PREVENTION OF STRESS-INDUCED DISTURBANCES OF CONTRACTILITY OF NONISCHEMIC REGIONS OF THE HEART IN MYOCARDIAL INFARCTION BY GAMMA-HYDROXYBUTYRIC ACID

R. S. Dosmagambetova

UDC 616.127-005.8-06:616.12-008.3-085.31:547.473.2/-039.71

KEY WORDS: myocardial infarction; atrium; gamma-hydroxybutyric acid; stress.

The state of regions of the heart in myocardial infarction outside the zone of ischemia largely determines the patient's fate and the outcome of the disease, for function of the residual part of the heart muscle is the main factor responsible for clinical compensation after infarction. Previous investigations showed that in experimental infarction of the left ventricle considerable disturbances of extensibility and contractility of the right atrial myocardium arise [2], similar to those found in emotional-painful stress [1], and evidently due mainly to the damaging action of an excess of catecholamines arising as a result of the stress which accompanies infarction [5, 6].

Since administration of gamma-hydroxybutyric acid (GHBA) prevents depression of the contractile function of the heart in animals subjected to emotional-painful stress [3], it seemed probable that this compound might be used to prevent stress disturbances of the function of nonischemic regions of the myocardium in infarction.

To test this hypothesis, in the investigation described below the effect of preliminary administration of GHBA was studied on the disturbance of extensibility and depression of contractility of the right atrial myocardium and the decrease in its resistance to hypoxia and to excess of Ca^{++} in experimental infarction of the left ventricle in rats.

EXPERIMENTAL METHOD

Experiments were carried out on male Wistar rats weighing 170-190 g. Experimental infarction was produced by ligating the descending branch of the left coronary artery by Selye's method [8]. The animals were decapitated 24 h after ligation of the artery. The area of the infarct (in mm^2) was more than 60% of the total area of the left ventricle from the outer surface and about 48% on the inner surface. Animals subjected to thoracotomy without occlusion of the coronary artery, and intact animals served as the control. Since there was no difference in the contractile function of the right atrium in the animals of the two control series, GHBA was injected into control intact rats and into intact rats in which myocardial infarction was later induced. GHBA was injected intraperitoneally in a dose of 100 mg/kg 1 h before production of the infarct, and again 2 and 4 h after the operation. GHBA was injected into the control animals in the same dose and at the same time intervals.

To study their contractile function the atria were removed immediately after decapitation of the animals and placed in a constant-temperature bath containing oxygenated Krebs—Henseleit solution (95% O_2, 5% CO_2, 34°C, pH 7.4). The base of the atrium was fixed and the auricle attached to the F-50 myograph of the DMR-4B Physiograph (from Narco Bio-Systems, USA), recording isometric contractions. The atrial contractile function was recorded under isometric conditions by the method described previously [2]. The following physiological parameters were ultimately determined: 1) maximal length of the atrium (l_{max}), corresponding to the maximal developed systolic tension (in mm); 2) extensibility of the atrial myocardium (Δl), determined as the increase in length of the atrium (in mm) for every 100 mg of applied

Institute of General Pathology and Pathological Physiology, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR P. D. Gorizontov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 96, No. 12, pp. 28-30, December, 1983. Original article submitted December 31, 1982.

TABLE 1. Effect of GHBA on Extensibility and Developed Systolic Tension of Atrium in Experimental Myocardial Infarction (M ± m)

Experimental conditions	Initial length of right atrium, mm	T_a, mg	Δl, mm	l, mm	ΔT_r, mg	$\Delta T_r/\Delta l$, mg/mm
Control (n = 18)	9,77±0,3	100	2,71±0,19	12,48±0,4	82,3±6,1	30,4±2,0
		400	6,42±0,38	16,19±0,7	300,4±19,2	46,7±3,1
		700	7,47±0,47	17,24±0,7	400,4±24,6	52,6±4,8
		800	7,64±0,54	17,41±0,5	401,5±24,6	52,5±4,8
Myocardial infarction (n = 21)	9,36±0,4	100	1,48±0,10*	10,84±0,5**	34,5±2,5*	23,3±1,4**
		400	4,09±0,21*	13,45±0,45**	144,4±13,1*	35,3±2,1**
		700	5,12±0,24*	14,48±0,5*	178,0±12,3*	34,8±3,5**
		800	5,24±0,26*	14,60±0,4*	177,3±12,5*	33,8±4,0**
GHBA (n = 10)	9,5±0,3	100	2,60±0,2	12,10±0,3	122,5±10,1	47,1±2,2
		400	6,22±0,33	15,72±0,5	342,5±20,1	55,1±3,5
		700	7,37±0,5	16,87±0,8	407,5±25,0	55,3±5,0
		800	7,52±0,51	17,02±0,6	415,0±24,4	55,2±4,6
GHBA + myocardial infarction (n = 11)	9,42±0,3	100	2,10±0,11***	11,52±0,3*	68,7±5,6*	32,7±1,9*
		400	4,74±0,25**	14,16±0,6***	218,5±12,4*	46,1±2,8**
		700	6,12±0,41**	15,54±0,8***	279,0±18,5*	45,6±4,0***
		800	6,45±0,42**	15,87±0,8***	275,5±20,0*	42,7±3,5***

Legend. n) Number of animals. *P < 0.001, **P < 0.01, ***P < 0.05 compared with corresponding control.

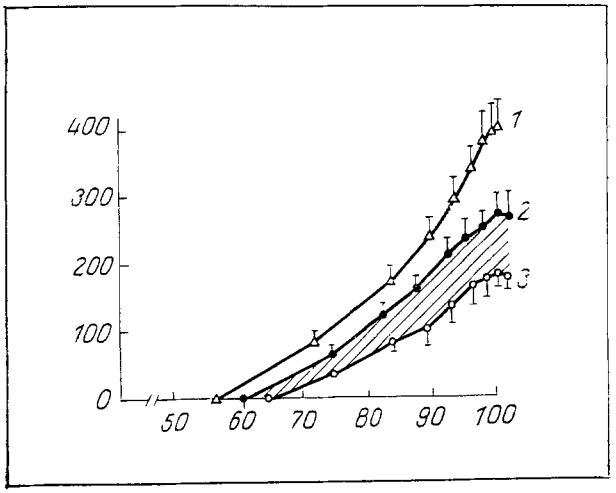

Fig. 1. Effect of preliminary injection of GHBA on Starling curve for right atrium of rats with myocardial infarction. Abscissa, length of atrium (in percent, 1 = 100%); ordinate, developed systolic tension (in mg). 1) Control; 2) GHBA + myocardial infarction; 3) myocardial infarction.

external load (T_a); 3) systolic tension (T_r) developed by the atrium in response to increasing loads at rest and at the initial length (in mg); 4) the efficiency of realization of the Starling mechanism, estimated as the increase in developed tension (in mg) per millimeter increase in length during stretching of the atrium ($\Delta T_r/\Delta l$). This parameter, which changes differently during stretching of the muscle of control animals and of animals developing infarction, characterizes the efficiency of realization of the Starling mechanism most accurately; 5) the ratio of systolic tension developed by the atrium to its length (in percent; l_{max}, i.e., the Starling curve, is taken as 100). These parameters were determined

TABLE 2. Effect of Preliminary Injection of GHBA on Contractility of Right Atrium in Experimental Infarction of Left Ventricle (M ± m)

Experimental conditions	Initial level of contractile function		Index of hypoxic contracture, percent	Index of calcium contracture, percent
	T_r, mg	IFS		
Control (n = 18)	387,6±21,3	4,1±0,2	47,8±4,8	41,4±5,9
Operation without occlusion (n = 13)	380,6±31,0	3,8±0,3	47,7±4,8	75,5±6,0
Myocardial infarction (n = 21)	193,3±12,1*	2,0±0,1*	73,7±6,5*	133,9±10,5*
GHBA (n = 10)	405,0±25,5	4,4±0,3	47,4±4,4	68,0±5,5
GHBA + myocardial infarction (n=11)	276,7±15,3**	3,4±0,3**	58,4±5,0†	94,9±7,9***

Legend. n) Number of animals. IFS) intensity of functioning of structures (in g/mg/min). *P < 0.001 compared with control; **P < 0.001, ***P < 0.01; ****P < 0.05 compared with myocardial infarction.

during stable functioning of the preparation, and also during the "hypoxic test" and during loading with excess Ca^{++}, by the method described previously [2]. During both these procedures the "index of contracture" was calculated. This parameter is equal to the ratio between the resting tension existing at a given stage of development of contracture to the maximal developed systolic tension before the beginning of action of the factor inducing contracture, multiplied by 100 (in percent).

EXPERIMENTAL RESULTS

Extensibility of the myocardium of the nonischemic part of the heart (right atrium) was reduced in infarction (Table 1). At the beginning of stretching, when the force applied to stretch the myocardium was 100 mg, this difference was particularly demonstrative: In animals with infarction the length of the atrium was increased by about half the control amount, and later these differences persisted although they were less marked. The increase in developed tension per unit of increase in length ($\Delta T/\Delta l$) for the control animals at different stages of stretching was between 30 and 52 mg/mm, whereas for animals with infarction it was between 22 and 42 mg/mm. In other words, the efficiency of realization of the Starling mechanism for the atrial myocardium of animals developing infarction was significantly reduced. Preliminary administration of GHBA reduced the depression of myocardial extensibility by 16-23%, and the increase in developed tension per unit increase in length was increased by 10%. The protective action of GHBA against depression of the Starling curve is illustrated in Fig. 1.

The developed tension for the atrium of animals with infarction was found to be reduced by half, the index of contracture induced by excess of Ca^{++} was doubled, and the index of hypoxic contracture was increased by 54% compared with the control (Table 2). Injection of GHBA reduced the depression of developed tension by 42%, the index of calcium contracture by 32%, and the index of hypoxic contracture by 55%. This is in agreement with clinical data [4, 7] showing the positive therapeutic action of GHBA in patients with myocardial infarction, and it suggests that an important role in the mechanism of this therapeutic effect is played by the ability of GHBA to protect nonischemic regions of the myocardium against the damaging action of stress.

LITERATURE CITED

1. E. Ya. Vorontsova, M. G. Pshennikova, and F. Z. Meerson, Kardiologiya, No. 11, 68 (1982).
2. F. Z. Meerson and R. S. Dosmagambetova, Kardiologiya, No. 3, 20 (1983).
3. F. Z. Meerson and A. M. Trikhpoeva, Byull. Eksp. Biol. Med., No. 11, 531 (1980).
4. V. G. Popov, D. A. Kharkevich, A. L. Syrkin, et al., Ter. Arkh., No. 12, 44 (1968).
5. M. Ya. Ruda, Kardiologiya, No. 1, 3 (1981).
6. E. I. Chazov, Vestn. Akad. Med. Nauk SSSR, No. 8, 3 (1975).
7. K. Yu. Yuldashev and A. S. Babadzhanov, Med. Zh. Uzbekistana, No. 10, 52 (1979).
8. H. Selye, E. Bajusz, S. Grasso, et al., Angiology, 11, 398 (1960).