACETYLCHOLINE AND VASODILATORS ON THE CORONARY BLOOD FLOW OF ATHEROSCLEROTIC RABBITS

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In the studies on coronary circulation mostly normal animals have been subjected to the experimental investigation. It seems important to investigate the effects of drugs on the coronary vascular bed in animals with atherosclerosis. Rinzler et al. (1) demonstrated that in atherosclerotic rabbits intravenous ergonovine produced electrocardiographic changes characteristic of coronary insufficiency. Further, Karp et al. (2) presented evidence that ergonovine decreased the rate of coronary flow in all atherosclerotic heart, whereas it increased the flow in a majority of the normals.

In the present experiments atherosclerosis was induced by feeding cholesterol in rabbits. The heart isolated from the atherosclerotic rabbits was perfused by using donor animals as described previously (3). Effects of epinephrine, acetylcholine and other drugs on the rate of coronary inflow of the cholesterol-fed rabbit heart were investigated by comparing with those of the normal rabbits.

METHODS

Twenty five adult female rabbits weighing 2.0 to 2.5 kg were divided into two groups. Ten control rabbits were fed commercial rabbit diet of common ration. Fifteen rabbits were kept on the experimental diet containing 0.5% cholesterol. The electrocardiogram was monitored before cholesterol feeding, at the 20th and 32nd week of experimental period. Blood samples were taken every two weeks from the ear vein of the rabbit. Cholesterol level of the whole blood was analyzed as described by Sperry and Webb (4). After 32 weeks of cholesterol feeding the rabbits were sacrificed and their aorta, carotid and renal arteries were removed for the observation of atheromatous lesions.

The heart was isolated and perfused with whole blood supplied by a donor animal. Using the rolling circular manometer system (5) the rate of coronary inflow was continuously recorded on smoked paper with the aid of electrically driven kymograph. Drugs were injected close to the heart into the blood stream through the rubber tubing. The following drugs were used: Acetylcholine, L-epinephrine, isoproterenol (M-isopropylnorepinephrine), ergonovine (ergometrin), chlorpromazine, papaverine, sod. nitrite, caffeine sod. benz., amino-phylline, diuretin (theobromine sod. salicyl.) and corphyllin (dihydroxypropyl theophylline).
After finishing the perfusion experiments, the heart was stored in 10% formalin for microscopic examination. In some rabbits aorta, carotid, renal and cerebral arteries were also examined histologically.

RESULTS

1) Electrocardiographic (ECG) changes

In 8 of 15 experimental rabbits the depression S-T segment was noted which was not seen before the cholesterol feeding (Fig. 1). Three of them showed inversion of the T wave and one, extrasystoles. No appreciable changes were found in the ECG of the other rabbits.

2) Blood cholesterol level

The average value of the whole blood cholesterol level in control group was 87 mg/dL. It was markedly elevated in the experimental group showing 647 mg/dL at the 14th week of cholesterol feeding.

3) Effects of epinephrine and isoproterenol

The response to epinephrine of the atherosclerotic coronary vascular bed was demonstrated in three types: An increase (26%), a decrease (39%, Fig. 2) and a decrease followed by an increase (35%) of the coronary blood flow. Such types of response were also found in control rabbits, however, the significant difference between them lies in the fact that the decrease of flow, indicating vasoconstriction, caused by epinephrine was observed in the atherosclerotic heart (74%) with greater frequency than in controls (50%). Following injection of isoproterenol (0.01-1.0 μg) the
coronary blood flow decreased in some atherosclerotic rabbits while it increased in all of
the control rabbits (Fig. 2).

4) Effect of acetylcholine

Acetylcholine (0.1–10 μg) produced an invariable increase of coronary flow in the
atherosclerotic rabbits as well as in the controls (Fig. 3). The response of the atheroscle-
rotic coronary vascular bed to acetylcholine appears to be similar to that of the controls.

5) Effect of ergonovine

Following the injection of ergonovine maleate (0.05–0.1 mg) a consistent increase in the
coronary flow was found in controls. Similarly in atherosclerotic rabbits, the drug also
produced an increase of coronary flow except for one very slight decrease caused by 0.05
mg of ergonovine (Fig. 4).

6) Effects of coronary vasodilators

Chlorpromazine, papaverine, sod. nitrite, caffeine, aminophylline, diuretin and corphyl-
lin produced an increase of coronary flow in controls. As can be seen in Fig. 2, 3, 5 and
6, a significant increase of coronary blood flow was demonstrated uniformly by these drugs in rabbits with atherosclerosis. The vasodilator action of the drugs was also observed even in the coronary vascular bed of the heart whose ECG showed depression of the S-T segment and inversion of the T wave.

![FIG. 5. The records are similarly arranged as Fig. 2. A: 2.0 mg of caffeine sod. benz., B: 0.5 mg of papaverine, and C: 1.5 mg of aminophylline.]

![FIG. 6. The records are similarly arranged as Fig. 2. A: 2.0 mg of diuretin, and B: 15 mg of corphyllin.]

7) Histologic examination

Atherosclerotic lesions were found in aorta and coronary arteries in all of the cholesterol-fed rabbits. Some of the renal and common carotid arteries also revealed atherosclerotic lesions. However, in the cerebral arteries there were no atheromatous changes.

DISCUSSION

The electrocardiographic observations of rabbits with experimental atherosclerosis have been made by other workers. Franco (6) showed modifications of the ECG in rabbits submitted to 1.5 g of cholesterol daily for 48 to 194 days.

Matsumoto (7) found a definite abnormality of ECG in rabbits fed lanolin for 40 to 45 weeks. In the present experiments alterations of ECG were observed in 8 of 15 rabbits.
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kept on cholesterol diet for 32 weeks. Although the ECG of normal rabbits shows spontaneous variations, it is evident that the ECG of the experimental atherosclerotic hearts exhibits depression of the S-T segment and inversion of the T wave indicating myocardial lesions.

Effects of epinephrine on the coronary blood flow have been extensively studied in normal rabbits (8). We have previously presented a paper dealing with the effects of the drug on the coronary flow of the isolated perfused cat heart (9). The results obtained in the present studies indicated some similarity to those seen in cats. The difference between normal and atherosclerotic rabbits is in the finding that any decrease of the coronary blood flow due to epinephrine was more frequently observed in the latter than in the former. Thus, it can be assumed that the atherosclerotic coronary vascular bed tends to respond more to epinephrine by vasoconstriction. Levine et al. (10) presented evidence that epinephrine provoked angina pectoris in patients with coronary atherosclerosis. The factors responsible for this finding may not only be a relative coronary insufficiency caused by increased work load of the heart due to epinephrine, but also to a direct vasoconstrictor action of the drug involved.

The vasoconstrictor response to ergonovine of the atherosclerotic coronary bed described by Karp et al. (2) could not be demonstrated uniformly in the present studies. More advanced stages of atherosclerosis seem to be necessary to produce such a response to ergonovine.

The vasodilator activity of acetylcholine, chlorpromazine, papaverine, sod. nitrite and some xanthine derivatives was demonstrated in the coronary vascular bed with atherosclerosis almost to the same extent as noted in normals. This fact may be of significance in the treatment of coronary atherosclerosis by using coronary vasodilators listed above.

SUMMARY

Experimental atherosclerosis was induced by feeding cholesterol in rabbits. The ECG was monitored before and after the rabbits were kept on cholesterol diet for 20 and 32 weeks. The isolated heart of rabbits with cholesterol-induced atherosclerosis was perfused with use of donor animals and the coronary inflow was measured by the rolling circular manometer system. The effects of drugs on the atherosclerotic coronary bed were compared with those in the normals.

The abnormality in the ECG was observed in 8 of 15 cholesterol-fed rabbits. Atherosclerotic lesions were found in all of the coronary arteries and the aortae, and some of the common carotid and renal, but not in the cerebral arteries.

Epinephrine decreased the coronary blood flow in 74% of the atherosclerotic rabbits, whereas it showed a decrease in 50% of the controls. The response to ergonovine of the atherosclerotic coronary bed was an increase of flow except for one very slight decrease. The vasodilator activity of acetylcholine, chlorpromazine, papaverine, sod. nitrite and some xanthine derivatives was invariably demonstrated in those hearts showing alterations in
the ECG tracings and associated with marked atheromatous changes as shown by histologic examination.

REFERENCES


