EFFECT OF NONACHLAZINE AND OXYFEDRINE ON THE CORONARY BLOOD FLOW IN DOGS

N. V. Kaverina, G. G. Chichkanov, V. B. Chumburidze, and D. D. Matsievskii

UDC 612.172.1.014:46-088.2:534.8

The coronary blood flow in anesthetized and unanesthetized dogs was measured by means of an ultrasonic Doppler radiotelemetric apparatus. The ultrasonic transducer was placed on the upper third of the descending branch of the left coronary artery. Nonachlazine was shown to increase the coronary blood flow considerably in both anesthetized and unanesthetized dogs. However, the action of the substance lasted only 2-3 min and depended on changes in cardiac activity. Oxyfedrine increased the coronary blood flow by a lesser degree than nonachlazine but for a longer time (mean 20 min). Considering the high effectiveness of the two substances in clinical practice the authors conclude that the increase in the coronary blood flow is not the main course of action when attempting to obtain an antianginal effect in patients with ischemic heart disease.

KEY WORDS: coronary blood flow; nonachlazine; oxyfedrine; antianginal effect.

In experiments on anesthetized cats in which the outflow of blood from the coronary sinus was recorded it was shown that nonachlazine and oxyfedrine increase the volume velocity of the coronary blood flow [2]. Since different species of animals may differ in their reactivity to the same pharmacological agents, it is interesting to study the effect of these drugs on the coronary blood flow in dogs.

Since the coronary blood flow can be recorded by the ultrasonic method in unanesthetized animals, one object of the investigation was to study the effect of nonachlazine and oxyfedrine on the coronary blood flow in dogs under free behavior conditions.

EXPERIMENTAL METHOD

The coronary blood flow was measured by means of a Doppler radiotelemetric apparatus [4, 6]. Ultrasonic transducers of the coronary blood flow were made in the form of a removable bandage of small size and not exceeding 1.5-2 g in weight. By means of a thin elastic guide 0.7 mm in diameter the transducer could be placed in any position on the surface of the heart without deforming the blood vessel. The ultrasonic instrument measures the linear and volume velocities of the blood flow and emits two signals: the phasic blood flow and its mean value with a time constant of integration of 2.5 sec. These signals were led to a recorder and also to a monitor for visual observation. A Mingograph-81 apparatus was used as the recorder. The velocity of the blood flow was recorded on magnetic tape throughout the experiment. The ultrasonic transducers were calibrated on a hydraulic test bench and in experiments on animals. On the test bench the operation of the transducers was studied in pulsating flows by means of a Pitot's tube [5]. In the experiments on dogs the transducers of the telemetric apparatus were implanted on the carotid artery, the descending part of the arch of the aorta, and the abdominal aorta. To compare the results of the measurements, transducers of a pulsed ultrasonic flowmeter were placed alongside on the vessel [1, 3]. Particular attention was paid to accuracy of measurement of the phasic blood flow (Fig. 1).

Laboratory of Pharmacology of the Cardiovascular System, Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR V. V. Zakusov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 83, No. 1, pp. 34-38, January, 1977. Original article submitted July 9, 1976.

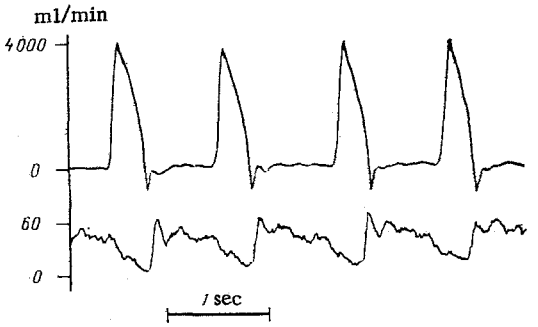

Fig. 1. Measurement of blood flow in dog by the ultrasonic method. Above: phasic blood flow in ascending arch of aorta; below: phasic blood flow in descending branch of left coronary artery. Curve of coronary blood flow characterized by a sharp rise of flow at beginning of diastole and considerable fall during systole.

Acute experiments were carried out on mongrel dogs weighing 13-20 kg anesthetized with urethane (600 mg/kg) and chloralose (40 mg/kg). Under artificial ventilation the thorax was opened in the fourth left intercostal space and the pericardium was divided. The ultrasonic transducer was placed on the upper third of the descending branch of the left coronary artery. The pressure in the aorta, the ECG in standard lead II, and the heart rate also were recorded. The volume velocity of the coronary blood flow also was recorded in the dog while behaving freely. For this purpose the ultrasonic transducer was implanted on the descending branch of the left coronary artery of the animal under pentobarbital anesthesia (40 mg/kg). A polyethylene catheter was introduced into the jugular vein for injection of the substances. The blood flow was recorded radiotelemetrically on the 7th day after the operation. The substances were injected intravenously: nonachlazine in doses of 1, 3, 5, and 6 mg/kg and oxyfedrine in doses of 0.3, 0.5, and 1 mg/kg.

EXPERIMENTAL RESULTS AND DISCUSSION

In doses of 1 and 3 mg/kg nonachlazine had no significant effect on the volume velocity of the coronary blood flow in anesthetized dogs. In a dose of 5-6 mg/kg it increased the coronary blood flow (in nine experiments by an average of 63 ± 5.8%). This effect was observed during injection of the drug and it continued for only 2-3 min. Meanwhile the aortic pressure fell very slightly (on average by 6 ± 0.7%) with no significant change in the heart rate. Later the aortic pressure increased by 15-20 mm Hg compared with initially, the bradycardia increased, but the coronary blood flow decreased (on average by 22.5 ± 2.8%). For 25-30 min the aortic pressure, pulse rate, and coronary blood flow gradually returned to their initial levels (Fig. 2A).

To ascertain the cause of the bradycardia and the decrease in the coronary blood flow a special series of experiments was carried out (on five animals) with bilateral division of the vagus nerve trunks. Under these conditions nonachlazine, while increasing the aortic pressure, did not slow the heart rate and did not induce a phase of decrease in the volume velocity of the coronary blood flow. After a brief increase (3 min) the coronary blood flow returned to its initial level or only a little above it (Fig. 2B). In anesthetized dogs nonachlazine thus causes only a transient increase in the coronary blood flow. Similar results were obtained in three experiments on an unanesthetized dog under free behavior conditions (Fig. 2C).

Oxyfedrine, in doses of 0.3 and 0.5 mg/kg, led to an increase in the volume velocity of the corondary blood flow (on average by 61.2 ± 3.8%) in the anesthetized dogs (six experiments). This effect was accompanied by a very small decrease in the aortic pressure (on average by 7.2 ± 1.8%) (Fig. 3A). With an increase in the dose of the drug to 1 mg/kg the hypotension was more marked (on average by 23 ± 3.2%) and the increase in the volume velocity of the coronary blood flow amounted to 36 ± 4.1%. In a dose of 0.5 mg/kg, besides increasing the coronary blood flow oxyfedrine also caused a marked increase in the heart rate (on average by 14 ± 2.8%). This effect of the drug was evidently due to stimulation of the β adrenoreceptors of the myocardium, for it was completely abolished after preliminary injection of practolol, a selective β blocker (Fig. 3B). Unlike nonachlazine, oxyfedrine gave a prolonged increase of the coronary blood flow. On average the action of the drug lasted 20 min. It is important to note that the effect of oxyfedrine on the volume velocity of the coronary blood flow in the dog behaving freely was indistinguishable from its action on anesthetized animals (Fig. 3C).

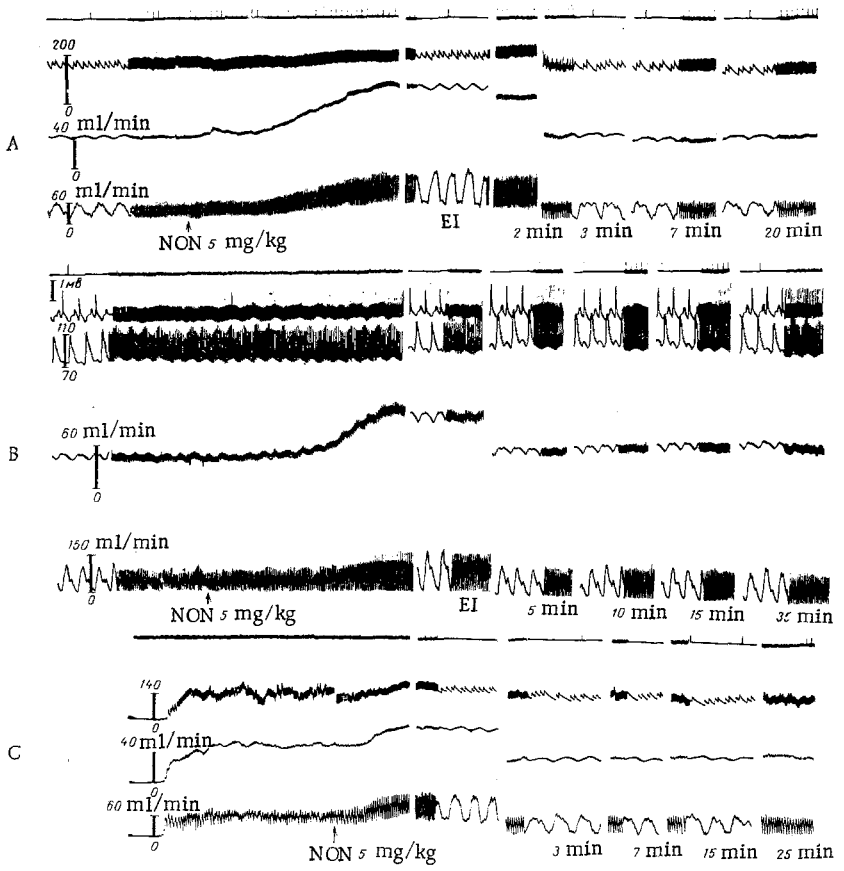

Fig. 2. Effect of nonachlazine on coronary blood flow and indices of hemodynamics. A) Change in coronary blood flow and heart rate of anesthetized dog produced by nonachlazine. From top to bottom: time marker, heart rate, averaged blood flow in coronary artery, phasic blood flow in coronary artery, marker of injection of drug. From left to right: background and injection of nonachlazine (NON), end of injection (EI), and 2, 3, 7, and 20 min after injection. B) Change in coronary blood flow and hemodynamics produced by nonachlazine in anesthetized dog after preliminary vagotomy. From top to bottom: time marker, ECG in standard lead II, aortic pressure, averaged blood flow in coronary artery, phasic blood flow in coronary artery, marker of injection of drug. C) Change in coronary blood flow and heart rate produced by nonachlazine in freely behaving dog. From top to bottom: time marker, heart rate, averaged blood flow in coronary artery, phasic blood flow in coronary artery, marker of injection of drug.

In experiments on anesthetized cats the writers showed previously that oxyfedrine increases the blood flow in the vessels of the heart by 43.6 ± 2.8%. The action of the drug continues for 15-20 min. Nonachlazine differed from oxyfedrine in increasing the coronary blood flow for 3-5 min on average by 69.7 ± 5.4%, and for the next 15-20 min the mean increase in the coronary blood flow was only 25.2 ± 3.3%. It is important to note that in the experiments on cats the changes in the coronary blood flow under the influence of nonachlazine fluctuated significantly from one experiment to the next (from a maximal increase of 120% compared with the initial value to a minimal increase of 31%). When the results are examined it will be noted that there was a difference in the intensity of the effect of nonachlazine on the coronary blood flow in the experiments on cats and dogs and also that there was no parallel between the action of the two drugs on the coronary blood flow and their clinical effectiveness.

The differences in the responses of cats and dogs to nonachlazine is evidently connected with predominance of sympathetic tone in cats compared with dogs. This view is confirmed by experiments on vagotomized dogs.

If the action of nonachlazine and oxyfedrine on the volume velocity of the coronary blood flow is compared with the analogous effect of such commonly used antianginal drugs as cordaron and intensain, the former can be seen to give effects of much lower intensity and shorter duration than the latter. Nevertheless, clinical investigations have shown that nonachlazine and oxyfedrine are highly effective in the treatment of patients with

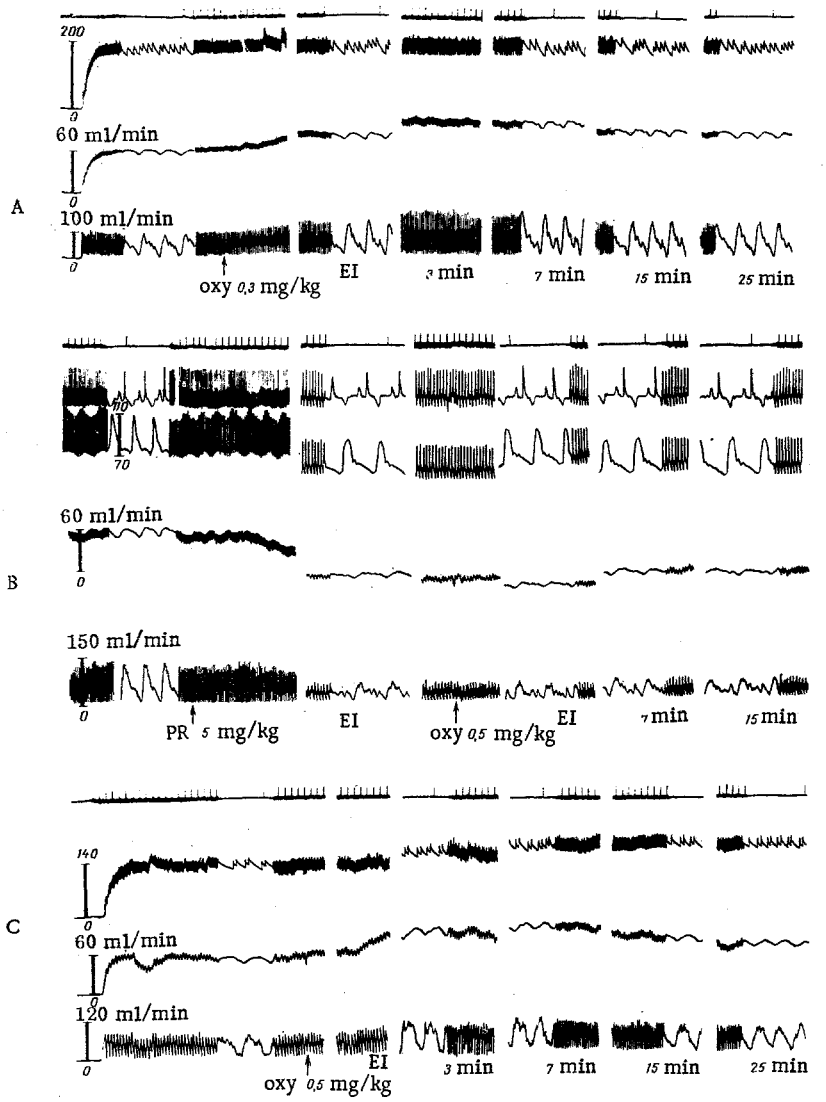

Fig. 3. Effect of oxyfedrine on coronary blood flow and hemodynamic indices. A) Change in coronary blood flow and heart rate produced by oxyfedrine in anesthetized dog. From top to bottom: time marker, heart rate, averaged blood flow in coronary artery, phasic blood flow in coronary artery, marker of injection of drug. From left to right: background and injection of oxyfedrine (OXY), end of injection (EI), and 3, 7, 15, and 25 min after injection of drug. B) Change in coronary blood flow produced by oxyfedrine in anesthetized dog after preliminary injection of practolol (PR). From top to bottom: time marker, ECG in standard lead II, aortic pressure, averaged blood flow in coronary artery, phasic blood flow in coronary artery, marker of injection of drug. C) Change in coronary blood flow and heart rate produced by oxyfedrine in freely moving dog. From top to bottom: time marker, heart rate, averaged blood flow in coronary artery, phasic blood flow in coronary artery, marker of injection of oxyfedrine.

ischemic heart disease. Consequently, the high effectiveness of these two drugs in clinical practice cannot be attributed entirely to their effect on the volume velocity of the coronary blood flow. An important role in the development of the antianginal effect of the drugs is evidently played by their ability to act on the metabolism and contractile function of the myocardium [7, 8].

The question of the re-evaluating role of the increase in the coronary blood flow as a basic test in the program of screening antianginal drugs accordingly arises.

LITERATURE CITED

1. A. A. Vishnevskii, A. M. Chernukh, Yu. D. Volynskii, et al., Éksp. Khir., No. 4, 6 (1968).
2. N. V. Kaverina, R. Griglevskii, A. N. Basaeva, et al., Byull. Éksp. Biol. Med., No. 11, 48 (1975).
3. D. D. Matsievskii, Byull. Éksp. Biol. Med., No. 10, 123-125 (1965).
4. D. D. Matsievskii, Byull. Éksp. Biol. Med., No. 9, 119-121 (1970).
5. D. D. Matsievskii and V. S. Sinyakov, in: Physiological Scientific Instrumentation [in Russian], Moscow (1971), pp. 12-14.
6. D. D. Matsievskii, in: The Technique of Biological Telemetry and Its Application in Biology and Medicine [in Russian], Moscow (1972), pp. 202-205.
7. H. Kammermeier, R. Bünger, V. Ziegler, et al., in: Action of Oxyfedrine (ed. by E. Gerlach and K. Moser), Stuttgart (1972), pp. 53-64.
8. W. R. Kukovetz and G. Poch, in: Action of Oxyfedrine (ed. by E. Gerlach and K. Moser), Stuttgart (1972), pp. 95-105.

AGGRAVATION OF INJURY TO LIVER LYSOSOMES OF RATS WITH CCl_4 HEPATITIS BY PRELIMINARY PROLONGED ADMINISTRATION OF CHLORPROMAZINE

T. A. Korolenko, E. I. Tsilli, T. V. Rusova, T. N. Tsytsorina, and G. S. Yakobson

UDC 616.36-002-099-092.9-07: 616.36-091.8-02:615.214.22

Preliminary prolonged administration of chlorpromazine (5 mg/kg for three weeks) aggravated the injury to liver lysosomes of rats with acute CCl_4 hepatitis. Similar marked changes were observed in lysosomes sedimented with "heavy" and "light" mitochondrial fractions.

KEY WORDS: heterogeneity of liver lysosomes; toxic hepatitis; chlorpromazine.

The developmental disturbances of liver function during chlorpromazine therapy suggests that this drug is a hepatotropic substance, with an effect at the cellular and ultrastructural levels [8, 10, 12]. During repeated administration of chlorpromazine, the drug remains for a long time in the liver and brain [12] and it probably accumulates in the lysosomes, subcellular structures capable of accumulating various cationic substances [11]. The changes in the properties of the lysosomes taking place under these circumstances, it can tentatively be suggested, may aggravate the injury to the liver caused by other factors.

In this investigation the degree of changes in the liver lysosomes was assessed in rats with CCl_4 hepatitis developing after preliminary administration of chlorpromazine. Considering that the formation of acute toxic hepatitis is accompanied by an increase in the specific acid hydrolase activity of the "heavy" mitochondria [1], a separate study was made of the integrity and vulnerability of the lysosomes sedimented with the "light" and "heavy" mitochondrial fractions.

EXPERIMENTAL METHOD

Experiments were carried out on 60 male Wistar rats weighing 150-180 g. Acute toxic hepatitis was induced by intraventricular injection of CCl_4 in a dose of 0.15 ml/100 g body weight. The animals were killed 24 h later. Chlorpromazine was injected subcutaneously in a dose of 5 mg/kg daily for three weeks and the

Central Scientific-Research Laboratory and Department of Psychiatry, Novosibirsk Medical Institute.

(Presented by Academician of the Academy of Medical Sciences of the USSR V. P. Kaznacheev.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 83, No. 1, pp. 38-41, January, 1977. Original article submitted June 22, 1976.