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EFFECT OF PROPRANOLOL ON METABOLIC PROCESSES IN BLOOD AND LYMPH IN ACUTE MYOCARDIAL INFARCTION

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Despite the widespread use of propranolol in clinical practice, including in acute myocardial infarction (AMI) [2, 4, 6], there is virtually no information about its effect on the biochemical parameters of the lymph. Yet the biochemical composition of the lymph reflects the most intimate processes of tissue metabolism and responses of the body to various exogenous factors [1, 3, 5]. The aim of this investigation was to study the action of propranolol on some parameters of carbohydrate and electrolyte metabolism and also on the acid-base balance (ABB) in the blood and lymph during development of AMI.

EXPERIMENTAL METHOD

Experiments were carried out on 30 mongrel dogs weighing 12-22 kg. A model of AMI was created by ligating the anterior interventricular artery under pentobarbital anesthesia (30 mg/kg, intravenously). Lymph was obtained from the drained thoracic duct (a parallel recording made of the rate of the lymph flow), and blood was obtained from the femoral artery. Parameters of ABB were determined on a Micro-Astrup apparatus (Denmark), Na, K, and Ca on a "Microlit" apparatus (Finland), by an ion-selective method. Lactate and glucose concentrations were studied spectrophotometrically on a "Labsystem-900" analyzer (Finland), using standard kits. Propranolol was injected immediately after ligation of the coronary artery and thereafter twice a day for 3 days in a dose of 0.1 mg/kg.

EXPERIMENTAL RESULTS

After creation of the model of AMI marked changes in metabolic processes were observed in both blood and lymph (Table 1, Fig. 1). Starting from 15 min of coronary arterial occlusion, an increase was observed in the lactate and glucose levels

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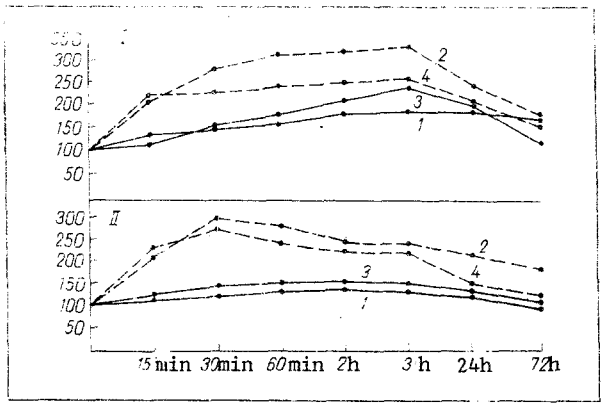

Fig. 1. Changes in lactate and glucose concentrations in blood and lymph during development of AMI (I) and administration of propranolol (II). Lactate concentration in blood (1) and lymph (2); glucose concentration in blood (3) and in lymph (4).

TABLE 1. Time Course of Changes in Electrolyte Metabolism and ABB during Development of Acute Myocardial Infarction

Parameter studied	Initial background	After ligation of anterior interventricular artery						
		15 min	30 min	60 min	2 h	3h	24 h	72h
Number of observations	6	6	6	6	6	6	5	5
K^+, mmoles/liter	4,44±0,3	4,41±0,02	4,27±0,09	4,24±0,03	4,1±0,12	3,9±0,18	4,8±0,07*	4,9±0,01*
	3,62±0,29	3,97±0,03	4,04±0,07*	4,24±0,01*	4,87±0,03*	4,58±0,04*	4,21±0,01*	3,5±0,33
Na^+, mmoles/liter	151,4±0,4	151,8±1,9	151,8±2,5	151,3±1,1	153,4±1,1	153,8±0,8	154,1±0,9*	154,0±0,7*
	154,2±0,5	153,8±0,3	154,1±0,7	156,8±0,8*	156,6±0,2*	154,0±0,1	153,0±0,8	154,1±1,5
Ca^{++}, mmoles/liter	1,35±0,03	1,33±0,02	1,37±0,09	1,33±0,06	1,18±0,06*	1,06±0,05*	1,21±0,07*	1,36±0,11
	1,31±0,02	1,33±0,06	1,31±0,03	1,34±0,05*	1,35±0,01*	1,38±0,03*	1,34±0,13*	1,32±0,27
pH	7,31±0,08	7,19±0,03	7,09±0,04	7,03±0,06*	7,05±0,04*	7,01±0,08*	7,02±0,01*	7,22±0,17
	7,45±0,06	6,63±0,02**	6,88±0,05**	7,05±0,01**	7,09±0,02**	7,03±0,05*	7,23±0,01*	7,43±0,05
pO_2, mm Hg	94,5±1,4	93,8±2,4	92,7±2,1	87,3±1,8	74,3±3,2	69,5±2,7	67,2±2,7**	89,5±1,3*
	55,5±2,6	37,0±1,8**	38,5±1,5**	41,3±2,1**	49,4±2,5	50,5±2,1	51,3±1,3	54,2±1,7
pCO_2, mm Hg	46,3±1,2	48,3±2,07	53,8±4,48	62,8±3,52*	71,6±6,8*	93,7±7,6*	99,2±2,7*	59,0±2,1*
	58,8±1,1	68,0±2,2*	71,0±1,7*	62,0±2,9*	64±1,9*	60,0±0,6	59,1±2,1	58,1±2,3

Legend. Numerator — blood, denominator — lymph; *$0.05 < p < 0.001$; **$p < 0.001$.

in the blood, and in particular, in the lymph. After 30 min, for instance, the lactate concentration rose by 2.8 and 1.6 times, respectively, in the blood and lymph, whereas the glucose concentration was 1.5 times higher in the blood and 2.3 times higher in the lymph that initially ($p < 0.005$). These changes progressed and were maximal 3 h after the beginning of the experiment, when the lactate concentration in the lymph was 331% and in the blood 242%, and the glucose concentration 257% in the lymph and 183% in the blood ($p < 0.001$) compared with the initial background values. Parameters of electrolyte metabolism and ABB underwent significant changes after ligation of the coronary artery, especially in the lymph. A significant increase in the K ion concentration in the blood was observed after 24 h, and in the lymph beginning with 30 min. A small but significant increase in the Na ion concentration was observed in the lymph after 60 min and in the blood after 24 h. The Ca ion concentration in the lymph was reduced after 3 h. Signs of metabolic acidosis after creation of the model of AMI also were more marked in the lymph than in the blood. The O_2 partial pressure in the lymph decreased in the lymph for 60 min, then gradually increased, whereas in the blood a progressive decline of O_2 was observed. pCO_2 in the lymph showed a maximal increase by 21% after 30 min ($p < 0.05$), whereas in the blood it was doubled after 3 h ($p < 0.001$).

TABLE 2. Parameters of Electrolyte Metabolism and ABB of Blood and Lymph in the Course of AMI Treated with Propranolol

Parameter studied	Initial background	After creation of model of AMI and injection of propranolol						
		15 min	30 min	60 min	2 h	3 h	24 h	72 h
K^+, mmoles/liter	4,44±0,3	4,24±0,2	4,11±0,3*	3,9±0,5*	4,09±0,3*	4,1±0,2	4,21±0,19**	4,11±0,27**
	3,63±0,29	3,47±0,3	3,37±0,07**	3,04±0,07**	3,25±0,05**	3,51±0,05**	3,89±0,1	3,61±0,2
Na^+, mmoles/liter	151,4±0,4	151,7±0,2	150,8±0,1	150,8±0,7	151,6±1,1	151,7±0,3	149,3±0,7**	149,0±0,9**
	154,2±0,5	151,1±0,3	153,7±0,7	154,1±0,5	153,6±0,2	154,1±0,1	153,0±0,6	153,8±0,3
Ca^{++}, mmoles/liter	1,35±0,03	1,33±0,01	1,35±0,03	1,37±0,05	1,21±0,06	1,09±0,06	1,24±0,07	1,37±0,02
	1,31±0,02	1,34±0,1	1,33±0,02	1,31±0,01	1,34±0,05	1,33±0,3	1,34±0,1	1,33±0,2
pH	7,31±0,08	7,22±0,07	7,18±0,05**	7,14±0,08**	7,14±0,05**	7,12±0,03	7,13±0,02	7,24±0,04
	7,45±0,06	6,23±0,07***	6,33±0,06***	6,87±0,09***	7,18±0,05**	7,2±0,06**	7,33±0,03**	7,44±0,04
pO_2, mm Hg	94,5±1,4	93,7±1,2	93,5±1,1	87,9±2,3*	83,6±3,1***	75,7±1,8***	73,4±1,6***	92,7±1,2
	55,5±2,6	40,1±1,1*	42,7±2,3*	44,7±1,7*	48,6±2,1*	50,3±2,7*	50,7±1,8*	54,5±1,9
pCO_2, mm Hg	46,3±1,2	48,5±1,5	52,7±1,7*	63,8±1,9*	72,5±2,1*	94,3±2,4*	97,3±1,7*	56,7±2,1
	58,8±1,1	67,3±1,3*	69,7±1,7*	63,5±1,2*	64,7±1,1*	59,2±1,5	57,3±1,3	58,2±1,6

Legend. Numerator denotes blood, denominator – lymph; *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

In the experiments with propranolol the lactate and glucose concentrations in the blood were significantly lower at all times of the investigation than in the control (Table 2). For instance, whereas in the control the lactate and glucose levels in the blood after 60 min amounted to 174 and 154%, respectively, in the experiments with propranolol the corresponding figures were 123 and 137% of the initial background ($p < 0.05$). An earlier and more marked increase in the lactate and glucose concentrations followed by more rapid normalization of their concentrations compared with the control were observed in the lymph after administration of propranolol. For instance, the increase in the lactate and glucose concentrations in the lymph after 30 min amounted to 296 and 252%, respectively, (against 280 and 226%, $p < 0.05$, in the control) compared with the initial background. At all subsequent times of the investigation their concentrations in the lymph were significantly lower than in the control. For instance, 3 h after injection of propranolol the lactate and glucose concentrations were 231 and 218% (compared with 331 and 257%, $p < 0.001$ in the control) of the initial background values, respectively. Administration of propranolol prevented the disturbance of the electrolyte balance induced by acute occlusion of the coronary artery, in both blood and lymph. A significant decrease in the potassium ion concentration in the lymph was observed 30 min after injection of propranolol, and a maximal decrease after 2 h. Later, during the investigation the K ion concentration was basically within the initial limits. In animals receiving propranolol, unlike the controls no increase was observed in the concentrations of Na and Ca ions in the lymph. Propranolol led to a significant decrease in blood levels of Na and K ions compared with the control experiments (after 24 h) and had no significant effect on the Ca concentration. During the first hour after injection of propranolol the Ph of the lymph was lower, but at later times during the investigation, on the contrary, it was higher than in the control ($p < 0.05$). In the experiments with propranolol a small but significant decrease in the degree of metabolic acidosis was observed in the blood. A significant increase in Po_2 in the blood was observed, starting with 2 h, whereas in the lymph there is a tendency for it to rise, but these results were not statistically significant compared with the controls. The partial CO_2 pressure both in the blood and in the lymph showed identical changes with the control parameters.

The experiments thus showed that during AMI marked metabolic shifts take place both in the blood and in the lymph, more especially the latter, as is shown by a sharp increase in concentrations of lactate and glucose and changes in parameters of electrolyte metabolism and ABB. Administration of propranolol during development of AMI largely corrects the metabolic disturbances in the blood and lymph. The more marked increase in concentrations of products of disturbed metabolism in the lymph in the early period of the investigations in the experiments with propranolol can be explained by the "flushing" of toxic metabolic products from the myocardium, due to the stimulating action of propranolol on lymph drainage, which we observed in our experiments.

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EFFECT OF ADAPTATION TO PERIODIC HYPOXIA ON STABILITY OF MYOCARDIAL ENERGY METABOLISM AND CONTRACTILITY PARAMETERS IN THE PRESENCE OF ACUTE ANOXIA AND REOXYGENATION

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Adaptation to periodic hypoxia is a powerful prophylactic factor limiting the onset of arrhythmias associated with acute local myocardial ischemia and reperfusion [1], and also heart damage and the development of arrhythmias in acute myocardial infarction and postinfarction cardiosclerosis [2, 7]. However, no research has been undertaken in order to study the effect of preliminary adaptation to hypoxia on, first, the contractile function of the heart and, second, on parameters of energy metabolism in acute anoxia and subsequent reoxygenation.

The aim of this investigation was to assess the effect of preliminary adaptation to periodic hypoxia on the stability of energy metabolism and contractility parameters of the heart in the presence of acute anoxia and subsequent reoxygenation.

EXPERIMENTAL METHOD

Experiments were carried out on male Wistar rats weighing 300-350 g. Adaptation to periodic hypoxia was carried out in a pressure chamber for 4 h daily for 40 days at an "altitude" of 4000 m. The course of adaptation began from 1000 m, the "altitude" being increased in steps up to 4000 mg by the 8th day. Acute experiments were conducted on the animals under pentobarbital anesthesia (50 mg/kg) under artificial respiration conditions. The rats' hearts were frozen actually in the chest with Wallenberger's forceps for biochemical tests: on the first group of animals in a state of relative physiological rest, on the second group in a state of hypoxia (4 min after disconnecting the artificial respiration), and on the third group during reoxygenation (5 min after resumption of breathing). The frozen hearts were used to determine parameters of myocardial energy metabolism. ATP, ADP, AMP, and lactate were determined with the aid of kits from "Boehringer," and creatine phosphate (CP) by the diacetyl method [3]. Glycogen was solubilized in hot 30% KOH and precipitated with ethanol, then subjected to enzymic hydrolysis by α-aminoglucosidase [4], and the quantity of glucose formed was measured by the glucose oxidase method [6]. Creatine phosphokinase (CPK) activity was determined on a "Hitachi-550" spectrophotometer by the method in [11] with certain modifications. The total and active forms of glycogen phosphorylase were determined by a modified method in [5]. Inorganic phosphorus was determined by the method in [10]. The contractile function of the heart was studied at the same stages of the experiment as parameters of energy metabolism, namely: under conditions of relative physiological rest, during anoxia for 4 min followed by reoxygenation for 5 min. The pressure in the left ventricle was recorded by means of a "Mingograf-35" electromanometer (Elema). The heart rate (HR), systolic and diastolic pressures, and rate of contraction and relaxation of the heart were measured from the pressure curve. The intensity of functioning of structures (IFS) was calculated by the formula ($P \times HR$/mass of left ventricle), where P denotes the pressure developed in the left ventricle.

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