that these substances cause virtually no change in the magnitude of delayed postdepolarization, but reduce the rate of development of depolarization in phase 4.

Conversely, blockers of the calcium current (verpamil and AHR-2666) reduced the steepness of spontaneous depolarization in this object and inhibited delayed postdepolarization [3]. These facts show that pacemaker activity in pathologically changed human myocardial fibers treated with adrenalin is due at least in part to the i_{s1} current. This conclusion is confirmed also by the results of the present investigation, which show that delayed postdepolarization is accompanied by a mechanical response of the muscle (Fig. 2, traces 1).

Drugs of the phenothiazine series, namely ethmozine and ethacizine, as was shown previously [1], have a TTX-like action: They reduce the fast sodium current [1]. Ethacizine also appreciably reduces i_{s1} [2]. This may be the explanation of the essentially greater effectiveness of ethacizine compared with ethmozine in reducing adrenalin-induced pacemaker activity in human atrial fibers. Ethacizine can simultaneously inhibit delayed postdepolarization and reduce the steepness of spontaneous depolarization. It will also be noted that the effects of ethacizine in partially depolarized fibers may be stronger, and this must also be taken into account, for there is a considerable population of partially depolarized fibers in the pathologically changed human myocardium [7].

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COMPARATIVE STUDY OF THE EFFECT OF ETHACIZINE AND LIDOCAINE ON BLOOD SUPPLY AND FUNCTION OF THE INTACT AND ISCHEMIC MYOCARDIUM

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Improvement of the blood supply and functional state of a focus of myocardial ischemia by the use of antiarrhythmic drugs may be an important mechanism lying at the basis of normalization of the rhythm and of the antianginal action of these drugs. However, until very recently there had been little attempt to study the effect of antiarrhythmics on the ischemic myocardium. This applies also to the new antiarrhythmic drug ethacizine, the diethylamino analog of ethmozine, synthesized in the Institute of Pharmacology, Academy of Medical Sciences of the USSR. Accordingly, in the investigation described below the effect of ethacizine on the blood supply and function of the intact and ischemic myocardium was studied and compared with that of lidocaine, a drug widely used in clinical medicine for the treatment of acute myocardial infarction [1-3, 6, 12].

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TABLE 1. Effect of Ethacizine on Hemodynamics and Activity of Intact Myocardium (M ± m)

Parameter	Dose, mg/kg	Number of animals	Changes, % of initial level, time after injection, min				
			5	15	20	30	45
BP, mm Hg	0,5	6	+6,6±1,9*	+2,8+2,4	—0,1±3,3	—4,3±5,4	—7,5±6,3
	1,0	7	+3,4±3,8	—0,9±4,3	—1,7±5,1	—1,5±6,1	—2,8±10,3
HR, beats/min	0,5	6	+4,3±8,2	+2,8±8,3	±4,4±8,2	+4,2±7,5	+2,8±6,3
	1,0	7	—2,7±3,3	—0,1±3,0	—0,1±3,3	+2,6±3,4	—4,7±4,2
Systolic ejection	0,5	6	—6,1±11,1	—5,7±8,9	—11,9±8,0	—14,7±8,7	—10,3±7,7
	1,0	7	—24,8—9,3*	—15±7,2	—28,2±9,9*	—33,0±8,4*	—36,0±8,4**
Cardiac output	0,5	6	—3,6±9,2	—9,6±3,3*	—10,0±4,1	—14,1±5,5*	—16,6±7,4
	1,0	7	—27,2±9,8*	—16,0±8,9	—27,4±9,6*	—32,9±8,2**	—27,9±10,2*
Mean acceleration of blood flow in aorta	0,5	6	+7,8±7,7	+2,4±5,4	+6,5±8,0	+7,2±11,8	+24,3±12,8
	1,0	7	—6,1±8,9	—4,6±4,9	—4,2±3,9	—5,4±12,4	—4,6±10,6
Work of the heart	0,5	6	+2,9±9,7	+3,2±10,1	—9,8±5,5	—16,7±8,5	—17,0±8,9
	1,0	7	—25,4±9,0*	—18,5±7,1*	—31,3±7,7**	—34,6±8,0**	—36,7±10,8*

Legend. Here and in Table 2: *P < 0.05, **P < 0.01.

TABLE 2. Effect of Lidocaine on Hemodynamics and Activity of Intact Myocardium (M ± m)

Parameter	Dose, mg/kg	n	Changes, % of initial level, time after injection, min				
			5	15	20	30	45
BP, mm Hg	1,0	7	—4,8±3,7	—3,9±3,3	—7,4±3,3	—8,8±2,6*	—16,5±3,6**
	2,0	7	—7,9±3,6	—8,0±1,9**	—5,1±2,8	—5,4±6,0	—17,6±3,5**
HR, beats/min	1,0	7	—3,4±1,2*	—3,3±2,7	—4,7±2,9	—3,9±3,8	—6,6±5,2
	2,0	7	—2,8±1,3	—2,4±2,5	—2,0±2,3.	+0,3±3,2	+0,1±2,4
Systolic ejection	1,0	7	—2,3±4,0	—3,4±2,9	—2,4±3,5	—2,7±4,3	—1,3±6,4
	2,0	7	—3,1±3,0	+0,8±5,8	—2,4±5,2	—4,1±3,9	—9,0±5,9
Cardiac output	1,0	7	—3,6±3,6	—6,6±3,3	—5,4±4,2	—8,9±4,0	—12,5±4,8*
	2,0	7	—5,9±2,4	—2,3±3,3	—3,6±3,8	—3,4±3,3	—10,0±4,6
Mean acceleration of blood flow in aorta	1,0	7	—1,2±5,2	—0,1±5,9	—3,9±7,1	—1,9±13,2	—9,7±8,4
	2,0	7	—2,2±2,4	+6,2±4,1	+3,0±4,0	—2,9±4,2	+10,7±12,7
Work of the heart	1,0	7	—12,2±5,0	—11,1±4,0*	—14,1±5,3*	—17,0±5,0*	—26,1±4,7**
	2,0	7	—13,3±4,4*	—9,8±4,8	—12,0±4,8*	—9,75±8,5	—25,4±5,8**

EXPERIMENTAL METHOD

To study the effect of ethacizine and lidocaine on the blood supply and activity of the intact myocardium four series of experiments were carried out on cats weighing 2.4-4.3 kg, anesthetized with pentobarbital (40 mg/kg, intravenously). The drugs were injected intravenously: ethacizine in doses of 0.5 and 1 mg/kg, lidocaine in doses of 1 and 2 mg/kg. The effect of the drugs on the blood supply to the heart was judged from changes in the velocity of the coronary blood flow, by recording the outflow of blood from the coronary sinus with an intervalograph. Simultanesouly, using a type 036M oxyhemograph, the oxyhemoglobin concentration was determined in the coronary venous blood, so that it was possible to calculate the uptake of oxygen by the intact myocardium. In these same experiments, using an electromagnetic RÉK-1 flowmeter, the blood flow was recorded in the ascending part of the arch of the aorta. The following parameters were calculated: heart rate (HR), systolic ejection and cardiac output, work of the heart, and mean acceleration of the blood flow in the aorta, from which the contractile function of the myocardium was estimated. The blood pressure (BP) was measured in the carotid artery by means of an electromanometer. The parameters of cardiac activity and the hemodynamics and the velocity of the coronary blood flow were recorded on a Mingograf-81 instrument.

To study the effect of ethacizine and lidocaine on the functional state of an ischemic focus in the myocardium experiments were carried out on cats weighing 2.5-3.8 kg, anesthetized with pentobarbital (40 mg/kg, intravenously). Thoracotomy was performed in the 4th and 5th left intercostal spaces. A short length (1-1.5 mm) of a small branch of the descending branch of the left coronary artery was isolated and a special clamp applied to it, so that the lumen of the coronary vessel could be occluded atraumatically and completely. Three or four epicardial electrodes were applied to the area of ichemia. Occlusion of the coronary vessel for 5 min was accompnaied by marked elevation of the ST segment on the epicardial electrogram. Reperfusion led to rapid and complete restoration of the normal electrogram. In the control, the coronary artery was occluded for 5 min 3 times. Reperfusion after each

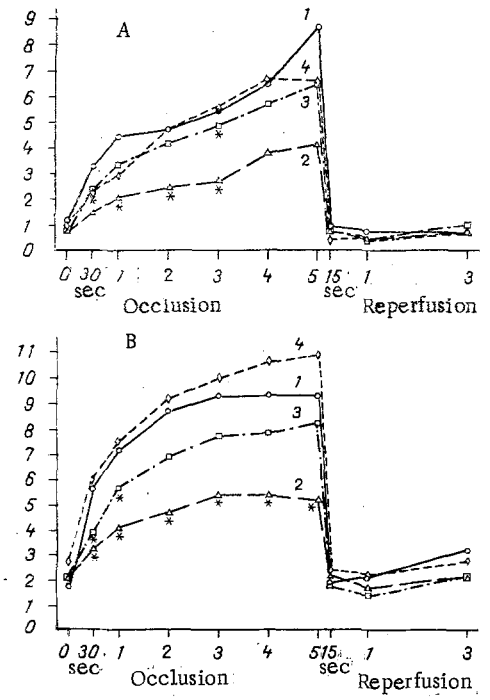

Fig. 1. Effect of ethacizine (A) in a dose of 0.5 mg/kg (intravenously) and of lidocaine (B) in a dose of 2 mg/kg (intravenously) on mean elevation of ST segment of epicardial electrogram during occlusion and reperfusion of coronary vessel (in min); ordinate, mean elevation of ST segement (in mV). 1) Control; 2) immediately after injection; 3) 20 min, 4) 40 min after injection. *P < 0.05.

occlusion continued for 15 min. Ethacizine and lidocaine were injected intravenously in doses of 0.5 and 2 mg/kg respectively. The artery was occluded immediately after injection of the drugs, and also 20, 40, and 60 min after injection. The degree of ischemia was judged by the mean elevation of the ST segment on the electrogram. The model of acute insufficiency of the coronary circulation used in these experiments is a modification of the usual model of coronary insufficienty in dogs, which is widely used to assess the antianginal action of drugs [11].

EXPERIMENTAL RESULTS

The experiments showed that ethacizine in a dose of 0.5 mg/kg, causes virtually no change in the velocity of the coronary blood flow. In the course of 5-10 min the oxyhemoglobin concentration rose in blood from the coronary sinus (on average by 10.4 ± 4.4%). Ethacizine in a dose of 1 mg/kg likewise caused no significant changes in the coronary blood flow during 15-20 min after its injection. A small decrease (on average by 15.5 ± 5.7%; $P < 0.05$) was observed only 20-30 min after injection of the drug. In this dose ethacizine caused a greater (on average by 16.6 ± 3.8%; $P < 0.01$) and more prolonged (up to 15-20 min) increase in the oxyhemoglobin concentration in blood from the coronary sinus, evidence of a significant decrease in oxygen uptake by the heart. Lidocaine, in doses of 1 and 2 mg/kg, reduced the coronary blood flow immediately after injection. This decrease, with the corresponding doses, was 13.5 ± 4.8% ($P < 0.05$) and 25.8 ± 7.4% ($P < 0.05$) 10 min after injection. By comparison with ethacizine, lidocaine led to a less marked and shorter increase in the oxyhemoglobin concentration in the coronary venous blood. The effect of the drug continued for not more than 5-10 min and did not exceed 7.6 ± 3.1%.

Thus if the oxygen consumption of the intact heart is judged by its uptake, it can be concluded that under the influence of ethacizine and lidocaine a definite oxygen reserve is created in the myocardium. Under these circumstances the effect of ethacizine is more marked and prolonged in character.

It must be pointed out that ethacizine has no significant effect on BP, HR, or the contractile function of the myocardium. Lidocaine likewise does not change the contractility of the intact myocardium. However, it induces a small decrease in BP and decreases HR temporarily (Tables 1 and 2).

The drugs also differ in their effect on the systolic ejection and cardiac output. Whereas ethacizine, especially in a dose of 1 mg/kg, reduces them significantly, which leads to a marked decrease in work of the heart, lidocaine reduces the work of the heart by a lesser degree, and mainly on account of a fall in BP. The systolic ejection and cardiac output remained virtually unchanged in this case. In this respect the results agree with observations made by other workers [13].

Considering the results showing the ability of ethacizine and lidocaine to reduce the work of the heart, to create a definite oxygen reserve in the heart muscle, yet at the same time, to have no significant effect on the contractile function of the myocardium, it might be supposed that the drug would have a favorable action on the ischemic myocardium. This may be all the more likely if it is recalled that these antiarrhythmics also have a marked membrane-stabilizing action [4, 5, 14]. By stabilizating cell membranes, and maintaining ionic homeostasis, ethacizine and lidocaine can improve the functional state of the ischemic focus. This point of view with respect to lidocaine has already been confirmed by a number of investigations [7].

Experiments conducted on the model of acute coronary insufficiency showed that ethacizine and lidocaine do in fact significantly increase the resistance of the myocardium to hypoxia and improve the functional state of the ischemic focus. The drugs considerably reduce the average elevation of the ST segment on the electrogram during coronary arterial occlusion. This effect was particularly marked immediately after injection of the drugs (Fig. 1). Incidentally the action of ethacizine is much more prolonged than that of lidocaine. Occlusion of the coronary artery 40 min after injection of lidocaine as a rule induced control changes in the electrogram. Ethacizine still gave an effect at this time, but control changes in the ST segment were not observed until 60 min after injection of the drug.

The degree of elevation of the ST segment on the epicardial electrogram is known to be a reliable indicator of the severity of ischemic damage to the myocardium [8, 10]. With this in mind, and also on the basis of the results of the present investigation, it can be concluded that ethacizine and lidocaine can improve the functional state of an ischemic focus in the myocardium.

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