LITERATURE CITED

1. Yu. D. Ignatov and Yu. N. Vasil'ev, Farmakol. Toksikol., No. 6, 676 (1976).
2. Yu. D. Ignatov and A. A. Zaitsev, Vestn. Akad. Med. Nauk SSSR, No. 11, 48 (1984).
3. Yu. D. Ignatov and A. A. Zaitsev, Byull. Éksp. Biol. Med., No. 4, 420 (1987).
4. A. Depaulis, R. N. Pechnick, and J. C. Liebeskind, Brain Res., **451**, 326 (1988).
5. D. L. Hammond and H. K. Proudfit, Brain Res., **188**, 79 (1980).
6. J. R. Haselton, R. W. Winters, D. R. Liskowsky, et al., Brain Res., **453**, 167 (1988).
7. R. H. W. M. Hoogen and F. C. Colpaert, Pharmacol. Biochem. Behav., **15**, 515 (1981).
8. A. J. Janss, B. F. Cox, M. J. Brody, et al., Brain Res., **405**, 140 (1987).
9. S. L. Jones and G. F. Gebhart, Brain Res., **460**, 281 (1988).
10. J. W. Lewis, G. Baldrighi, and H. Akil, Brain Res., **424**, 65 (1987).
11. T. A. Lovick, Pain, **31**, 401 (1987).
12. A. L. L. McDougall, R. Dampey, and R. Bandler, Neurosci. Lett., **60**, 69 (1985).
13. C. B. Saper, Trends Neurosci., **10**, 343 (1987).

EFFECT OF DIFFERENT TEMPERATURE CONDITIONS OF REPERFUSION ON RECOVERY OF MYOCARDIAL CONTRACTILITY AFTER HYPOTHERMAL CARDIAC ISCHEMIA

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One cause of acute cardiac failure (ACF) following open heart operations with an assisted circulation is reperfusion [7, 9]. In order to prevent the development of postoperative ACF, a technique of pharmaco-hypothermal cardioplegia is nowadays mainly used for anti-ischemic protection of the myocardium during the period when the heart is by-passed [3]. It must be noted that despite cooling of the heart muscle during the period of ischemia to 8-12°C [2], no attention has yet been paid to the temperature conditions of reperfusion during the first minutes after opening of the aorta.

The aim of the present investigation was to study the effect of various temperature conditions of reperfusion on the restoration of contractility and the cAMP concentration of the myocardium after hypothermal ischemia of its tissues.

EXPERIMENTAL METHOD

Experiments were carried out on noninbred male and female rats weighing 180-200 g. Under intraperitoneal pentobarbital anesthesia (25 mg/kg) the heart was removed from intact animals and perfused with oxygenated Krebs—Henseleit solution at 37°C. After perfusion for 15 min the heart was stopped by simultaneous compression of the aorta and external cooling of the myocardium to 8-12°C. Hypothermal ischemia of the heart lasted 90 min. Reperfusion was then commenced with perfusion fluid

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TABLE 1. Effect of Different Temperature Conditions of Reperfusion on Contractile Function and cAMP Concentration of Myocardium (M ± m)

Temp. of perfusion fluid, °C	Parameter	Period of observation, min		
		perfusion, 15	reperfusion	
			7	90
28	P_{dev}, mm Hg	133±15	126±76,1	48±8,9*
32		116,5±5,3	112,9±6,5	83,2±4,4
37		198±12	112,9±6,9*	41,9±4,9*
28	EDP_{lv}, mm Hg	8,8±0,6	10,6±0,6	21,3±0,7
32		8,4±0,7	11,8±1,0*	7,6±0,6
37		11,6±0,7	15,1±0,7*	33,3±2,3*
28	Velocity of contraction, mm Hg/min	1725±131	1449±190*	1115±263
32		1519,8±91	1651±113	1150±86*
37		1329±91	863,9±130*	738±97*
28	Velocity of relaxation, mm Hg/min	1472±226	868±115*	675±173*
32		1083±61	1434±124	829±56*
37		1089±80	1263±165	543±52
28	cAMP	2,47±0,15	2,55±0,14	1,62±0,14*
32		2,47±0,15	2,32±0,08	1,87±0,09*
37		3,7±0,32	1,89±0,13	1,67±0,08*

Legend. *$p < 0.05$ compared with 15 min of perfusion.

at a temperature of 28°C in series I, 32°C in II, and 37°C in III. During the first 7 min of reperfusion in the first two series the temperature of the perfusion fluid was adjusted to 37°C. After 15 min of perfusion, at the 7th and 90th minutes of reperfusion, parameters of myocardial contractility were studied by the method in [6]. The cAMP concentration in the myocardium was determined by radioimmunoassay using kits from "Ria Kit" (Czechoslovakia).

EXPERIMENTAL RESULTS

Restoration of cardiac activity after ischemic cardiac arrest for 90 min with hypothermal protection of the myocardium (8-12°C) was spontaneous in all series of experiments, although it differed in character depending on the initial temperature conditions of reperfusion. For instance, in the case of reperfusion with fluid at a temperature of 32°C, regular contractions were recorded at the first minute of reperfusion, whereas in hearts perfused with fluids at 28 and 37°C, initially small wave, but later large-wave ventricular fibrillation was discovered during the first 4 min. Regular contractions were not restored until the 5th minute of reperfusion.

After 7 min of reperfusion at temperatures of 28 and 37°C cardiac contractility was depressed (Table 1). In experiments with a temperature of perfusion fluid of 37°C the developed pressure (P_{dev}) and the velocity of contraction fell by 43 and 35% respectively. The end-diastolic pressure of the left ventricle (EDP_{lv}) rose by 30% but the rate of relaxation of the myocardium increased by 16% compared with initial values. This trend of changes in contraction and relaxation indicates profound disturbances of myocardial contractility. With the heart in this functional state, a fall of the cAMP concentration in the myocardial tissue by 23% was observed compared with the initial value.

After 7 min of reperfusion with fluid at a temperature of 28°C P_{dev} and the velocity of contraction of the myocardium were reduced by 15 and 16% respectively, EDP_{lv} was increased by 21%, and the velocity of relaxation of the heart muscle was reduced by 41°%. Changes in the above-mentioned parameters of myocardial contractility are evidence of the formation of a myofibrillar contracture with a normal cAMP concentration in the heart muscle tissue.

Reperfusion with an initial temperature of the perfusion fluid of 32°C did not cause a decrease in myocardial contractility. At the 7th minute all the parameters were a little higher than the initial values, to which they later quickly returned. Only EDP_{lv} exceeded its initial value by 18%. The cAMP concentration in the myocardium corresponded to its initial level.

Continuation of reperfusion in series I and III was accompanied by inhibition of myocardial contractility. For instance, after 90 min of reperfusion of the heart in series III P_{dev} fell progressively to 21%, the velocity of myocardial contraction fell by 44%, and EDP_{lv} was increased by 3.3 times, while the velocity of relaxation of the myocardium was reduced by half compared with the initial values. Under these circumstances the cAMP concentration was only 45% of its initial value. This trend of the parameters described above is convincing evidence of the formation of profound myocardial contracture.

After reperfusion for 90 min, myocardial contracture also developed in series I, but it was less marked than in hearts in which reperfusion was carried out at 37°C. The value of P_{dev}, and velocities of contraction and relaxation, tested during the control period, were 36, 65, and 46% of their initial values respectively, EDP_{lv} was increased by 2.4 times, and the cAMP concentration reduced by 34%.

After reperfusion at 32°C for 90 min, much less marked changes were observed in the parameters of myocardial contractility. In these experiments P_{dev} was 71%, the velocity of myocardial contraction and relaxation 75 and 76% respectively, EDP was 90%, and the cAMP concentration 76% of the initial values.

Thus the development of myofibrillar contracture during reperfusion of the heart with fluid at a temperature of 37°C was due to rapid rewarming of the cooled myocardium. The progressively rising temperature of the heart muscle evidently activated metabolic processes in the latter, before an adequate coronary blood flow was present. This conclusion is confirmed by the low cAMP level and the prolonged period of recovery of spontaneous cardiac activity. The reason for the low cAMP level is disparity between the high rate of its utilization and the low rate of its synthesis, as a result of the reduced concentration of myocardial ATP — the substrate for adenylate cyclase [4, 8]. Considering the important role of cAMP in the regulation of the contractile function of the heart [5, 10] it can be tentatively suggested that the considerable disturbance of the latter in the experiments with reperfusion of the cooled myocardium with fluid at a temperature of 37°C is due to the low cAMP concentration.

Reperfusion of the heart with fluid at a temperature of 28°C also leads to the development of myofibrillar contracture, but with a normal cAMP concentration in the heart muscle, which can be explained by the inhibitory action of a low temperature (28°C) of the perfusion fluid on cAMP utilization in the myocardium, for we know that the velocity of enzyme reactions falls with a fall of temperature [1].

The minor changes in contractile function of hearts reperfused with a temperature of 32°C are evidently attributable to restoration of the equilibrium state of cAMP synthesis and utilization in the cardiomyocytes during reperfusion at this temperature.

It can be concluded from these results as a whole that reperfusion of the heart after hypothermal ischemia at 8-12°C for 90 min with perfusion fluid at a temperature of 32°C leads to rapid recovery of spontaneous cardiac activity, does not cause the formation of reperfusion contracture, or significant changes in the contractile function of the heart, and normalizes cAMP synthesis and utilization in the cardiomyocytes. The use of reperfusion with fluid at this temperature in heart surgery centers during open heart operations with an assisted circulation will reduce the number of cases of development of postoperative ACF.

LITERATURE CITED

1. V. Ya. Aleksandrov, Cells, Macromolecules, and Temperature [in Russian], Leningrad (1975), pp. 162-171.
2. B. A. Korolev, G. A. Boyarinov, N. A. Shvets, et al., Grud. Khir., No. 3, 14 (1982).
3. G. I. Tsukerman, A. I. Malashenkov, D. O. Faminskii, et al., Anest. Reanimatol., No. 4, 7 (1985).
4. D. de Witt, K. Johim, and D. Behrendt, Circulation, **62**, No. 2, 892 (1980).
5. M. L. Entman, Advances in Cyclic Nucleotide Research, Vol. 4, ed. by P. Greenguard and G. A. Robinson, New York (1974), pp. 163-193.
6. E. F. Fallen, W. S. Elliot, and R. Yorin, Appl. Physiol., **22**, 836 (1967).
7. C. Kourouclis, G. Timogianuakis, A. Generalis, et al., 7th European Congress of Cardiologists, Abstracts, Amsterdam (1976), p. 688.
8. H. Lazar, G. Buckberg, A. Manganaro, et al., J. Thorac. Cardiovasc. Surg., **80**, 350 (1980).
9. G. Rona and C. Bier, J. Molec. Cell Cardiol., **12**, Suppl. 1, 137 (1980).
10. B. E. Sobel and S. E. Mayer, Circulat. Res., **32**, 407 (1973).