EFFECT OF STRESS ON RESISTANCE OF THE MYOCARDIUM TO HYPOXIA

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Emotional stress is known to potentiate the development of ischemic disease [5]. One possible mechanism whereby stress realizes its role in the development of this disease is lowering of the resistance of the myocardium to hypoxia.

The aim of this investigation was to test this hypothesis by studying the effect of emotional-painful stress (EPS) on resistance of the isolated atria of animals to hypoxia and subsequent reoxygenation.

EXPERIMENTAL METHOD

Experiments were carried out on male Wistar rats weighing 200 ± 7 g. EPS was produced once in the course of 6 h in the form of an "anxiety neurosis" [7]. The rats were decapitated 2 h after the end of EPS and the right atrium was isolated and placed in a constant-temperature bath containing oxygenated Krebs–Henseleit solution (95% O_2, 5% CO_2, pH 7.4, 34°C); the base of the atrium was rigidly fixed and the apex of the auricle was connected to the F-50 myograph of a "Physiograph DMP-4B" ink-writing apparatus (Narco Biosystems, USA). The atrium contracted spontaneously for 40-50 min, after which it was stretched by means of a load to a length at which it developed maximal systolic tension when contracting isometrically (T), which was called l_{max}. The change in length was recorded by a micrometer for every 100 mg increase in the load. The load which corresponded to l_{max} was called the maximal resting load (Tr_{max}). The experiments were carried out on the plateau of the Starling curve when the length of the atrium was equal to or a little more than l_{max}. The initial length of the atria and their weight in animals exposed to EPS were found not to differ statistically significantly from the controls. Exposure to hypoxia (hypoxic test) was produced by replacing the oxygenated solution in the bath by an unoxygenated solution for 20 min, during which time pO_2 in the solution fell from 600 to 150 mm Hg. The effect of hypoxia was assessed from the reduction in developed systolic tension (T), the increase in Tr after

TABLE 1. Effect of EPS on Atrial Contractility during Hypoxia and Reoxygenation

Parameter of contractility	Experimental conditions	Before hypoxia	Hypoxia			Reoxygenation		
			1 min	5 min	20 min	1 min	5 min	20 min
Developed systolic tension, mg	Control (n=20)	345±14,5	123±10,0	14,5±0,5	0	210±13	253±11,9	252±11,4
	EPS (n = 16)	201±8,7	69,3±7,5	8,4±3,10	0	126±19,6	131±16,0	139±9,3
Number of contractions per minute	Control	250±4,0	181±4,0	113±15,0	0	188±6,0	238±10,0	243±4,6
	EPS	255±5,0	188±5,0	65,0±11,0	0	166±16,0	217±15,5	244±4,0
IFS, g/(mg · min)	Control	3,6±0,20	0,90±0,08	0,10±0,03	0	2,1±0,13	2,42±0,14	2,54±0,14
	EPS	2,01±0,160	0,51±0,050	0,04±0,001	0	1,01±0,2	1,15±0,13	1,38±0,1
Increase in resting tension, mg	Control	—	13,0±3,0	219±27,5	510±35	148,5±20	97±12,5	35,5±9,0
	EPS	—	32,2±6,5	244±33,0	602±20	224±25	152±17	51,4±10
Contracture index, percent	Control	—	4,0±0,7	63±8,0	136±9,0	43,0±5,0	28,0±3,0	10,0±3,0
	EPS	—	18,0±4,0	130±16	312±15	119±10,0	78,0±10	28,0±8,0

Legend. IFS) intensity of functioning of myocardial structures, calculated as ratio of product of developed systolic tension and frequency to weight of atrium.

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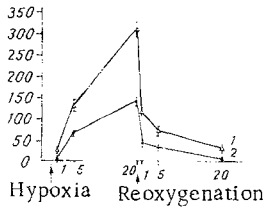

Fig. 1. Effect of EPS on development of hypoxic contracture of right atrium and its disappearance on reoxygenation. Abscissa, time (in min) of action of hypoxia (upper row of numbers) and of reoxygenation (lower row of numbers); ordinate, contracture index (percent). 1) EPS, 2) control.

the beginning of exposure to hypoxia, and the hypoxic contracture index (HC), equal to the ratio of the hypoxic increase in Tr (Δ Tr) to the value of T before the beginning of hypoxia (T_{orig}), i.e., HC = (Tr × 100%/T_{orig}). The experimental results were subjected to statistical analysis by Student's test.

EXPERIMENTAL RESULTS

The study of contractility of the right atrium in animals exposed to EPS revealed two basic changes: first, depression of the Starling curve and a corresponding decrease in the maximal developed systolic tension; second, a decrease in resistance of the atrial myocardium to hypoxia. This was manifested as a stronger negative chronotropic effect of hypoxia than in the control and also as the more rapid development of hypoxic contracture.

The data given in Table 1 show that under normal oxygenation conditions the developed systolic tension of the atria in rats exposed to stress was reduced by more than one-third compared with the control. The frequency of spontaneous contractions was unchanged and, correspondingly, the integral index reflecting contractile function per unit weight of the atrium (IFS) was reduced in these animals by more than 40%.

The decrease in the frequency of contractions, i.e., inhibition of pacemaker activity, under the influence of hypoxia and the contracture developing in animals exposed to EPS were more marked than in the control. For instance, at the 5th minute of exposure to hypoxia the frequency of contractions in the control was reduced by about 2.2 times, compared with almost four times in animals exposed to EPS. The value of IFS was correspondingly reduced by a greater degree than in the control. The increase in resting tension under the influence of hypoxia, characterizing the hypoxic contracture quantitatively, was 13 mg in the first minute and 510 mg in the 20th minute of hypoxia in the control. The corresponding values for "poststress" atria were 32.2 and 602 mg respectively, i.e., they were substantially increased. The index of hypoxic contracture of the atria in animals exposed to stress was correspondingly twice as high as in the control. The values of this index in rats exposed to EPS and in control animals are compared in Fig. 1. Finally, it will be clear from Table 1 that disappearance of hypoxic contracture and restoration of atrial contractility during reoxygenation took place much more slowly in animals with EPS in the control.

Besides reducing contractility of the myocardium, EPS thus also caused a marked decrease in its resistance to hypoxia. When the probable mechanism of this phenomenon is contemplated, it must be recalled that in the particular model of EPS used, a decrease in the glycogen reserves and inhibition of glycogen synthesis [4], together with activation of lipid peroxidation [3] and disturbance of function of the membrane calcium pump [2] have been shown to take place in the heart muscle. Glycolysis plays an exceptionally important role in the mechanism of relaxation [1] and of functioning of the Ca^{++}-pump of the sarcoplasmic reticulum [6, 8]; it is regularly activated in hypoxia. It can accordingly be postulated that it is the disturbance in the system of glycolysis and of the Ca^{++}-pump which play an important role in the poststress lowering of myocardial resistance to hypoxia, and this lowered resistance, in turn, may potentiate injury to and disturbance of the function of the heart muscle in ischemic heart disease.

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COMBINED USE OF HYPERBARIC OXYGENATION AND ANTIOXIDANTS IN THE TREATMENT OF EXPERIMENTAL MYOCARDIAL INFARCTION

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Oxygen deficiency is the leading factor triggering injury to cardiomyocytes and disturbance of intercellular metabolic relations in a focus of myocardial ischemia and in the periischemic zone. Naturally increased oxygenation or a reduced oxygen demand of the ischemized heart are the main methods used in pathogenetic treatment of myocardial infarction (MI). Hyperbaric oxygenation (HBO), as various experimental and clinical investigations have shown, occupies an important place among antihypoxic measures directed toward the ischemized myocardium [1, 11, 12].

Meanwhile evidence is constantly accumulating to show that in ischemia the oxygen-dependent process of lipid peroxidation is considerably activated in the heart [3, 7, 9], because, it is suggested, of disturbance of the mechanisms of antioxidant cell protection [5, 10, 13]. The use of synthetic or natural antioxidants has been shown to limit the size of the focus of ischemic necrosis and to accelerate repair processes should MI develop [8, 9, 10].

The investigation described below showed that a combination of increased oxygenation with an antioxidant gives an additive therapeutic effect on the state of the cardiac function during experimental MI.

EXPERIMENTAL METHOD

In 28 chinchilla rabbits weighing 2.3-3.3 kg the left descending coronary artery was ligated in its middle third. Of the 28 animals used, 14 were placed in a BKI-191 pressure chamber in an atmosphere of pure oxygen under a pressure of 2026 GPa (2 atm) for 1 h, 30-40 min after the operation. During the next six days these animals were subjected to one session of HBO daily. Of the 14 with MI, both treated and untreated by HBO, seven rabbits began one day before coronary occlusion to receive the antioxidant ionol by intraperitoneal injection in a sessional dose of 20 mg/kg, using Tween-80 as emulsifier. The control consisted of seven intact rabbits. The antioxidant activity (AOA) of the cardiac lipids was determined on a model of oxidation of the methyl ester of oleic acid [4] and superoxide dismutase (SOD) activity was determined by a method based on the ability of the enzyme to inhibit autooxidation of adrenalin, mediated by the superoxide anion [2], in the intact and ischemic zones

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