INCREASING THE RESISTANCE OF THE HEART TO LOCAL REVERSIBLE ISCHEMIA

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The widespread occurence of various forms of coronary insufficiency determines the urgency for development of methods of increasing the resistance of the myocardium to oxygen lack. One such method is training by means of hypoxia, during which certain adaptive effects can be achieved, some of them at the heart level. They include an increase in the throughput of the coronary circulation [5], an increase in the myoglobin concentration in the myocardium [4], an increase in the power of oxidative phosphorylation [3] and of glycolytic ATP synthesis [7], and an increase in the reserves of the sympathetic regulatory mechanism [10]. On the whole these changes are evidence of widening of the range of compensatory and adaptive powers of the heart of the adapted animal and potentiation of resistance of the myocardium to hypoxia.

Chiefly two waves of adaptation of the body to hypoxia have been developed in recent years training by physical exertion and by periodic exposure to a lowered atmospheric pressure [3]. However, both these methods may be limited in their application, for they require either a considerable increase in physical activity of the subject or special conditions for training (a pressure chamber, for example). The method of adaptation to hypoxia using gas mixtures deficient in oxygen at normal barometric pressure for breathing [9] is free from these disadvantages.

The object of this investigation was first, to study the effect of preliminary adaptation to hypoxia (breathing a gas mixture with reduced O_2 concentration) on the resistance of the heart to reversible ischemia of the myocardium of coronary etiology and of varied duration; second, to study the role of the sympathetic and parasympathetic regulatory mechanisms of the heart in the change in its resistance to ischemia under these conditions.

EXPERIMENTAL METHOD

Experiments were carried out on 240 noninbred male albino rats weighing initially 190-210 g. Local reversible myocardial ischemia (LRMI) was induced by the method described previously [1]. The duration of myocardial ischemia preceding revascularization was 10, 20, and 40 min. The following indices of the contractile function of the heart (CFH) were determined: the cardiac frequency (from the ECG); the systolic pressure in the left ventricle at rest and during isometric contractions; the mean rate of rise and fall of pressure in the left ventricle; the index of intensity of CFH (using Opie's index [13]). Changes in the concentrations of noradrenalin (NA) [2], acetylcholine-like substances (ACLS) [12], and cholinesterases (CE) [6] in the tissue of the left ventricular myocardium also were investigated. Adaptation of the animals to hypoxia was obtained by the use of a gas mixture deficient in oxygen at normal barometric pressure, by the scheme suggested by Khitrov and Alaverdyan [10].

EXPERIMENTAL RESULTS AND DISCUSSION

In animals unadapted to hypoxia (control group) a decrease in the indices of CFH was observed during local myocardial ischemia (Table 1). In 95.8% of rats during the first 5-15 min of myocardial ischemia a transient disturbance of the cardiac rhythm was noted; 66% of rats developed paroxysmal tachycardia and ventricular fibrillation. Restoration of the coronary blood flow in the animals of this group was accompanied by significant changes in

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TABLE 1. Dynamics of CFH during Reversible Myocardial Ischemia of Coronary Etiology in Animals Unadapted and Adapted to Hypoxia (M ± m)

CFH index	Group	Initial data	Myocardial ischemia for 10 min	Period of RCB, min		Initial data	Myocardial ischemia for 10 min	Period of RCB, min	
				10	40			10	40
Pressure in left ventricle during its isometric contraction, mm Hg	Control	200±4,7	186±5,3*	190±8,5	196±8,4	194±5,4	170±7,5*	171±6,8*	161±5,7*
	Experimental	208±7,2	208±8,0	206±7,8	210±8,3	204±6,6	193±7,6	189±9,7	192±7,5
Rate of rise of pressure in left ventricle, mm Hg/sec	Control	1280±52,2	1360±54,5	1148±56,2	1237±57,6	1229±54,6	1074±49,8*	952±57,8*	1029±52,5*
	Experimental	2009±46,0	2208±52,0*	2159±51,3	2309±56,4*	2011±46,1	2084±51,7	2029±53,1	2128±48,1
Rate of fall of pressure in left ventricle, mm Hg/sec	Control	532±35,2	700±39,4*	480±40,1	497±39,1	568±36,8	532±39,6	448±45,5*	416±43,2
	Experimental	631±31,0	830±33,6*	823±35,3*	708±32,0	612±30,1	657±37,8	650±39,7	632±32,6
Opie's index ($1 \cdot 10^3$)	Control	23,5±2,4	27,4±3,6	23,1±3,6	24,5±3,2	24,7±2,5	22,4±3,6	19,5±4,1*	19,2±3,4*
	Experimental	27,1±1,9	34,9±3,0*	35,8±3,5*	31,2±2,8	26,3±2,3	29,8±2,3	26,3±4,9	25,7±4,3

*Values differ significantly from initial data ($P < 0.05$).

Legend. Control group consisted of ten, experimental group of eight animals.

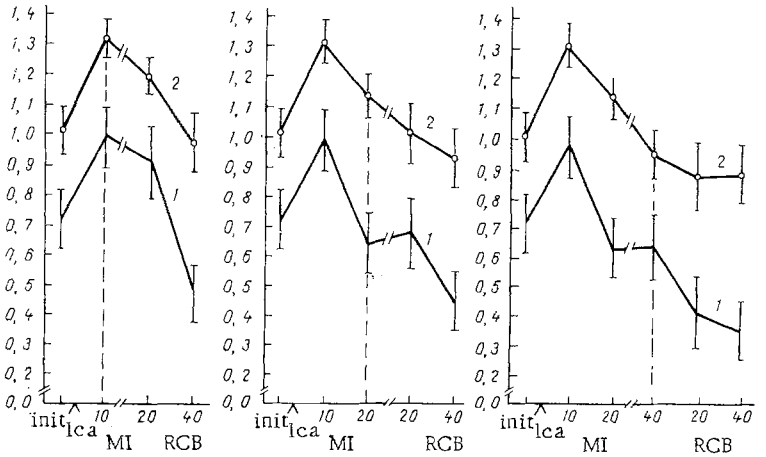

Fig. 1. Dynamics of NA concentration in tissues of left ventricle during reversible local ischemia of the heart (M ± mt). Abscissa, duration of period of myocardial ischemia (MI) and RCB in coronary arteries (in min); broken line indicates end of MI; ordinate, NA concentration (in μg/g). init) initial data; lca) ligation of coronary artery. 1) Control; 2) experiment.

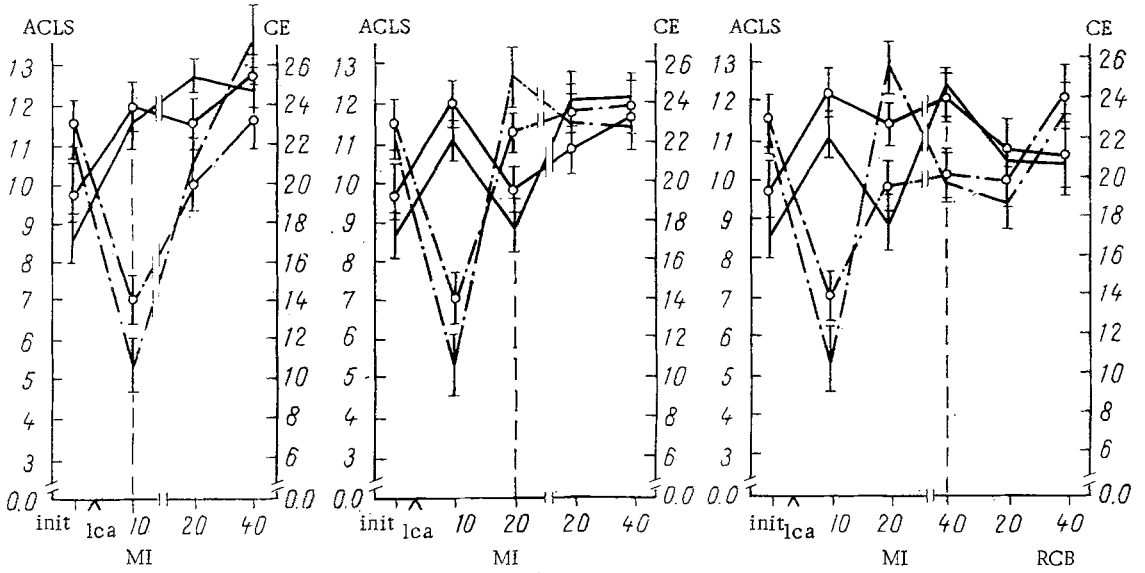

Fig. 2. Dynamics of total ACLS concentration and CE activity in tissue of left ventricle during its reversible local ischemia (M ± mt). Abscissa, the same as Fig. 1; ordinate, total ACLS concentration (in mg/g) and CE activity (in μmoles/g). Continuous line denotes ACLS, line of dots and dashes, CE. Remainder of legend as in Fig. 1.

cardiac activity, the character of which depended on the duration of myocardial ischemia preceding recirculation of the blood (RCB) in the coronary artery. After brief myocardial ischemia for 10 min, 100% of the animals developed arrhythmias (paroxysmal tachycardia and ventricular fibrillation, sometimes irreversible, occurred in 56% of them). Meanwhile, during the first 5-10 min of the period of RCB a decrease in CFH was recorded, followed by restoration of its original level. RCB after prolonged (40 min) myocardial ischemia was accompanied by a further decrease in CFH. On resumption of the coronary blood flow arryth-

mias were observed in 50% of animals. Paroxysmal tachycardia and ventricular fibrillation were not observed in these animals.

Myocardial ischemia in animals adapted beforehand to hypoxia (experimental group) were characterized by much less severe disturbances of CFH (Table 1). Arrhythmias were observed in 79% of rats during the period of myocardial ischemia, and paroxysmal tachycardia and ventricular fibrillation were found in only 5.3% of cases. In the adapted animals RCB was accompanied by changes in CFH compared with the initial level. Restoration of the coronary blood flow after ischemia for 10 min was accompanied by an increase in the strength of cardiac contractions, in the rate of rise and fall of the pressure in the left ventricle, and also of Opie's index. Arrhythmias during RCB were observed in 78% of animals of the experimental group, but paroxysmal tachycardia and ventricular fibrillation were found in only 14.3% of animals. RCB after myocardial ischemia for 40 min was accompanied by some decrease in the strength of cardiac contraction compared with the period of ischemia and, conversely, by an increase in the rate of the contractile process. Opie's index remained close to its initial level. Only one-third of animals developed arrhythmia on resumption of the coronary blood flow. No case of paroxysmal tachycardia or ventricular fibrillation was noted.

The results are evidence of a significant increase in the resistance of the heart to acute LRMI in animals previously adapted to hypoxia. This is shown by the stability of CFH and of the cardiac rhythm both during myocardial ischemia and on restoration of the coronary blood flow.

To study the role of the sympathetic and parasympathetic regulatory mechanisms of the heart in the increase in its resistance to LRMI in the adapted animals the dynamics of the concentrations of NA and ACLS was studied in the myocardial tissues of the left ventricle. The experiment revealed a higher level of neuromediators in the heart of the adapted rats than in the control animals, both in the initial state (before the operation) and in myocardial ischemia (Figs. 1 and 2). This fact is evidence of the greater stability of the reserves of sympathetic and parasympathetic neuromediators in the heart of animals adapted to hypoxia under conditions of LRMI. Restoration of the coronary blood flow is accompanied by a smaller decrease in the NA concentration in the heart of animals of the experimental group compared with the control. This observation, together with data on the higher concentrations of ACLS in the adapted rats only during the first 30-35 min of myocardial ischemia (irrespective of CE activity), is evidence of the rather lower stability of the reserves of parasympathetic than of sympathetic neuromediator. These results suggest that the sympathetic components of regulation play a more important role in determining the high resistance of the heart to LRMI in the adapted animals. Besides other factors, this high resistance is due to an increase in the functional reserve of the system for regulating cardiac activity in the course of training by adaptation to hypoxia. Mobilization of this reserve during ischemic changes in the heart helps to maintain adequate work of the heart under these conditions. This conclusion is supported by data showing the more rapid rise and fall of pressure in the left ventricle of adapted animals, both in the initial state and in LRMI. This phenomenon is based on an increase in the rate of systolic contraction and diastolic relaxation of the myocardium, associated with activation of mechanisms of Ca^{++} ion translocation by the sarcoplasmic reticulum of the myocytes [14]. Calcium transport in turn is initiated by catecholamines through activation of adenylate cyclase and the formation of cyclic AMP in the myocardiocytes [11]. The process of diastolic relaxation of the heart in the adapted animals also can be intensified through activation of parasympathetic influences in them, with a consequent increase in the compliance of the myocardium to stretching by the filling pressure [8]. Another contributory factor in the smaller decrease in CFH of the adapted animals during LRMI is evidently the lower ability of mitochondria from the heart to accumulate calcium [15]. Accumulation of calcium in the mitochondria leads first, to inhibition of ATP resynthesis (as a result of uncoupling of oxidative phosphorylation), and second, to a decrease in the concentration of calcium ions — a powerful inotropic agent — in the sarcoplasm of the myocytes. Both these factors likewise may determine the greater depression of CFH in animals unadapted to hypoxia.

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ROLE OF THE SYMPATHETIC NERVOUS SYSTEM IN THE PATHOGENESIS OF EXPERIMENTAL GLAUCOMA

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The study of the complex and still largely debatable problem of the role of the sympathetic nervous system in the pathogenesis of glaucoma is of practical as well as theoretical interest. A transient increase in the intraocular tension and certain forms of glaucoma can be regarded as a model of pathological states belonging to the diseases of regulation [6, 7], which are connected with hyperactivity of structures constituting the apparatus regulating the activity of an affected organ [4, 5]. There is evidence that the sympathetic nervous system participates in the pathogenesis of glaucoma [1, 2, 9-11], but the information is contradictory. The writers have attempted to shed light on this problem by using models of transient ocular hypertension and experimental glaucoma developed previously [3, 8] and to test the effects of lithium and α- and β-adrenoblockers on these models.

EXPERIMENTAL METHOD

Experiments were carried out on 58 adult rabbits of the White Giant breed. A transient increase in intraocular tension was induced by daily intravenous injections of vasopressin in a dose of 0.75 biological unit for 3 months. Experimental glaucoma was produced by intravenous injections of adrenalin in a dose of 0.1 ml of a 1:1000 solution on alternate days for 3 months. Healthy rabbits served as the control. The action of the adrenoblockers was studied during reproduction of experimental glaucoma. The α- or β-blocker was given on alternate days for 3 months a few minutes before injection of adrenalin: a 1% solution of pyrroxan (α-blocker) in a dose of 0.1 ml subcutaneously, a 0.1% solution of obsidan (propranolol; β-blocker) in a dose of 0.2 ml intravenously. The level of the intraocular tension (IOT) was measured by a Maklakov tonometer with a weight of 7.5 g daily or on alternate days in the morning for 1 month before the beginning of the experiment in order to determine the

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