EFFECT OF LONG- AND SHORT-TERM STRESS ON RESISTANCE OF THE HEART TO ANOXIA

F. Z. Meerson and E. E. Ustinova

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The stress reaction that develops regularly in response to any considerable shift in the external environment is largely responsible for the development of stable adaptation to that shift [1, 12]; only if the stimulus is extremely strong or long-lasting, so that adaptation cannot take place, is the stress reaction converted into a stage in the pathogenesis of the widely different forms of stress injuries [4]. The pathogenesis of stress injuries to the organism has been investigated often during the last decades. Yet although the contribution of the stress reaction to increased resistance of the organism is well known, it has received much less study. In particular, the theoretically and practically important problem of the effect of stress on resistance of the heart to anoxia has not been studied at all.

The object of this investigation was to compare the effect of short-and long-term stress on resistance of the heart to anoxia.

EXPERIMENTAL METHOD

Experiments were carried out on male Wistar rats weighing 220-250 g. The animals were divided into three groups: 1) control animals, 2) rats receiving prolonged emotional-painful stimulation, 3) rats receiving a short period of emotional-painful stimulation.

Emotional-painful stress (EPS) was produced in the form of an anxiety neurosis by the method described in [9]. For animals of group 2 this stimulation lasted 6 h, but for the animals of group 3 it lasted only 1 h, i.e., six times less. Control animals were not stimulated.

When 1 h had elapsed after the end of stress the heart was removed under urethane anesthesia and its contractile function tested under isovolumic conditions by the method in [10]. The right atrium was removed and a latex balloon with constant volume introduced into the left ventricle; by compression of this balloon isovolumic contractions of the heart were induced. Contraction at a particular frequency was imposed by means of an ÉSL-1 electrostimulator; the pressure in the latex balloon was measured by means of a Mingograph-34 electromanometer (Elema-Schönander). The developed and diastolic pressure and also the maximal rates of development and fall of pressure were determined from the traces recorded. The coronary blood flow was determined by collecting and measuring the volume of perfusion fluid flowing through the coronary system in unit time. The heart was perfused with Krebs–Henseleit solution at 37°C. The solution was oxygenated with a gas mixture containing 95% O_2 and 5% CO_2. After perfusion of the heart for 60 min under normal oxygenation conditions, the oxygenated Krebs–Henseleit solution containing glucose was replaced by a solution aerated with a mixture of 95% N_2 and 5% CO_2, and not containing glucose. This anoxic situation continued for 10 min, after which reoxygenation was carried out.

EXPERIMENTAL RESULTS

The isolated hearts of animals exposed to EPS for 6 h were found to have depressed contractile function under aerobic conditions (Table 1). This was expressed as a decrease

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TABLE 1. Effect of Long- and Short-Term EPS on Parameters of Contractile Function of Rat Heart during Anoxia and Reoxygenation (M ± m)

Parameter	Group of animals	Duration of anoxia, min					Duration of reoxygenation, min			
		0	1	3	5	10	1	3	5	10
Developed pressure, mm Hg	Control (15)	77,8±3,4	41,9±3,4	28,0±2,1	12,3±1,0	4,5±0,4	42,3±3,9	45,6±4,1	50,4±4,4	57,9±3,9
	2 (14)	56,7±5,1*	48,0±4,1	26,3±2,4	12,0±1,2	4,6±0,5	42,5±5,0	28,7±2,9*	39,0±4,0*	46,4±4,0*
	3 (8)	79,4±3,9	52,6±5,0*	33,3±3,1*	18,8±1,6*	8,4±0,8*	65,5±6,3*	60,3±6,0*	69,4±4,0*	71,3±7,1*
Diastolic pressure, mm Hg	Control (15)	4,0±0,3	8,1±0,5	11,7±0,8	24,0±1,8	31,5±2,7	13,5±1,0	11,6±0,9	10,7±0,7	10,7±0,3
	2 (14)	4,4±0,3	5,0±0,4	9,0±0,6	20,5±1,9	37,0±3,0	11,8±0,8	9,0±1,0	9,3±1,0	8,6±0,8
	3 (8)	5,2±0,5	5,6±0,5	8,4±0,8	12,2±1,2*	20,0±2,1*	10,0±1,0	5,6±0,6	4,8±0,5	4,6±0,5
Maximal rate of development of pressure, mm Hg/sec	Control (15)	1640±96	822±63	683±45	408±34	—	831±55	891±65	1117±83	1129±95
	2 (14)	1054±82*	888±90	633±49	425±41	—	850±45	583±49*	825±70*	961±84
	3 (8)	1600±100	1050±100*	780±70*	780±70*	—	1250±110*	1166±110*	1380±120	1366±125
Maximal rate of fall of pressure, mm Hg/sec	Control (15)	910±70	405±37	318±24	207±19	—	425±38	466±41	550±51	629±31
	2 (14)	731±65*	425±40	366±35	240±19	—	425±44	300±24*	437±37	510±41*
	3 (8)	998±55	560±60	492±41*	370±27*	—	725±70*	683±62*	792±75*	800±78*
Coronary flow, ml/min	Control (15)	9,7±0,5	9,3±0,6	9,1±0,6	8,6±0,4	8,8±0,7	8,6±0,5	7,4±0,4	7,7±0,4	7,6±0,4
	2 (14)	6,8±0,4*	7,6±0,5	6,7±0,6*	8,1±0,5	7,8±0,6	8,2±0,5	7,3±0,3	8,0±0,5	8,2±0,6
	3 (8)	11,0±0,7	12,1±0,9	12,1±1,0*	11,9±1,1*	11,5±0,9*	13,0±1,1*	12,6±1,1*	11,8±1,0*	11,5±1,0*

Legend. Number of animals given in parentheses. *P < 0.05 compared with control.

in the developed pressure by 37%, in the rate of development of the pressure by 30%, and in the rate of all of the pressure by 20%. Meanwhile the coronary blood flow was reduced by 30%. During short-term EPS (1 h) these adverse changes in contractile function of the heart and the coronary flow were not present. There was actually a tendency for the coronary flow to increase.

The isolated hearts of the animals of all groups responsed to anoxia by depression of their contractile function and an increase in diastolic tension, evidence of the development of anoxic contracture. On reoxygenation these changes were largely reversed.

For the isolated hearts of animals exposed to long-term EPS depression of the contractile function and contracture during anoxia were just as severe as in the control, and on reoxygenation the disturbances of contractile function were restored more slowly, with respect to all parameters, than in the control. This corresponds to the fact established previously that exposure to EPS potentiates reoxygenation disturbances of the contractile function of the heart [5], for both these phenomena (stress [6] and reoxygenation [2, 11]) activate lipid peroxidation — a process which plays an important role in injury to cardiomyocyte membranes.

The isolated hearts of animals exposed to short-term stress responded to anoxia with a lesser degree of depression of their contractile function and by less marked anoxic contracture than the hearts of the control animals; the coronary flow against the background of anoxia was significantly greater in these hearts than in the control; under the experimental conditions used (constant perfusion pressure) this meant a decrease in the resistance of the coronary vascular bed, i.e., a decrease in tone of the smooth muscles of the vessels in the hearts of animals exposed to short-term EPS.

At the 5th minute of anoxia the developed pressure in the control was reduced to 12.3 $\pm$ 1.0 mm Hg and the rate of development of the pressure to 418 mm Hg/sec. In other words, these parameters were lower than those under aerobic conditions by 6.3 and 4.0 times respectively. Meanwhile, for the hearts of animals exposed to short-term stress, these same parameters were reduced compared with the corresponding values under aerobic conditions and compared with the initial levels by 4.2 and 2.0 times respectively. At the same stage of anoxia, contracture of the heart was manifested in the control as a decrease in the rate of fall of the pressure to 207 $\pm$ 19 mm Hg/sec, i.e., by 4.4 times, and as an increase of the diastolic pressure to 24.0 $\pm$ 1.8 mm Hg, i.e., a sixfold rise.

For the hearts of animals exposed to short-term stress these values were 370 $\pm$ 27 mm Hg/sec and 12.2 $\pm$ 1.2 mm Hg respectively, i.e., they were reduced by only 2.3 and 2.7 times. In other words, after short-term emotional-painful stress, certain sufficiently stable changes occurred in the myocardium of the animals, which had the result that the hearts of these animals, when removed from the influence of a spectrum of neurohormonal factors and placed under conditions of isolation, were more resistant to anoxia; this was expressed most of all, moreover, as an increase in preservation of relaxation of the heart muscle and smooth muscle of the coronary arteries, which is usually disturbed in anoxia. This protective antianoxic effect of short-term stress, as Table 1 shows, also was exhibited in the reoxygenation stage, when restoration of the contractile function and abolition of anoxic contracture in animals exposed to short-term EPS took place faster.

When an attempt is made to evaluate the increased resistance of the heart to anoxia after short-term stress, it must be recalled that at least three factors may play a role in the mechanism of this phenomenon.

First, a moderate adrenergic effect characteristic of short-term stress ought to as a rule lead to increased entry of Ca^{++} into the cell [13], conversion of inactive calmodulin into active [14] and, simultaneously, to increased cAMP formation [7]; cAMP and active calmodulin catalyze phosphorylation of the protein phospholambam [14], an activator of the calcium pump of the sarcoplasmic reticulum and sarcolemma, which is the cause of the well-known effect of activation of relaxation during the adrenergic effect on the heart [3].

Second, the calmodulin formed by the mechanism mentioned above is an activator of glycogenolysis and glycolysis [14], which are known to play an important role in the provision of energy for relaxation and in increasing the resistance of the heart to anoxia.

Third, the observed increase in the resistance of the heart to anoxia may be connected with the fact that during short-term stress the moderate adrenergic effect is

accompanied by a much stronger glucocorticoid effect, and glucocorticoids are known to be cell membrane stabilizers [8] and antioxidants.

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