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REDISTRIBUTION OF THE BLOOD FLOW IN HEART MUSCLE DURING CHRONIC ISCHEMIA UNDER THE INFLUENCE OF DRUGS

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Redistribution of the blood flow in the ischemic heart muscle under the influence of drugs plays an important, and at times decisive, role in the mechanism of their antiischemic (antianginal) action [3, 7, 8]. However, until very recently this problem still remained inadequately studied.

The aim of this investigation was to study the effect of certain drugs with antiischemic action, namely the β-adrenoblocker propranolol, the calcium antagonist diltiazem, the antihypoxic agents sodium and lithium hydroxybutyrate — on the redistribution of the blood flow in the ischemic heart muscle in the presence of a developed collateral circulation.

EXPERIMENTAL METHOD

Experiments were carried out on mongrel male and female dogs weighing 12-17 kg, in two stages. In Stage 1, under general anesthesia (pentobarbital sodium 40 mg/kg, intravenously) and artificial respiration, thoracotomy was performed on the first animal in the fourth left intercostal space, and the anterior descending branch of the left coronary artery was ligated in its upper third. At the second stage, 2 months later, the animals were used in an acute experiment. By means of an ultrasonic doppler technique, the blood flow in the coronary vein (CV), draining blood directly from the ischemic focus [1], and in the great cardiac vein (GCV), collecting blood from the whole of the left ventricle, was recorded simultaneously. Ultrasonic transducers, in the form of a bandage 2.0-2.5 mm long, with an internal diameter of 1.0-3.0 mm, and calibrated in units of volume velocity of blood flow, were placed on the veins. The redistribution of blood flow in the ischemic myocardium of the left ventricle was estimated by means of an analog computer, as the quotient obtained by dividing the mean values of the blood flow in the coronary and great cardiac veins (CV/GCV).

The pressure in the left ventricle and carotid artery, and in some experiments the retrograde arterial pressure in the basin of the occluded coronary artery, were recorded by means of a micromanometer. The N3031 instrument was used as recorder.

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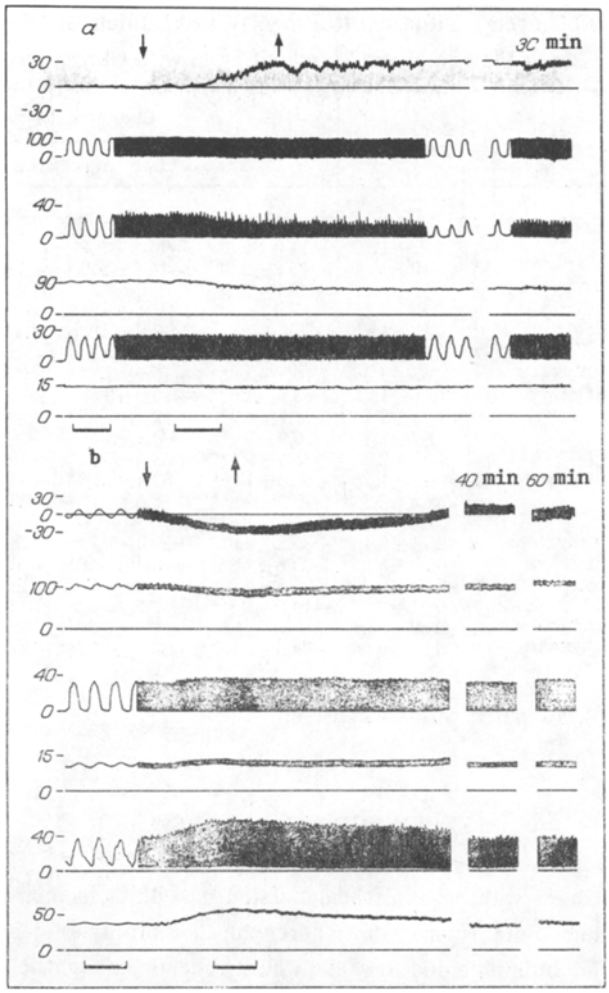

Fig. 1. Changes in blood flow in coronary and great cardiac veins under the influence of propranolol (a) and diltiazem (b). a) From top to bottom: redistribution of blood flow in left ventricular myocardium, per cent of initial level; blood pressure in left ventricle, mm Hg; linear velocity of blood flow in great cardiac vein, cm/sec; volume velocity of blood flow in great cardiac vein, ml/min; linear velocity of blood flow in coronary vein, cm/sec; volume velocity of blood flow in coronary vein, ml/min. Time scale 1 sec and 1 min. b) From top to bottom: redistribution of blood flow, per cent of initial level; blood pressure in carotid artery, mm Hg; linear velocity of blood flow in coronary vein, cm/sec; volume velocity of blood flow in coronary vein, ml/min; linear velocity of blood flow in great cardiac vein, cm/sec; volume velocity of blood flow in great cardiac vein, ml/min. Time scale 1 sec and 2 min. Arrows indicate beginning and end of injection of drugs; from left to right — background and immediately after beginning of injection of drugs, and 30, 40, and 60 min after their injection.

The preparations were injected intravenously in the following doses: propranolol 0.1 mg/kg, diltiazem 0.3 mg/kg, lithium and sodium hydroxybutyrate 200 mg/kg. The results were subjected to statistical analysis by Student's t test. The total number of dogs used was 30.

TABLE 1. Effect of Propranolol (0.1 mg/kg), Diltiazem (0.3 mg/kg), and Lithium and Sodium Hydroxybutyrate (200 mg/kg) on Redistribution of Blood Flow in Heart Muscle of Dogs with Chronic Ischemia (M ± m)

Parameter	Drug	n	Background	Changes in percent of initial level				
				Time after injection of drug, min				
				3	10	20	30	40
HR, beats/min	Propranolol	6	132±12,2	−11,0±2,8*	−14,8±3,7*	−13,0±2,9*	−11,7±3,0*	−11,7±3,0*
	Diltiazem	7	140±10,4	−15,8±2,3**	−16,7±2,4	−12,7±2,1**	−12,1±2,1**	−12,1±2,1**
	Lithium hydroxybutyrate	8	131±7,8	−10,9±2,7**	−9,6±3,0*	−7,8±2,0**	−3,1±1,3	−2,1±1,1
BP, mm Hg	Sodium hydroxybutyrate	9	125±5,5	−7,2±2,6*	−7,4±1,3**	−4,5±1,2**	−1,1±0,8	−1,1±0,8
	Propranolol	6	102±3,8	−5,0±2,1	−7,8±2,9*	−7,7±2,5*	−6,4±2,3*	−7,9±2,1*
	Diltiazem	7	100±3,3	−5,4±2,2*	−3,7±2,5	−3,1±3,4	−2,1±4,0	−3,1±3,6
	Lithium hydroxybutyrate	8	103±2,2	+16,7±2,8**	+19,0±2,7**	+15,7±2,6**	+9,6±3,1*	+6,7±2,8*
	Sodium hydroxybutyrate	9	119,6±13,5	+13,5±4,5**	+10,0±3,5*	+7,9±3,0*	+5,4±2,8	+4,6±3,8
Blood flow in CV, ml/min	Propanolol	6	10,4±2,1	−12,7±4,3*	−12,3±2,6*	−13,6±2,6**	−13,6±2,8**	−18,1±4,1**
	Diltiazem	7	11,7±2,8	+6,9±4,4	+0,9±3,5	−5,6±4,5	−3,8±4,9	−4,6±5,3
	Lithium hydroxypbutyrate	8	11,2±2,2	+35,4±9,1**	+33,2±11,1*	+25,7±9,1*	+20,1±7,1	+21,1±8,6
	Sodium hydroxybutyrate	9	9,6±1,2	+56,6±13,8**	+62,4±15,3**	+57,1±18,2**	+50,4±16,6**	+30,5±19,2
Blood flow in GCV, ml/min	Propranolol	6	32,8±3,3	−15,0±3,8**	−18,8±3,6**	−22,9±4,1**	−24,7±5,4**	−27,1±7,7*
	Diltiazem	7	37,6±4,7	+33,0±7,6**	+17,4±5,8*	+9,0±6,0	+5,2±6,8	+4,3±7,7
	Lithium hydroxybutyrate	8	35,1±5,1	+35,2±6,8**	+20,4±4,7**	+18,0±6,9*	+11,9±5,1	+6,1±7,2
	Sodium hydroxybutyrate	9	40,0±5,2	39,8±11,6**	+46,4±18,9*	+43,7±18,7*	+2,6±12,3	+15,2±13,8
Ratio CV/GCV	Propranolol	6	0,34±0,06	+3,5±4,0	+13,0±4,1*	+13,6±2,7**	+13,6±3,9*	+14,6±4,7*
	Diltiazem	7	0,31±0,07	−18,8±4,3**	−9,7±4,0	−8,8±2,3*	−5,7±7,1	−4,6±3,9
	Lithium hydroxybutyrate	8	0,32±0,04	−5,6±4,5	−2,1±6,0	−2,1±4,2	−0,3±5,3	+2,1±5,4
	Sodium hydroxybutyrate	9	0,27±0,04	+34,4±10,5**	+33,1±10,7**	+21,5±10,8	+15,9±9,9	+10,5±16,2

Legend. *$p < 0.05$, **$p < 0.01$ compared with background.

EXPERIMENTAL RESULTS

The experiment showed that drugs with an antiischemic action may differ in their effect on the redistribution of the blood flow in the ischemic myocardium. For instance, the β-adrenoblocker propranolol reduced the blood flow by a much greater degree in the great cardiac vein, draining blood from the whole ischemic left ventricle, compared with the blood flow in the coronary vein, draining blood only from the ischemic focus. This was accompanied by an increase in the CV/GCV ratio and was evidence of redistribution of the blood supply in favor of the zone of chronic ischemia of the heart muscle (Fig. 1a, Table 1). Our data are in agreement with observations made by other workers, who also showed that propranolol, under conditions of chronic myocardial ischemia, redistributes the blood flow in favor of the focus of ischemia in the heart muscle [7].

Diltiazem, in the presence of acute coronary arterial occlusion, increases the blood flow in the left ventricle, but mainly in nonischemic regions. The ratio of the blood flow in the ischemic and nonischemic zones is considerably reduced under these circumstances [6]. Under the influence of diltiazem, under certain conditions the collateral coronary circulation may actually be reduced [2]. As our experiment showed, diltiazem considerably increases the blood flow in the great cardiac vein (by 50.4 ± 7.7% at the 2nd minute after injection, $p < 0.05$), whereas in the coronary vein it increases it briefly and only by a slight degree (by 10.0 ± 3.4% at the 2nd minute after injection, $p < 0.05$). In this case the ratio CV/GCV decreased statistically significantly during the first 20 min, evidence of redistribution of the blood flow at this time in favor of the conventionally intact zones of the ischemic left ventricular myocardium (Fig. 1; Table 1). Thus under conditions of chronic myocardial ischemia also, when a network of collateral vessels had developed, diltiazem increased the blood flow by a much greater degree in conventionally intact zones of the ischemic left myocardium compared with the ischemic focus.

Using a different method to assess the distribution of the blood flow in the ischemic heart muscle the writers previously showed that the antihypoxic agents sodium and lithium hydroxybutyrate significantly increase the blood flow in both ischemic and conventionally intact zones of the left ventricle. The blood supply to the ischemic focus was judged from the retrograde inflow of blood and the retrograde perfusion pressure [4, 5]. As the present investigation showed, the antihypoxic agents studied significantly increased the coronary blood flow in the ischemic myocardium when there was a developed coronary collateral circulation. In this case the effect of sodium hydroxybutyrate was stronger. Both agents, just as in the case of acute ischemia of the heart muscle, increased the systemic blood pressure and caused bradycardia (Table 1). However, there were also certain differences in the action of the antihypoxic agents on the redistribution of the blood flow in the heart muscle. Whereas lithium hydroxybutyrate increased the blood flow about equally in the focus of ischemia and in conventionally intact zones of the left ventricle, thus not altering the CV/GCV ratio, sodium hydroxybutyrate increased the blood flow by a greater degree in the

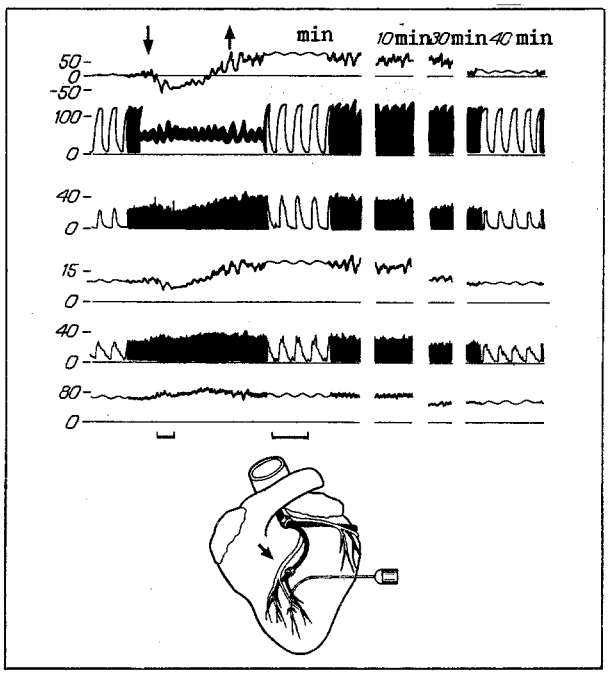

Fig. 2. Effect of sodium hydroxybutyrate on redistribution of blood flow in ischemic heart muscle. From top to bottom: redistribution of blood flow in left ventricular myocardium, per cent of initial level; blood pressure in left ventricle and retrograde arterial pressure in basin of occluded coronary artery, mm Hg; linear velocity of blood flow in coronary vein, cm/sec; volume velocity of blood flow in coronary vein, ml/min; linear velocity of blood flow in great cardiac vein, cm/sec; volume velocity of blood flow in great cardiac vein, ml/min. Time scale: 1 sec and 1 min. From left to right: background and immediately after injection of preparation, and 3, 10, 30 and 40 min after injection. Arrows indicate beginning and end of injection of sodium hydroxybutyrate. Scheme of experiment shown bottom center. Two ultrasonic transducers applied to coronary and great cardiac veins. Arrow indicates site of occlusion of coronary artery. Retrograde arterial pressure recorded by means of a catheter. Ischemic zone is shaded.

ischemic focus, leading to an increase in the CV/GCV ratio (Fig. 2, Table 1). The reason for this difference in the action of the two antihypoxic agents still awaits explanation.

Thus by means of this new technique, whereby the blood supply to the heart muscle can be correctly determined over a period of time, it was shown that significant changes can be produced in the blood supply to different zones of the left ventricular myocardium and the blood flow in it can be redistributed pharmacologically in cases of chronic ischemia.

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