

## THE EFFECT OF SOME GANGLION-BLOCKING SUBSTANCES ON THE CORONARY CIRCULATION

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Substances which block transmission of excitation in autonomic ganglia are now widely used for the treatment of hypertensive disease and disorders of peripheral circulation. In view of the fact that treatment of hypertensive disease is complicated, in most cases, by manifestations of angina pectoris it is important that in the clinical use of hypotensive substances their influence on blood supply of the heart be taken into due consideration.

At the same time the abundant literature dealing with the pharmacology of ganglion-blocking substances lacks detailed data on the influence of these preparations on coronary circulation.

Investigations devoted to the study of ganglion-blocking agents and their action on the cardio-vascular system are mainly concerned with their hypotensive effect. References made in some papers to the effect of tetrammonium and hexonium on the blood supply of the heart [7, 12] do not give a sufficiently full idea of the action of these substances. A few papers contain information about the influence of the substances mentioned on cardiac activity; minute volume and circulation in certain vascular areas [3, 4, 5, 8, 11]. Similarly few and contradictory are data on the results of using ganglion blocking agents in angina pectoris [1, 2, 6].

The aim of the present work was to study the effect of a series of ganglion-blocking substances on the coronary circulation. Four preparations were selected for investigation: tetrammonium, hexonium, pentamine and a new ganglion blocking substance – mecamine.\*

### EXPERIMENTAL METHODS

Experiments were performed on cats under urethane and chloralose anesthesia. The cardiac circulation was judged by the rate of volume output from the coronary sinus.

After opening the chest and instituting artificial respiration a polyethylene catheter was passed through the right auricle into the ostium of the coronary sinus. Coagulation of the blood was prevented by heparin (1000-1500 units/kg intravenously). The polyethylene catheter was connected by a system of rubber tubes with

\* Mecamine (corresponding to mevasine) – 3-methylaminoisocamphane hydrochloride – was synthesized at the Institute of Pharmacology and Chemotherapy, AMN SSSR by A. Ya. Khorlin. Detailed pharmacologic studies on this compound were carried out by Yu. V. Uranov (1957).

a special apparatus for recording blood flow. A detailed description of the techniques has been reported earlier [3]. The amount of blood output by the cat coronary sinus varies from animal to animal within the range of 5 to 15 ml/min. Blood pressure was recorded from the carotid artery by means of mercury manometer.

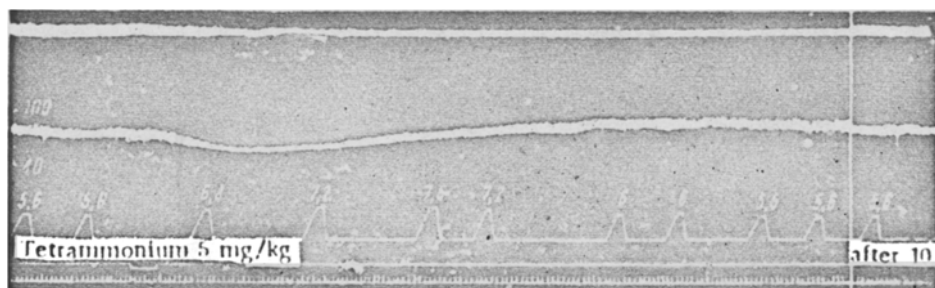


Fig. 1. The effect of tetrammonium on the rate of volume output from the cat coronary sinus. Records from above down: amplitude of cardiac contractions, blood pressure, blood output (in ml/min), administration of the substances, time marker (5 seconds). The height of the deflections corresponds to the rate of volume output of blood over 15 seconds. Figures above the deflections – volume of blood flow per minute.

In a number of experiments the amplitude of cardiac contractions was recorded with the help of a myocardiograph with pneumatic transmission. The preparations under investigation were administered intravenously.

#### EXPERIMENTAL RESULTS

The experiments showed that tetrammonium in doses of 2-3 mg/kg increased the coronary sinus blood output by 8-10% as compared with the initial level. It increased the output by 25-30% in cases where the initial values of the rate of blood flow were low (5-6 ml/min). Increasing the doses of tetrammonium to 5-10 mg/kg led to an increase of output by 40-60% in relation to the initial level (Fig. 1).

Tetrammonium thus possesses the ability to increase the rate of coronary blood flow. Its effect increases with increasing doses. However, depending on the initial state of blood supply to the heart, analogous doses of tetrammonium may elicit different effects. The increase in blood supply to the heart caused by tetrammonium lasts 10-15 minutes. Even when 10 mg/kg tetrammonium is given the coronary sinus blood output returns to the initial value after 15 minutes.

Administration of tetrammonium was accompanied by falls of blood pressure to different degrees in different animals.

The average fall in blood pressure following administration of 2-5 mg/kg tetrammonium was 15-20 mm Hg and persisted for 12-15 minutes.

It must be noted that tetrammonium decreased the amplitude of cardiac contractions.

If the action of tetrammonium on coronary circulation depends in each case on the state of the blood supply to the heart, then it is even more true of hexonium. As shown by the experiments, in cases in which the values of blood output were medium (7-8 ml/min) hexonium in doses of 2-3 mg/kg increased the rate of blood flow by 25-40% as compared with the initial level. A fall in blood pressure was noted at the same time; the average drop was 20-25 mm Hg and there was a slight diminution in the amplitude of cardiac contractions. In animals with a more vigorous blood supply to the heart muscle (minute blood flow volume – 10-15 ml/min) analogous doses of hexonium led to marked (20-40%) decrease of blood flow rate (Fig. 2). Such dependence of the reaction and its degree is also characteristic for the action of large doses of hexonium (5-7 mg/kg).

Pentamine in doses of 2-3 mg/kg decreased blood output from the coronary sinus. In the presence of adequate blood supply to the heart (output value 10-12 ml/min) the decrease of volume output per minute under the influence of pentamine constituted 40-50% while in cases of lower blood supply (5-6 ml/min) it constituted 15-20%.

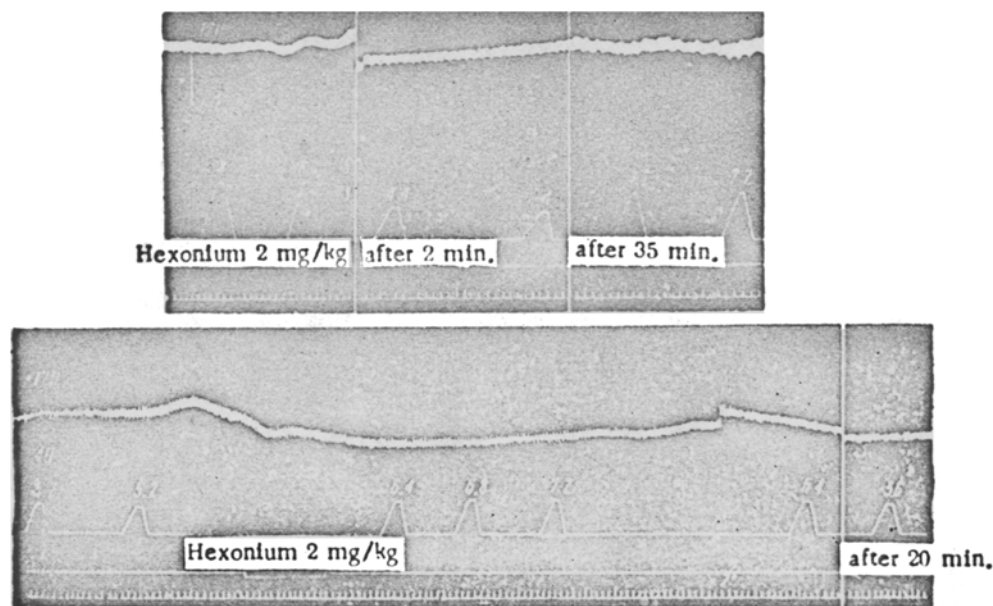


Fig. 2. The effect of hexonium on the rate of volume output from the cat coronary sinus. Top - high values of initial coronary volume output per minute; bottom - low values of initial coronary volume output per minute. Records from above down: blood pressure, blood output (in ml/min), administration of substance, time marker (5 seconds).

Pentamine in doses of 5-7 mg/kg led to less definite decrease of minute blood flow and in some cases, in which the blood supply to the myocardium was lowered, caused its slight increase (by 12-15%).

Administration of pentamine was seen to be accompanied by considerable (20-25 mm Hg) lowering of blood pressure and diminution of amplitude of cardiac contractions.

Changes in the minute coronary blood flow caused by pentamine were observed during 20-30 minutes after which cardiac blood supply became stabilized at the initial level (Fig. 3).

Mecamamine, like pentamine, usually decreased coronary circulation. In doses as low as 0.5-1 mg/kg mecamamine lowered the rate of blood flow by 20-50% compared to the initial level. The action of mecamamine on coronary circulation lasted 20-30 minutes. Variations in the changes elicited by mecamamine were connected with different states of cardiac blood supply in different animals. In cases where the initial values of minute blood volume were low (5-6 ml/min) the latter was slightly (by 12-15%) decreased by mecamamine or, as occurred in a number of cases, no effect on coronary circulation was observed. Unlike the other ganglion-blocking agents investigated, mecamamine, even in large doses (3-5 mg/kg) never led to increased blood output from the coronary sinus. Administration of mecamamine (1-2 mg/kg) was accompanied by a gradually developing, prolonged lowering of blood pressure amounting, on the average, to 20-30 mm Hg.

Mecamamine caused some diminution in the amplitude of cardiac contractions.

The results of these investigations permit the conclusion that changes in coronary circulation elicited by ganglion-blocking substances vary within wide limits.

Variation in the reactions of the vascular system of the heart in response to the administration of ganglion-blocking agents depends in each individual case on the state of blood supply. The value of the initial minute coronary blood flow in many cases determines not only the degree but also the sign of the reaction.

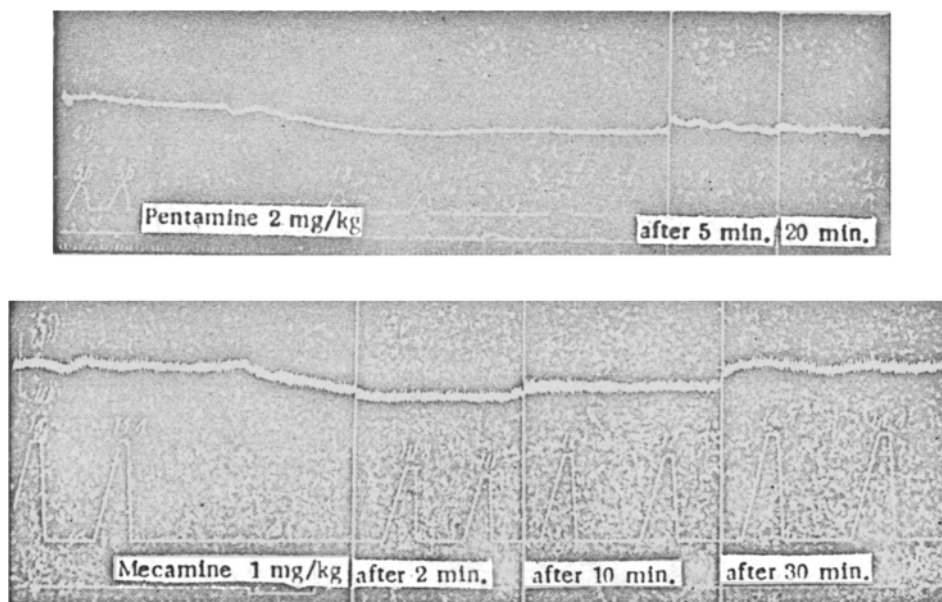


Fig. 3. The effect of pentamine (top figure) and of mecamine (lower figure) on the rate of volume output from cat coronary sinus. Records as in Fig. 1.

Experimental and clinical observations show that the hypotensive action of ganglion-blocking substances is not constant. The intensity of hypotension elicited by them depends on the initial tonus of the vasoconstricting nerves [9, 10]. Our observations indicate that this is evidently also significant for the vascular system of the myocardium.

Among the ganglion-blocking substances investigated tetrammonium gave the most constant increase of coronary circulation. Increase of the minute coronary blood flow is observed upon administration of hexonium if the blood supply to the heart is initially low. Pentamine and mecamine decrease the rate of coronary blood flow in most cases.

The experimental data presented should be taken into account when selecting ganglion-blocking substances for the treatment of hypertensive disease accompanied by impairment of coronary circulation.

### SUMMARY

Acute experiments were performed on cats. The study of the effect of ganglioblockers (tetrammonium, hexonium, pentamine and mecamine) on the blood flow from the coronary sinus was carried out.

The effect of these substances on the coronary circulation is variable and depends on the initial conditions of the blood supply of the heart.

Tetrammonium in the dose of 2-10 mg per kg of body weight increases the blood flow from the coronary sinus by 10-40%. Hexonium (2-5 mg per kilogram) increases the blood flow from the coronary sinus by 25-40% in case of the average and low, initial values of the volume of the blood flow per minute. Hexonium in the above dose causes decrease of the volume velocity of the coronary blood flow by 20-40% in animals with intensive myocardial blood supply.

In majority of cases pentamine in the dose of 2-5 mg per kilogram of body weight and mecamine in the dose of 0.5-2 mg per kilogram cause decreased blood flow from the coronary sinus.

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\* Original Russian pagination. See C. B. Translation.

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