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PREVENTION OF DISTURBANCES OF ELASTICITY AND THE CONTRACTILE FUNCTION OF THE NONISCHEMIC PART OF THE HEART IN EXPERIMENTAL INFARCTION WITH THE ANTIOXIDANT IONOL

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Activation of lipid peroxidation (LPO) has been shown to develop in heart muscle of the ischemic and nonischemic portions of the heart in experimental infarction [4] and also after emotional-painful stress [5] and marked disturbances of elasticity and contractility of the myocardium arise [1, 3]. It has been suggested that activation of LPO in the nonischemic parts of the heart in infarction may play a role in injury to the sarcolemma and sarcoplasmic reticulum of the cardiomyocytes, with a resulting disturbance of Ca^{++} transport and depression of the elasticity of the myocardium and of its contractile function [1, 3]. Since the contractility of the residual parts of the myocardium largely predetermines the work of the heart and the fate of the patient with an infarct, it is important to study ways of preventing disturbances of the contractile function of the nonischemic parts of the myocardium by means of LPO inhibitors, namely antioxidants.

The object of this investigation was to study the effect of preliminary administration of of the powerful synthetic antioxidant ionol on the contractile function of a region of the heart known to be nonischemic (the right atrium) in experimental infarction of the left ventricle.

EXPERIMENTAL METHOD

Experiments were carried out on female 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 [9]. 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 on the outer surface and about 45% on the inner surface. Animals subjected to thoracotomy but without occlusion of the coronary artery, and also intact animals served as the controls. Since there were no differences in the contractile function of the right atrium in the animals of these two series, the ionol used to protect the nonischemic myocardium was injected into control intact animals and into intact animals in which a myocardial infarction was subsequently formed. Ionol (2,6-di-tert-butyl-4-methylphenol) was injected in a dose of 50 mg/kg daily for 3 days before creation of the infarct and again 2 h after the operation. The compound was injected in the same dose and at the same time intervals into the control animals.

The atria were removed for study of their contractile function 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 attached to a "Physiograph DMR-4B myograph, recording isometric contractions (from Narco Bio-Systems, USA). The atrium contracted spontaneously for 40-50 min, after which it was gradually stretched to a length at which it developed maximal tension during isometric

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TABLE 1. Effect of Preliminary Injection of Ionol on Elasticity and Developed Systolic Tension of the Right Atrium in Rats with Myocardial Infarction

Experimental conditions	Number of animals	External load applied (T_{rest}), mg	Increase in length from initial (Δl), mm	Total length of atrium (l), mm	Systolic tension (ΔT), mg	$\Delta T/\Delta l$, mg/mm
1. Control	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	16,8±0,35	409,0±11,4	53,8±2,2
2. Myocardial infarction	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	4,80±0,13	13,56±0,23	174,3±6,0	36,3±1,7
	P_{1-2}	P < 0.001 for all values of external load applied				
3. Ionol	10	100	3,35±0,1	12,37±0,1	137,5±12,5	41,0±1,9
		400	6,6±0,4	15,62±0,6	382,5±13,7	57,9±3,0
		700	7,79±0,4	16,81±0,6	435,0±12,5	55,8±3,0
		800	7,99±0,4	17,01±0,5	437,0±6,2	54,6±2,9
4. Ionol + infarction	11	100	2,70±0,1	11,36±0,1	108,1±7,5	40,0±1,5
		400	5,81±0,2	14,49±0,4	282,5±17,5	48,4±3,0
		700	6,81±0,3	15,47±0,5	315,5±13,7	46,3±2,4
		800	6,98±0,2	15,64±0,4	314,6±8,3	45,0±2,4
	P_{2-4}	P < 0.001 for all values of external load applied				

contraction, described as l_{max}. This was done by gradually increasing the load, and the change in length was recorded by means of a micrometer for every 100 mg step. The size of the load corresponding to l_{max} was described as the maximal load. The weight of the atria and their initial length were similar in all series of experiments. The following physiological parameters were determined: 1) the elasticity of the atrial myocardium, determined as the increase in length of the atrium in millimeters for every 100 mg of externally applied load (1 mm/100 mg, T_{rest}). As the total applied load increased, this parameter fell, for the elasticity of the atrium is limited; 2) the ratio of the force applied to stretch the atrium to the increase in its initial length, resulting from stretching; 3) systolic tension (in mg) developed by the atrium during increasing values of the resting load and initial length; 4) the index of efficiency of realization of the Starling mechanism, equal to the increase in developed tension during stretching of the atrium ($\Delta T/\Delta l$, in mg/mm). This index, which showed different changes during stretching of the muscle of the control animals and animals with infarction, gives the most direct answer to the question of the efficiency of realization of the Starling mechanism; 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 results of these experiments, given in Table 1, show that, just as was demonstrated previously, the elasticity of the myocardium of the nonischemic part of the heart (right atrium) is reduced in infarction. Initially, when the external 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 only half as much as in the control. These differences persisted later. The increase in length with an increase in the external force used for stretching was 48-34% less in animals with infarction than in the control. Simultaneously with disturbance of elasticity of the atrial myocardium in the animals with infarction the effectiveness of realization of the Starling mechanism was reduced, as shown by 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 the contractile function of the atria in animals with infarction was thus due, first, to the fact that the reduced elasticity impeded the flattening out of the Starling curve on a plateau, and second, to the fact that the increase in tension per millimeter of increase in length of the myocardium — the efficiency of the Starling mechanism, was reduced. As a result depression of the Starling curve and of the maximal tension developed by the atrium was observed (curve 2 in Fig. 1).

Preliminary injection of ionol (Table 1) almost completely prevented both these phenomena. At the beginning of stretching of the atrium, on application of a force of only 100 mg the

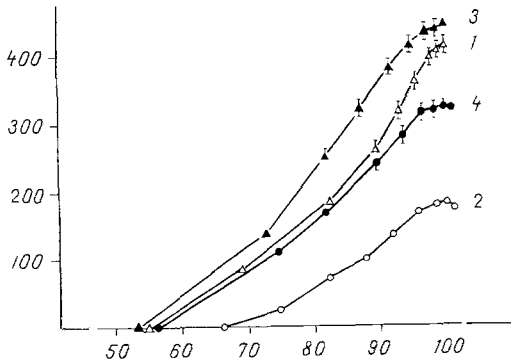

Fig. 1. Effect of preliminary injection of ionol on Starling curve for right atrium of rats with myocardial infarction. Abscissa, length of atrium (in %, 100% = l_{max}); ordinate, developed tension (in mg). 1) Control; 2) myocardial infarction; 3) ionol; 4) ionol + myocardial infarction.

elasticity of the myocardium in animals receiving ionol before creation of the infarct did not differ in general from the control. Later a difference did appear, but the elasticity was always significantly greater than in unprotected animals with infarction. The efficiency of the Starling mechanism in animals with infarction protected with ionol did not differ from the control with initial degrees of stretching, and later it differed significantly less than in the unprotected animals.

The antioxidant ionol thus largely prevented depression of the Starling curve and reduced the tension developed in animals with myocardial infarction (Fig. 1). Since ionol, as an inhibitor of LPO, behaves in this particular case as stabilizer of the cardiomyocyte membranes, this result is in agreement with the view that injury to the membranes is the basis of disturbance of the contractile function of the nonischemic parts of the heart in infarction. It can be tentatively suggested that the stress which accompanies infarction leads in unprotected animals to the same disturbances of membrane transport of Ca^{++} [2] and energy supply [6, 7] as are found in the heart in emotional stress. This in turn disturbs the two processes essential for relaxation of the myofibrils and destruction of actomyosin bridges, namely removal of Ca^{++} into the stores 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 which remain in diastole increases and the elasticity of the myocardium is reduced. This, in turn, has the result that during excitation, when Ca^{++} enters the perimyofibrillary space, some of the binding sites of Ca^{++} with troponin are occupied and the tension which can be developed is reduced. A membrane stabilizer, in this case ionol, prevents disturbance of the functioning of the Ca pump and the energy transport system, and thus prevents these phenomena. On the whole the results indicate that the antioxidant ionol is worthy of study as a factor restricting the disturbance of cardiac function in myocardial infarction in man.

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