EFFECT OF NUCLEOSIDES, STROPHANTHIN, AND COMBINATIONS OF THESE FACTORS ON THE DEVELOPMENT OF FATIGUE IN THE MYOCARDIUM

(UDC 612.172.014.3:615.711.5+615.7.11.5-092:612.172.014.3)

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Presented by Active Member AMN SSSR V. V. Parin
Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 57, No. 5, pp. 27-31, May, 1964
Original article submitted January 17, 1964

Compounds concerned in the synthesis of nucleic acids and in energy formation, such as uridine, uracil, inosine, and hypoxanthine, and also UTP, UDP, and ATP, are known to have a positive inotropic action on the isolated heart of mammals and the frog [3, 4, 6, 7]. An inotropic effect is also given by the cardiac glucosides, which mobilize the contractile function of the heart through changes in the cation exchange [9]. In the present research the separate and combined action of nucleosides and strophanthin on the process of fatigue in the myocardium was studied in the intact mammal.

EXPERIMENTAL METHOD

Experiments were conducted on 39 male rabbits weighing 2.2-2.8 kg, in which fatigue of the myocardium of the left ventricle had been reproduced by a special technique. For this purpose a wide thoracotomy was performed under intravenous chloralose-urethane anesthesia (60 mg/kg and 1 g/kg respectively), using artificial respiration with air. Beneath the initial portion of the ascending aorta a special device was inserted, acting in accordance with the principle of a bayonet clamp and enabling the aorta to be compressed instantaneously by simple pressure on a button outside the operation wound. A needle (No. 12) was passed through the region of the apex of the heart into the cavity of the left ventricle and connected to an electromanometer by means of a catheter. The pressure inside the left ventricle was measured by means of a "Barovar" electromanometer, manufactured by the firm of Alvar, and recorded on an ink-writing "Cardiovar" apparatus made by the same firm.

The initial pressure before clamping the aorta varied from 110 to 138 mm Hg. Complete occlusion of the aorta for 30 sec was performed 8 times, at intervals of 5 min, distally to the origin of the coronary arteries. The maximal strength of contraction was indicated by the "maximal systolic peak"—the maximal height of the systolic pressure in the left ventricle in the period of total occlusion of the aorta. During the first compression this index was 204-219 mm, and varied slightly from one animal to another: with each successive compression it fell by 2-19 mm. Hence, as a result of repeated compressions of the aorta a curve could be plotted, reflecting the gradual fall in the maximal level of the contractile function of the left ventricle and characterizing the process of development of fatigue of the myocardium.

To study the action of these agents on the development of this process, the animals were divided into 4 groups, each containing 9-10 rabbits. The animals of the 1st (control) group received an intravenous injection of 12 ml physiological saline immediately after the 5th compression; the animals of the 2nd group received an injection of a mixture containing 50 μ M each of uridine, uracil, inosine, and hypoxanthine in 12 ml physiological saline; the animals of the 3rd group received strophanthin in the same volume of physiological saline in a dose of 0.01 mg/kg. The animals of the principal (the 4th) group received the above-mentioned doses of uridine, uracil, inosine, and hypoxanthine immediately after the 5th compression, followed 1 min later by strophanthin in a dose of 0.01 mg/kg.

TABLE 1. Maximal Systolic and Endodiastolic Pressure in the Left Ventricle (in mm) during Repeated Compressions of the Aorta

Group of animals	Pressure	Before injection of agents					After injection of agents		
		Serial number of compression of aorta							
		1st	2nd	3rd	4th	5th	6th	7th	8th
1-st	Systolic	204±4,4	192±4,7	184±4,0	175±3,1	172±3,4	166±4,8	163±4,8	162±4,2
	Endodiastolic	16,6±4	15,4±2,7	16,4±3,0	13,6±2,3	16,0±2,7	19,0±2,8	15,2±2,6	19,6±2,2
2-nd	Systolic	219±8,4	200±6,0	188±5,8	186±7,0	173±4,8	181±6,1	179±6,1	176±6,8
	Endodiastolic	19,9±2,3	16,9±2,7	20,3±2,5	17,9±3,7	19,8±3,0	29,3±4,3	27,8±4,4	31,8±4,2
3-rd	Systolic	210±9,0	192±5,4	180±6,0	169±4,8	166±4,8	174±5,6	177±7,1	169±5,3
	Endodiastolic	10±3,0	22,4±2,5	20,8±3,1	24,8±2,0	23,2±2,5	28,5±3,7	33,2±3,1	30,9±3,7
4-th	Systolic	209±5,5	195±4,0	184±4,0	179±2,8	177±3,3	190±4,7	184±3,4	178±3,3
	Endodiastolic	8,6±2,6	12±1,9	17,7±1,9	23,9±4,3	26,6±4,5	28,8±4,3	30,5±5,5	25,5±4,8

The effect of the injected drugs on the height of the systolic peaks during the 6th, 7th, and 8th compressions was used as the criterion of their influence on the process of myocardial fatigue.

EXPERIMENTAL RESULTS

The results presented in Table 1 show that the height of the maximal systolic peak during the 5th compression of the aorta was 46-32 mm lower than during the 1st compression. The height of the endodiastolic pressure either showed no significant change from compression to compression or increased. The differences in the height of the systolic peak during the 5th compression between the 4 series of experiments were not statistically significant.

The results shown in Table 2 demonstrate that during the 6th compression of the aorta the height of the systolic peak in the animals of the 1st (control) group fell by 5.4 mm, while in the animals of the remaining groups, on the other hand, it rose (Figs. 1 and 2). After injection of the nucleosides and bases this increase was 8.2 mm after injection of strophanthin—8.8 mm, and after injection of a combination of nucleosides, bases, and strophanthin it was considerably greater——13.0. It was significant that the difference between the peaks of the 5th and 6th compressions in the control group itself differed significantly from the difference between these peaks in the experimental groups. The increase in the height of the systolic peak observed after injection of a combination of all the factors used was not only the largest, but also the most prolonged. This follows from the analysis of the data given in Table 2: the increase in the systolic peak observed during the 6th compression—5 min after the separate injection of strophanthin and nucleosides, was completely absent during the 7th and 8th compressions—10 and 15 min after injection of the above-mentioned substances. After injection of a combination of nucleosides, bases, and strophanthin, the systolic peaks on the contrary increased, not only during the 6th, but also during the 7th and 8th compressions. The endodiastolic pressure during the compressions was not significantly changed after injection of all the tested factors.

The principal result of the experiments was as follows: injection of a combination of nucleosides, bases, and strophanthin caused a larger and more prolonged increase in the maximal level of the contractile function of the fatigued myocardium than the injection of these factors separately.

The lowering of the maximal systolic peaks during repeated compressions of the aorta in the control animals, which received injections of physiological saline only, was very conspicuous in these experiments: the maximal level of the contractile function of the heart fell after the first five compressions by an average of 15.7%. It is highly significant that this process was not accompanied by any lowering of the endodiastolic pressure inside the left ventricle.

The fact that the decrease in the maximal strength of cardiac contraction during periodic, repeated occlusion of the aorta was not accompanied by a fall in the endodiastolic pressure means that the lowering of the strength of the contraction was independent of the decrease in the influx of blood into the left ventricle and the degree of stretching of the myocardium. Consequently, the lowering of the

TABLE 2. Changes in Maximal Systolic Peak during Compression of Aorta

Group of animals	Number of animals	Difference between maximal systolic peak observed during 5th and 6th compressions of aorta (in mm) (P_5-P_6)	Significance of differences (in relation to 1st group)
1st	10	-5.4±2.7	
2nd	10	+8.2±3.6	<0.01
3rd	10	+8.8±2.2	<0.001
4th	9	+13 ±4.2	<0.01

strength of the contractions observed in these experiments is a true expression of the lowering of the contractile power of the myocardium—the result of fatigue of the heart muscle.

Injection of the nucleosides and bases into the animals of the 2nd group and of strophanthin into the animals of the 3rd group had an undoubted effect on the development of the process of fatigue. Injection of these substances after the 5th compression of the aorta had the result that the systolic peak was not reduced in size during compression but, on the contrary, became larger than the preceding systolic peak.

Injection of a combination of strophanthin, nucleosides, and bases (4th group) gave the same effect, qualitatively speaking, but it was greater in magnitude and more prolonged.

Evaluation of the fact that inosine, uridine, hypoxanthine, and uracil, when injected in a single large dose, possess the power of abolishing myocardial fatigue to some extent must take into account the finding that uridine-C^{14}, when introduced into heart muscle from an external source, is incorporated in UTP, whereas inosine-C^{14} is incorporated in ATP. UTP and ATP are known to be initial products of nucleic acid synthesis and donors of energy for muscular contraction; both these compounds have a positive inotropic action on the isolated heart [2, 3]. Hence, it may be assumed that the effect of these substances on the process of fatigue of the myocardium was brought about as a result of increased formation of UTP and ATP in the myocardial cells, and led to an improved supply of energy-providing and plastic material to satisfy the contractile function of the myocardium.

The tension developed by the myocardial fibers during contraction is known to be proportional to their potassium loss and calcium absorption [5]. Cardiac glucosides inhibit the reverse transport of potassium into the myocardial fibers during diastole [11, 15] and the transport of sodium from the myocardial fibers into the extracellular fluid [10, 13]. The degree of their influence on the contractile function of the myocardium is proportional to their influence on the transport of these cations [8] and it is not exerted in the absence of calcium [12, 14].

Hence, it may be supposed that the changes in the cation exchange constitute the primary effect of the cardiac glucosides. As a result of these changes the degree of tension of the myofibrils is increased, the utilization of energy in the form of ATP is increased, and an intensification of oxidation and oxidative phosphorylation and other changes in energy formation, as observed during the action of cardiac glucosides, take place.

By regarding the cardiac glucosides as a factor mobilizing function through changes in cation exchange, it may be concluded that there are advantages to be gained from combining this mobilization with influences stimulating protein synthesis and energy formation, for the increased function is provided for with an increased supply of energy-forming and plastic materials. In face of these considerations a combination of strophanthin with nucleosides and bases was used for the treatment of fatigue of the heart. The effect of this combination was more marked than the effect of strophanthin and nucleosides administered separately. These observations demonstrate the desirability of studying the prolonged administration of cardiac glucosides in conjunction with factors promoting stimulation of energy formation and protein synthesis.

SUMMARY

A study was made of the effect produced by nucleosides (uridine, inosine and bases included into their composition—uracil and hypoxanthine) on the development of fatigue in the myocardium. The latter process was induced in acute experimental conditions by repeated overloading of the left cardiac ventricle by complete occlusion of the ascending aorta for 30 sec. The interval between the occlusions was 5 min. The maximal systolic pressure observed during aortic compression decreased with each subsequent compression, notwithstanding the unchanged or

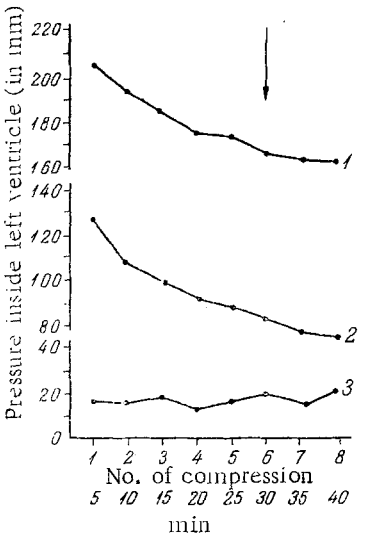

Fig. 1. Dynamics of systolic and endodiastolic pressure in the left ventricle during repeated occlusion of the aortic orifice in the animals of the control group. 1) Maximal systolic pressure during occlusion of aorta; 2) systolic pressure before occlusion of aorta; 3) endodiastolic pressure during occlusion of aorta carried out in the same cardiac cycle as the maximal pressure. The arrow indicates injection of physiological saline after the 5th compression.

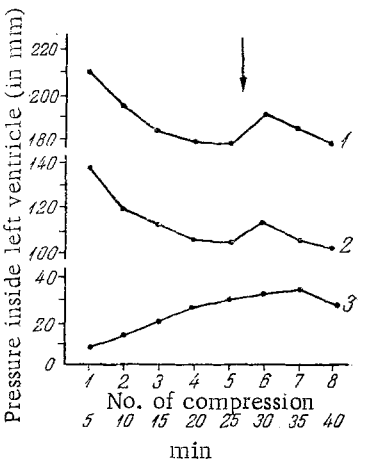

Fig. 2. Dynamics of systolic and endodiastolic pressure in the left ventricle during repeated occlusion of the aortic orifice in the animals of the experimental groups. Legend as in Fig. 1. The arrow indicates injection of uridine, uracil, inosine, hypoxanthine, and strophanthine after the 5th compression.

rising endodiastolic pressure. The dynamics of reduction of the maximal level of cardiac contractile function characterizes the process of fatigue. Administration of uridine, inosine and hypoxanthine following the fifth compression inhibits the further development of the fatigue process; the same effect is produced by strophanthin. Administration of a combination of uridine, uracil inosine, hypoxanthine and strophanthin eliminated the fatigue phenomena and increased the maximal level of the cardiac contractile function to a greater degree and for a longer time than separate administration of the same agents.

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