DISTURBED CONTRACTILITY OF THE NONISCHEMIZED PART OF THE HEART IN EXPERIMENTAL INFARCTION AND ITS PREVENTION BY PHOSPHOLIPASE INHIBITOR CHLOROQUINE

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UDC 616.127-005.8-039.71-07:
616.12-009.1-092

KEY WORDS: atrium; stress; infarct; phospholipases; chloroquine.

In experimental myocardial infarction of the left ventricle considerable disturbances of extensibility and contractility of the myocardium arise [3], similar to those found in emotional-painful stress [1] and prevented by the administration of propranolol. It has been suggested that these disturbances, of stressor origin, are the result of injury to cardiomyocyte membranes and are caused by a disturbance of the processes essential for complete relaxation, i.e., a disturbance of removal of Ca^{++} from the myofibrils and of energy transport thereto [2].

Since phospholipase activation is the probable mechanism of injury to the cardiomyocyte membranes in stress and ischemia [6], in this investigation an attempt was made to study the possibility of preventing disturbances of extensibility and contractility of nonischemized regions of the myocardium in experimental infarction by the use of the phospholipase A inhibitor chloroquine [6].

EXPERIMENTAL METHOD

Experiments were carried out on male Wistar rats weighing 180-220 g. Experimental infarction was produced by ligation of the descending branch of the left coronary artery by Selye's method [7]. The animals were decapitated 24 h after ligation of the artery. The area of the infarct, measured in square millimeters, was over 60% of the total area of the left ventricle on its outer surface and about 45% on its inner surface. Animals undergoing thoracotomy without occlusion of the coronary artery and intact animals served as the controls. Since there were no differences in contractility of the right atrium in the animals of these two series, the chloroquine used to protect the nonischemized myocardium was injected into control intact animals and also into intact animals in which a myocardial infarct was subsequently created. Chloroquine (from Egyt, Hungary) was injected in a dose of 20 mg/kg 1 h before and 6 h after creation of the infarct. The drug was injected in the same dose into the control animals, at the same time intervals.

Atria for the study of their contractile function were isolated immediately after decapitation of the animals and placed in a constant-temperature bath with oxygenated Krebs–Henseleit solution (95% O_2, 5% CO_2, 34°C, pH 7.4), so that the base of the atrium was fixed and the auricle was secured to a "Physiograph" DMP-4B myograph (Narco BioSystems, USA), recording isometric contractions. The atrium contracted spontaneously for 40-50 min, after which it was gradually stretched to a length at which it developed maximal tension when contracting isometrically; this length was designated l_{max}. This was achieved by gradually increasing the stretching load, and the change in length was recorded by means of a micrometer, with every 100 mg increase in the load. The load corresponding to l_{max} was described as the maximal load. Weight of the atria and their initial length were similar in all series of experiments. The following physiological parameters were determined: 1) extensibility of the atrial myocardium, equal to the increase in length of the atrium in millimeters for every 100 mg addition to the external load (l_{mm}/100 mg T_{rest}). As the total applied load increased, this parameter naturally decreased, because extensibility of the atrium is limited; 2) the ratio

Laboratory of Pathophysiology of the Heart, 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 A. M. Chernukh (deceased).] Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 95, No. 2, pp. 7-9, February, 1983. Original article submitted June 4, 1982.

0007-4888/83/9502-0167$07.50

TABLE 1. Effect of Preliminary Injection of Chloroquine on Extensibility and Developed Systolic Tension of Right Atrium in Rats with Myocardial Infarction

Series of experiments	Applied external load (T_a), mg	Increase in length from initial value (Δl), mm	Total length of atrium (l), mm	Systolic tension (ΔT), mg	$\Delta T/\Delta l$, mg/mm
I. Control (n = 23)	100	2,41±0,09	11,64±0,07	85,3±4,2	36,3±0,9
	400	6,43±0,29	15,65±0,40	317,9±12,6	49,4±1,1
	700	7,43±0,24	16,66±0,45	407,9±13,8	54,8±2,2
	800	7,59±0,16	16,82±0,35	409,0±11,4	53,8±2,2
II. Myocardial infarction (n = 23)	100	1,19±0,05	10,01±0,25	25,1±1,1	21,1±0,7
	400	3,55±0,1	12,31±0,25	137,2±6,5	38,7±1,0
	700	4,63±0,12	13,37±0,25	175,9±6,1	38,0±1,7
	800	4,8±0,13	13,56±0,25	174,3±6,0	36,3±1,7
III. Chloroquine (n = 10)	100	2,6±0,12	11,76±0,09	100, ±5,0	38,5±0,5
	400	5,9±0,10	15,06±0,2	311 ±10,1	52,7±1,2
	700	7,4±0,04	16,56±0,3	390 ±12,1	52,7±1,3
	800	7,71±0,03	16,87±0,2	395,4±13,4	51,2±1,3
IV. Chloroquine + myocardial infarction (n = 12)	100	2,14±0,10	11,05±0,11	71,2±4,1	33,3±0,9
	400	5,03±0,06	13,94±0,2	273,3±7,3	46,0±1,1
	700	5,79±0,03	14,7±0,15	258,2±10,1	44,6±1,0
	800	5,93±0,03	14,84±0,16	257,3±10,0	43,4±1,0

Legend. For all values of applied external load $P_{I-II} < 0.001$. $P_{II-IV} < 0.001$.
n) Number of animals.

of the force applied to stretch the atrium to increase in its initial length produced by stretching; 3) the systolic tension (in mg) developed by the atrium with increasing values of the resting load and at the initial length; 4) the efficiency of operation of the Starling mechanism, equal to the increase in developed tension, in mg/mm increase in length during atrial stretching ($\Delta T/\Delta l$); 5) the ratio of the length of the stretched atrium to the tension developed by the atrium, i.e., the Starling curve.

EXPERIMENTAL RESULTS

The main experimental results are given in Table 1. They show, as did a previous investigation, that the extensibility of the myocardium of the nonischemized part of the heart (right atrium) is reduced in the presence of infarction. Initially, when the external force applied to stretch the myocardium was 100 mg, this difference was particularly marked. The length of the atrium in animals with infarction was increased only half as much as in the control; these differences were still present later, but to a lesser degree. The increase in length with an increase in the external force used to stretch the myocardium was 34-48% less in animals with infarction than in the control, but these differences were always significant. Simultaneously with a disturbance of atrial myocardial extensibility, a decrease in the efficiency of operation of the Starling mechanism was observed in the animals with infarction, as reflected in the fact that the increase in developed tension per unit increase of initial length of the myocardium was reduced by 40%, and later by 33%. Disturbance of atrial contractility in animals with infarction was thus due, first, to the fact that the reduced extensibility prevented the Starling curve from flattening out on a plateau and, second, the increase in tension for every millimeter of increase in length of the myocardium achieved (the efficiency of the Starling mechanism) was reduced. Ultimately the Starling curve and the maximal tension developed by the atrial myocardium were depressed (Fig. 1).

Preliminary injection of chloroquine considerably reduced both these phenomena (Table 1). At the beginning of atrial stretching with a force of only 100 mg the extensibility of the myocardium in animals receiving chloroquine before creation of the infarct did not differ whatsoever from the control. Later a difference appeared, but extensibility was always significantly higher than in unprotected animals with infarction. The efficiency of the Starling mechanism in animals with infarction protected by chloroquine was indistinguishable from the control at initial degrees of stretching, but later it differed significantly less than in unprotected animals.

Ultimately chloroquine largely prevented depression of the Starling curve and of the developed tension in the animals with infarction (Fig. 1). Since the phospholipase inhibitor behaved in this case as a stabilizer of the cardiomyocyte membranes, this result is in harmony

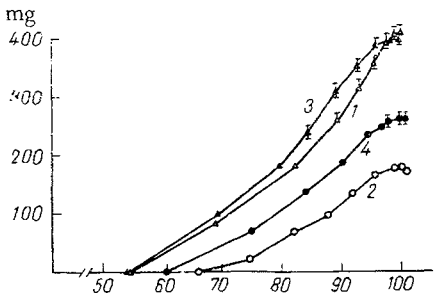

Fig. 1. Effect of preliminary injection of chloroquine on Starling curve for right atrium of rats with myocardial infarction. Abscissa, length of atrium (in %), l_{max} taken as 100%; ordinate, developed tension (in mg).

with the view that damage to the membranes is the basis of disturbance of the contractile function of nonischemized parts of the heart in infarction. It can be tentatively suggested that the stress which accompanies infarction led in the unprotected animals to the same disturbances of membrane Ca^{++} transport [2] and of energy metabolism [4] as were found in the heart in emotional-painful stress. In turn, this disturbed two processes essential for relaxation of the myofibrils and rupture of the actomyosin bridges, namely removal of Ca^{++} into the depots of the sarcoplasmic reticulum and sarcolemma and the supply of ATP into the perimyofibrillary space. As a result, the number of so-called residual actomyosin bridges preserved in diastole increased and the extensibility of the myocardium was reduced. Accordingly during excitation, when Ca^{++} entered the perimyofibrillary space, some of the binding sites of Ca^{++} with troponine were occupied and the developed tension was reduced. The membrane stabilizer, chloroquine in this case, prevented disturbance of function of the calcium pump and of the energy transport system, thus preventing these changes. It can be concluded from the results in general that the phospholipase inhibitor is worth studying as a factor limiting the disturbance of cardiac function during myocardial infarction in clinical practice.

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