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EFFECT OF TRANQUILIZERS OF THE BENZODIAZEPINE SERIES ON A FOCUS
OF ISCHEMIA AND REDISTRIBUTION OF THE BLOOD FLOW
IN THE ISCHEMIC MYOCARDIUM

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Tranquilizers of the benzodiazepine series (diazepam and chlordiazepoxide) are widely used in the combined treatment of ischemic heart disease (IHD). These drugs abolish autonomic components of emotional reactions, including tachycardia and high blood pressure (BP), which are risk factors in IHD, and they strengthen cardiac activity. The aim of this investigation was to study the direct effect of tranquilizers on the functional state of the ischemic myocardium and its blood supply.

EXPERIMENTAL METHOD

A model of acute coronary insufficiency [8] in the authors' modification [6] was used. The essence of the model was creation of an ischemic focus in the myocardium of dogs by simultaneous narrowing of the lumen of the anterior descending branch of the left coronary artery and imposition of a high artificial rhythm on the heart. The degree of ischemia was judged from elevation of the ST segment in the epicardial electrogram. To judge the effect of drugs on the blood supply to the ischemic focus in the myocardium, the method of alternate recording of the retrograde coronary blood flow and retrograde pressure in the distal segment of the anterior descending branch of the left coronary artery, ligated in its middle third, in dogs was used [1, 4]. Redistribution of the blood flow in the heart muscle was judged from the ratio of retrograde coronary blood flow in the territory supplied by the ligated coronary artery and the coronary blood flow in the circumflex branch of the left coronary artery, supplying blood to intact regions of the myocardium (RBF/CBF) [7, 9]. For this purpose, simultaneously with recording the retrograde blood supply to the ischemic focus, the volume velocity of the coronary blood flow in the circumflex branch of the left coronary artery was measured by an ultrasonic method in the coronary arteries [3]. Experiments were carried out on mongrel dogs (15 animals), anesthetized with pentobarbital (40 mg/kg, intravenously), with artificial respiration. Systemic BP (in the carotid artery), the velocity of the coronary blood flow in the circumflex branch of the left coronary artery, and retrograde pressure in the territory of the ligated coronary artery were recorded on the Mingograph-81 apparatus. Drugs were injected intravenously: diazepam in doses of 0.1 and 0.3 mg/kg, chlordiazepoxide in a dose of 1 mg/kg.

EXPERIMENTAL RESULTS

It was shown previously [2, 5] that diazepam and chlordiazepoxide have a marked effect on the blood supply and activity of the intact myocardium. The marked increase in oxyhemoglobin concentration in blood from the coronary sinus of the heart under the influence of the drugs, despite a decrease in volume velocity of the total coronary blood flow, is a noteworthy

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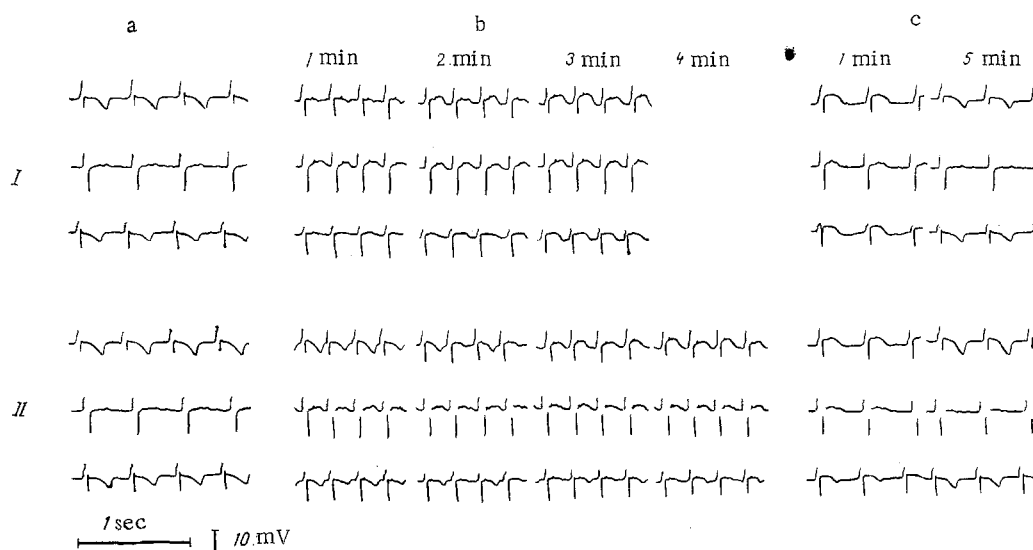


Fig. 1. Effect of diazepam (0.3 mg/kg, intravenously) on functional state of focus of myocardial ischemia. I) Three derivations of epicardial electrogram recorded from myocardial zone in which ischemic changes (elevation of ST segment) appeared during stimulation; II) same derivations 15 min after injection of drug. a) Control; b) during stimulation (end of 1st, 2nd, 3rd, and 4th minutes); c) recovery (end of 1st and 5th minutes) after end of stimulation.

TABLE 1. Effect of Chlordiazepoxide (1 mg/kg, intravenously) on Blood Supply to Focus of Ischemia and on Redistribution of Blood Flow in Acute Myocardial Ischemia ($M \pm m$; $n = 5$)

Parameter measured	Control, absolute values	Change in parameters, % of initial level		
		time of investigation, min		
		5	15	40
BP	103.7 ± 2.3	$-6.0 \pm 1.0^{**}$	$-8.5 \pm 1.1^{**}$	$-11.5 \pm 3.3^*$
RP	31.25 ± 3.1	-5.4 ± 2.0	-7.1 ± 3.5	-7.7 ± 5.7
CBF	27.6 ± 3.7	$-12.3 \pm 4.4^*$	$-12.3 \pm 4.4^*$	-9.15 ± 7.5
RBF	2.5 ± 0.2	0	-3.7 ± 2.3	-5.4 ± 3.1
HR, beats/min	151.7 ± 9.9	$-7.7 \pm 1.3^{**}$	$-7.1 \pm 1.8^*$	-7.5 ± 3.0
RBF/CBF ($\cdot 100$)		$+14.7 \pm 4.5^*$	$+9.6 \pm 5.9$	$+9.4 \pm 6.0$

Legend. Here and in Table 2: BP) systemic blood pressure in carotid artery (in mm Hg); RP) retrograde arterial pressure (in mm Hg); CBF) volume velocity of coronary blood flow in circumflex branch of left coronary artery (in ml/min); RBF) volume velocity of retrograde coronary blood flow in distal segment of ligated descending branch of left coronary artery (in ml/min). * $P < 0.05$; ** $P < 0.01$.

TABLE 2. Effect of Different Doses of Diazepam (A, 0.1 mg/kg; B, 0.3 mg/kg, intravenously) on Blood Supply to Ischemic Focus and on Redistribution of Blood Flow under Conditions of Acute Myocardial Ischemia ($M \pm m$, $n = 5$)

Parameter measured	Control, absolute values	Change in parameters, % of initial level		
		time of investigation, min		
		5	15	40
Dose of diazepam 0.1 mg/kg				
BP	98.7 ± 8.4	-12.4 ± 3.0*	-10.6 ± 1.2**	-5.7 ± 2.0*
RP	36.6 ± 3.3	-9.8 ± 3.2*	-4.9 ± 3.0	-4.9 ± 3.0
CBF	31.5 ± 2.1	-14.0 ± 3.0**	-14.0 ± 3.0**	-14.3 ± 3.1**
RBF	2.8 ± 0.2	-6.9 ± 4.9	-3.65 ± 2.1	-2.8 ± 1.8
HR	152.5 ± 17.0	-7.6 ± 1.9	-10.6 ± 2.0**	-10.6 ± 2.0**
RBF/CBF (x100)		+10.7 ± 2.3**	+14.0 ± 6.3	+12.3 ± 5.7
Dose of diazepam 0.3 mg/kg				
BP	97.5 ± 9.4	-18.6 ± 3.9**	-14.0 ± 1.6**	-15.2 ± 2.6**
RP	36.2 ± 2.3	-19.6 ± 8.3	-9.8 ± 6.0	-9.8 ± 6.0
CBF	35.2 ± 1.7	-18.0 ± 6.0*	-20.7 ± 4.5**	-20.7 ± 4.5**
RBF	2.4 ± 0.1	-6.2 ± 3.8	-10.4 ± 3.8*	-8.3 ± 3.8
RBF/CBF (x100)		+15.3 ± 4.8*	+16.2 ± 4.4*	+10.1 ± 2.3*

fact. This may be evidence of a considerable decrease in the oxygen consumption of the myocardium. Taking these data into consideration, the effect of the tranquilizers was studied on the functional state of the ischemic myocardium.

Experiments carried out on a model of acute coronary insufficiency showed that diazepam and chlordiazepoxide, in the doses tested, as a rule did not change the epicardial electrogram (judging from the size of the ST segment) recorded from the ischemic focus during stimulation of the heart compared with the control. The drugs did not worsen the functional state of the focus of myocardial ischemia in any of the experiments. On the contrary, in

some experiments (in two of seven in which diazepam was used, in one of 50 experiments in which chlordiazepoxide was used) they reduced the severity of the ischemic changes, as shown by some decrease in rise of the ST segment during stimulation of the heart or the later appearance of control changes (Fig. 1). These tranquilizers thus had no unfavorable effect on the functional state of the ischemic myocardium.

It was next shown that diazepam and chlordiazepoxide lower the systemic BP, slow the heart rate (HR), and reduce the volume velocity of the coronary blood flow in the circumflex branch of the left coronary artery. These drugs, incidentally, when given in acute myocardial ischemia, lower the retrograde perfusion pressure. This effect was most marked during the first 5 min after injection. Meanwhile, the retrograde coronary blood flow decreased very little under these circumstances, especially if diazepam was injected in a dose of 0.1 mg/kg and when chlordiazepoxide was given (Tables 1 and 2). It is important to note that the retrograde inflow of blood into the zone of ischemia was lowered by a much lesser degree than the velocity of the coronary blood flow in intact zones of the myocardium (the RBF/CBF ratio increased). This means that diazepam and chlordiazepoxide did not induce a redistribution of the blood flow in the myocardium detrimental to the ischemic focus. Although the total coronary blood flow decreased under the influence of the drugs, the ischemic zone received a better blood supply than the intact zones of the heart. This blood supply was evidently adequate if it is recalled that the tranquilizers chosen for study slow the heart, lower BP, and reduce the cardiac output [5]. Other evidence in support of the same conclusion is given by data cited above, obtained in experiments on a model of acute insufficiency of the coronary circulation. The drugs chosen for study, incidentally, resemble to a certain degree in their effects the β -adrenoblocker propranolol, which also reduces the blood flow in intact zones of the myocardium by a much greater degree than the retrograde inflow of blood to the ischemic zone, evidence of a redistribution of the blood flow in favor of the latter [7, 9].

Diazepam and chlordiazepoxide, despite the fall of BP and the decrease in total coronary blood flow produced by them, thus have no unfavorable effect on the functional state of a focus of myocardial ischemia and they induce a redistribution of blood flow in the ischemic heart in favor of the ischemic focus.

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