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CATECHOLAMINES AND MYOCARDIAL CONTRACTILE FUNCTION DURING
HYPODYNAMIA AND WITH AN ALTERED THYROID HORMONE BALANCE

G.M. Pruss, V.I. Kuznetsov, and A.A. Zhilinskaya

(NASA-TM-76000) CATECHOLAMINES AND MYOCARDIAL CONTRACTILE FUNCTION DURING HYPODYNAMIA AND WITH AN ALTERED THYROID HORMONE BALANCE (National Aeronautics and Space Administration) 17 p HC A02/MP A01 N80-16720 Unclas G3/51 47002

Translation of "Katekholaminy i sokratitel'naya funktsiya miokarda pri gipodinamii na fone izmenennogo balansa tireo-
idnyx gormonov," Izvestiya Akademii nauk SSSR., Seriya biologicheskaya, 2, March - April 1975, pp. 187-195



CATECHOLAMINES AND MYOCARDIAL CONTRACTILE FUNCTION DURING
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G. M. Pruss, V. I. Kuznetsov, and A. A. Zhilinskaya
Vitebsk State Medical Institute

In experiments on rats the dynamics of the content of catecholamines and the contractile function of the myocardium were investigated under hypodynamia (for a period of up to 30 days) for a background of altered balance of thyroid hormones. It was established that the content of catecholamines and contractile function of the heart in conditions of rigorous hypodynamia change according to phase. In the first 5 days the adrenalin content and noradrenalin content, and also, the strength and rate of contraction of myocardial tissue were lowered. The administration of thyroidin in small doses (1.5 mg per 100 g animal weight) raises the content of catecholamines, increases the contractile function of the heart and its tolerance. On the fifteenth day of hypodynamia the content of noradrenalin in the heart approached the norm, the contractile function of the myocardium improved and the administration of thyroidin had but little effect. On the thirtieth day of hypodynamia the content of noradrenalin, strength and rate of contraction of the myocardium approached normal values, but the functional reserve of the heart decreased. /187*

In experiments on rats the contractile function of the heart and the content of catecholamines in the myocardium were studied for 5, 15, and 30-day severe hypodynamia, and also the possibility of direct action on the indicated properties by small doses of thyroid hormones (1.5 mg per 100 g of weight).

*Numbers in the margin indicate pagination in the foreign text.

The experiments conducted showed that on the fifth day of hypodynamia there occurs a decrease in the content of adrenalin (A) and noradrenalin (NA) in the tissue of the left ventricle, a decrease in the parameters characterizing the contractile function of the myocardium: intraventricular pressure (VD), average and maximal rate of increase of pressure (SPD) in the left ventricle, Opie's index (Opie, 1965; IO), contractile index (IS) (following Veragut) and a decrease in the tolerance of the heart for physical load. The administration of thyroidin led to an elevation in the content of A and NA in the myocardium, an increase in the properties characterizing the strength and contractile rate of myocardial tissue, (VD, average and maximum SPD in the left ventricle, IS), and also increase in the cardiac stability under excess loads.

On the fifteenth day of hypodynamia the content of NA, strength and rate of contraction of the myocardium approached normal levels. The functional reserve of the heart decreased.

The motor activity belongs to the number of basic factors, determining the level of changed processes of the organism and the condition of its cardio-vascular system. Under the influence of prolonged restriction of mobility, cardiac activity was disturbed, 188 as was vascular tone (Kakurin, 1968; Buyanov and coauth., 1966, Panferova, 1972; Miller et al., 1964, and others), orthostatic stability of the organism (Lamb, Roman, 1961; Kotovskaya and coauth., 1971). In the development of these changes the essential role belongs to the disturbance of the regulatory apparatus of the circulation, termed detrenification of the organism (Myasnikov and coauth., 1963; Mikhaylovskiy and coauth., 1967; Korobkov, 1968; Loffe, 1971; Georgievski and Mikhaylov, 1968). The energy of the mechanical activity of the myocardium is closely connected with catecholamines, therefore the regular interest in the content of noradrenalin and adrenalin in the heart under hypodynamia. It was shown that under restricted mobility there occurs a decrease in noradrenalin in the tissues of the myocardium and the hypothalamus of experimental animals (Parin and coauth., 1969; Vitollo, Ushakov, 1970; Vitollo, 1971).

The question of the condition of the contractile function of the heart and its regulation under hypodynamia has not found the necessary elucidation in the literature. The investigation conducted by us had the purpose of studying the contractile capability of the myocardium and the sympathetic influences on the heart according to the data for content of catecholamines in the myocardium under hypodynamia, and also the possibility of direct effect upon the indicated properties by thyroid hormones.

Methodology

The investigations were carried out on 109 half-grown nonlinear white male rats weighing 170-250 g for 5, 15 and 30 days of hypodynamia. The experimental animals were contained in individual gripping cages of organic glass, severely limiting their motor activity, thus removing the possibility of squeezing. The control rats were confined in groups of ten in cages measuring 1000 by 450 by 250 mm. Both groups of rats received food and water ad libitum. The weight of the animals was determined every 5 days.

The content of A and NA in the left ventricle was determined by the method of E. Sh. Matlinoy and T. B. Rakhmanovoy (1967) on the MPF-2A "Hitachi" spectrophotofluorimeter.

Precise experiments for the determination of the parameters of contractile function of the myocardium were carried out under urethane anesthesia (100 mg per 100 g of weight intra-abdominally) with a closed chest cage and artificial respiration. In the cavity of the left ventricle a cannulus was introduced, connecting with the pickup of an electromanometer of type EM2-01. The pressure in the cavity of the left ventricle was registered on a five-channel electrocardiograph of type EKG 5-01. The rate of change of pressure in the ventricle was recorded with the help of a differentiating device. At the orifice of the aorta the distal exits of the coronary arteries were clothed with a special device, which ensured the rapid compression of

the aorta. Eleven contractions were produced, evoking, in such a manner, contractions of the myocardium of the left ventricle which were maximal in strength and isometric in system. The duration of each contraction was 30 sec, the interval between contractions 3 min. The recording pressure in the cavity of the left ventricle was produced by 5 and 25 sec contractions. The rate of motion of the photographic paper was 100 mm/sec.

The following properties were determined: the frequency of cardiac contractions; the magnitude of intraventricular pressure up until compression of the aorta -- $R_{\max 5}$ and $R_{\max 25}$ in mm of mercury; time of increase of pressure in sec; time of relaxation in sec.

On the basis of the data obtained the following were calculated.

1. The average of SFD in the left ventricle by means of dividing the pressure in the left ventricle by the time of increase of pressure in mm of mercury/sec.

2. Opie's index (IO) -- the product of the peak intraventricular 189 pressure by the frequency of cardiac contractions, in mm of mercury times $1/\text{min} \times 10^{-3}$.

3. The average rate of relaxation as the quotient of the division of the pressure in the left ventricle by the time of relaxation, in mm of mercury/sec.

4. Maximal rate of development of tension of the walls of the ventricle dp/dt_{\max} in mm of mercury/sec (Sonnenblich et al., 1965).

5. By means of the division of magnitudes characterizing the contractile function of the left ventricle by its weight, the intensity of structural functioning (IFS) was calculated in mm of mercury/g, a property which gives some representation of the quantity of functioning, accomplished by each unit of myocardial mass (Meerson, 1965).

6. The contractile index (IS) according to the method of Veragut and Krayenbühl (Veragut, Krayenbühl, 1965) -- as the quotient of the division of the maximum rate of increase of pressure in the ventricular cavity by the magnitude of the pressure at the

point corresponding to maximal rate, in sec^{-1} . IS characterizes the rate of the contractile process. The rate of contraction does not depend on the original length of muscle fiber, but consequently, on the final diastolic pressure, that is it is not regulated by the Frank-Starling mechanism. The change in contractile rate is most closely correlated with the energetic expenditure of the heart.

The properties of contractile function of the heart in animals of all the groups were determined before and after complete compression of the mouth of the aorta. The relationship of the subsequent magnitude to the first one was viewed as a property characterizing the functional reserve of the heart. The functional reserves of the myocardium were evaluated according to the "scale of fatigue" (Bakli and coauth., 1964), taking the value of the pressure in the left ventricle at the time of the first contraction of the aorta as 100%. The steepness of the slope of the curves at the time of subsequent contractions characterizes the capacity of the heart to perform with increased load for a long time, i.e. its tolerance.

Results and Discussion

On the fifth day of hypodynamia a significant reduction in the content of catecholamines in the myocardium was found: NA at 41, A at 53% (Table 1). In this same period occurred the reduction in the parameters characterizing the contractile function of the myocardium as well: R_{zh} by 28%, average and maximum SPD in the left ventricle by 40 and 47% respectively (at the time of contraction by 41 and 34% respectively), IS by 24% (at the time of contraction by 27%), Opie's index by 53% (during contraction by 32%) and the rate of relaxation of the cardiac muscle by 44%. The frequency of /190 cardiac contractions diminished by 30% (during contraction by 28%). For a unit of mass of the left ventricle there was found a great load (to which the increase in IFS per R_{zh} testifies). The relative weight of the left ventricle was increased. The data were completed with the like data in the control group of animals (Table 2).

Table 1. Content of catecholamines in the Myocardium under Hypodynamia (in mkg per 1 g of tissue).

| Property | Control rats n=7 | Duration of Hypodynamia | | | | | |
|----------|---------------------|-------------------------------------|-------------------------------------|-------------------------------------|------------------------------------|-------------------------------------|---|
| | | Group of Animals | | | | | |
| | | 5 days n=9 | 5 days + thyr. n=8 | 15 days n=11 | 15 days + thyr. n=9 | 30 days n=10 | |
| | | 1 | 2 | 3 | 4 | 5 | 6 |
| NA | 0.536 ±0.042 | 0.316 ±0.053 $P_{2-1} < 0.01$ | 0.489 ±0.041 $P_{2-1} < 0.05$ | 0.412 ±0.050 $P_{4-1} < 0.1$ | 0.440 ±0.058 $P_{5-4} < 0.5$ | 0.490 ±0.053 $P_{6-1} > 0.5$ | |
| A | 0.171 ±0.023 | 0.081 ±0.014 $P_{2-1} < 0.01$ | 0.100 ±0.022 $P_{2-1} < 0.01$ | 0.114 ±0.014 $P_{4-1} < 0.05$ | 0.099 ±0.024 $P_{5-4} < 0.5$ | 0.094 ±0.009 $P_{6-1} < 0.01$ | |

n = number of animals

On the 15th day of the experiment there was noticed a tendency toward the restoration of content of catecholamines in the heart. The quantity of NA increased by 18% and certainly was not to be distinguished from the control, and A increased by 30%, but turned out to be less than the norm by 33%. As far as the contractile function of the heart is concerned, several recorded changes had a clear tendency toward weakening, and other important properties even became normalized (\bar{R}_{zh} , the average SPD in the left ventricle before contraction of the aorta, IS at the time of contraction and the rate of relaxation of the myocardium).

On the 30th day of hypodynamia the content of NA in the left ventricle increased by 12% in comparison with the 15th day of hypodynamia and constituted 90% of the control, while A was decreased by 45%. The fundamental parameters, characterizing the strength and rate of contraction of the myocardium, certainly were not to be distinguished from those of the control group of animals, while several properties became greater than in the control. Thus, IS

increased by 56% (during contraction of the aorta by 71%). Yet the functional reserve of the heart was decreased.

In such a way, in the first period of hypodynamia (until the 15th day) the content of catecholamines in the myocardium decreases and the contractile function of the heart lessens. Through the work accomplished in our laboratory (Zhilinskaya, 1971) it was demonstrated that small doses of thyroidin restore the content of catecholamines in the myocardium when these are reduced. This allowed us to suggest that the doses of thyroidin close to physiological ones, can raise the content of catecholamines in the myocardium and, possibly, increase its contractile function under hypodynamia. For the solution of this problem a series of experiments were conducted, in which the strength and rate of contraction of myocardial tissue were determined for the left ventricle in isometric and isotonic conditions, and also the content of NA and A in the myocardium of hypodynamic rats, to which small doses of thyroidin were administered.

Thyroidin was administered through a probe into the stomach in a 1% amyloid paste in a dosage of 1.5 mg per 100 g of weight of the rat. The administration of thyroidin was begun on the fifth day before the experiment and daily during the course of the test period for hypodynamia. A starchy paste was administered to the control rats.

Upon the determination of the content of catecholamines in the left ventricle of the heart it turned out that on the 5th day of hypodynamia the application of thyroidin led to an increase in content of NA of 54%, and of A by 97%. The data were compared with those for the animals with a five-day curtailment of mobility without the administration of thyroidin (Table 1). The application of thyroidin was accompanied by the increase of the following parameters, which characterize the contractile function of the heart: R_{zh} by 32%, average SPD in the left ventricle by 45% (during contraction by 46%), maximum rate of growth of pressure and IS during contraction by 69 and

48% respectively, and also the rate of relaxation of the myocardium by 72%. Several parameters, such as IO, maximum SPD and IS, before the contraction of the aorta rose in comparison with the animals who had the 5-day limited motor activity and certainly were not distinguished from those of the intact rats (Table 2). It is necessary to observe that the increase of strength and rate of contraction of the myocardium upon administration of thyroidin in the applied dose is not accompanied by increase in frequency of cardiac contractions, decrease in functional reserve or the heart and decrease in body weight of the animals, which is characteristic for the administration of large doses of thyroid hormones (Golber, Kandror, 1969). Moreover, upon construction of the "scale of fatigue" of the myocardium it turned out that upon subsequent short-time contractions of the aorta the hypodynamic heart more quickly and to greater extent reduces the strength of its contractions, than such a heart in animals into which was introduced thyroidin (diagram). In such a way, small doses of thyroidin averted to a significant degree the fall in functional reserves of myocardium under hypodynamia, and increased its tolerance. /191

"Scale of fatigue" of the myocardium in rats of different experimental groups. On the x-axis -- ordinal numbers of subsequent contractions of the aorta; on the y-axis -- decrease in intraventricular pressure after subsequent contractions of the aorta relative to the pressure after the first contraction, taken as 100%; on the left -- 5, on the right -- 15 days



On the 15th day of the experiment, when the content of NA in the heart certainly could not be distinguished from the control, the application of thyroidin did not lead to any significant changes in the content of catecholamines in the heart. As far as the contractile function of the myocardium is concerned, an insignificant increase in several of its properties was observed ($R_{max 5}$, $R_{max 25}$, average SPD, IO, IS and the rate of relaxation of the left ventricle), which upon comparison with the animals who had the 15-day curtailment

of mobility without the administration of thyroidin, turned out to be insignificant. In connection with this, on the 30th day of hypodynamia, when the content of NA in the myocardium was normalized, we declined to apply thyroidin.

In such a way under hypodynamia was found a unidirectional change in the content of catecholamines and contractile function of the myocardium. In the future the content of NA, A increases and the contact capacity of the heart improves.

The decrease in the content of NA in the myocardium testifies to the decrease of sympathetic influences on the heart, since it was established that in warm-blooded animals a fundamental sympathetic mediator, to be found in the myocardium, is NA and the greater part of it is synthesized in the nerve endings (Kopin, 1964; Euler, 1956; Goodall, 1951).

The mechanism of action of the catecholamines on the effector cell has not been studied significantly. It is known, however, that the weakening in sympathetic influences on the myocardium leads to the disruption of the energetic security of the heart muscle, the decrease of krist in the mitochondria and the disturbance of the exchange of the rich energies of the phosphorus-containing bonds (Parin with coauth., 1969; Farrell et al., 1966). The catecholamines influence the synthesis of cyclic 3,5-AMP, by means of the activation of adenocyclase, and it in its turn participates in the activation of phosphorylase and lipase (Govyrin, 1971, Sutherland, Rall, 1960; Butcher et al., 1965). Lipolysis is activated not only in the heart, but also in the fatty tissue, increasing the ingress of unesterified fatty acids into the plasma and heart. Thus the catecholamines are not only fat-mobilizing factors, but also activators of the uptake of free fatty acids by the myocardium (Andreev, Korobova, 1970). These processes have significance for the mobilization of the energetic resources of the myocardium, constituting the sympatho-adrenergic system. Except for the activating influence of cyclic 3,5-AMP on the phosphorylase and lipase it was found that it hastens the transport across the membrane of the Ca^{++}

Table 2. Dynamics of the Properties Characterizing the Contractile Function of the Myocardium under Hypodynamia

| control | Duration of Hypodynamia | | | | | | | | | |
|---------------------------|---------------------------|--------------------------|-----------------------------|-----------------------------|--------------------------|--------------------------|---------------------------|---------------------------|---------------------------|---------------------------|
| | Groups of animals | | | | | | | | | |
| | 5 day P n=9 | 5 day P n=9 | 3-1 P n=11 | 15 day P n=11 | 4-1 P n=7 | 5-1 P n=7 | 30 day P n=10 | 6-1 P n=10 | 5-1 P n=10 | 6-1 P n=10 |
| 2.40 ± 0.15 208 ± 18.0 | 3.30 ± 0.11 208 ± 15.7 | 3.8 ± 0.10 230 ± 20.0 | 3.15 ± 0.08 202.5 ± 11.3 | 3.15 ± 0.08 202.5 ± 11.3 | 3.3 ± 0.15 203 ± 10.0 | 3.3 ± 0.15 203 ± 10.0 | 2.93 ± 0.08 196 ± 17.2 |
| 15.2 ± 9.9 | 15.2 ± 9.9 | 22.0 ± 23.3 | 18.7 ± 16.7 | 18.7 ± 16.7 | 18.5 ± 10.8 | 18.5 ± 10.8 | 18.5 ± 10.8 | 18.5 ± 10.8 | 18.5 ± 10.8 | 18.5 ± 10.8 |
| 97.8 ± 9.9 | 70.0 ± 5.1 | 82.5 ± 8.1 | 97.1 ± 14.0 | 97.1 ± 14.0 | 97.1 ± 14.0 | 97.1 ± 14.0 | 97.1 ± 14.0 | 97.1 ± 14.0 | 97.1 ± 14.0 | 97.1 ± 14.0 |
| 124.4 ± 12.3 | 176.4 ± 11.5 | 181 ± 11.0 | 124.0 ± 27.7 | 124.0 ± 27.7 | 131.1 ± 20.1 | 131.1 ± 20.1 | 171.0 ± 21.7 | 171.0 ± 21.7 | 171.0 ± 21.7 | 171.0 ± 21.7 |
| 24.2 ± 11.4 | 102.4 ± 15.3 | 218 ± 9.3 | 102.5 ± 13.9 | 102.5 ± 13.9 | 212 ± 19.4 | 212 ± 19.4 | 172.0 ± 9.4 | 172.0 ± 9.4 | 172.0 ± 9.4 | 172.0 ± 9.4 |
| 171.7 ± 18.4 | 151.0 ± 11.0 | 151 ± 11.0 | 115.1 ± 17.4 | 115.1 ± 17.4 | 171 ± 13.7 | 171 ± 13.7 | 113.1 ± 10.2 | 113.1 ± 10.2 | 113.1 ± 10.2 | 113.1 ± 10.2 |
| 2.5 ± 0.30 | 2.0 ± 0.19 | 2.0 ± 0.23 | 2.1 ± 0.21 | 2.1 ± 0.21 | 2.4 ± 0.24 | 2.4 ± 0.24 | 1.85 ± 0.20 | 1.85 ± 0.20 | 1.85 ± 0.20 | 1.85 ± 0.20 |
| 1912 ± 170 | 1164 ± 80 | 1670 ± 100 | 1571 ± 134 | 1571 ± 134 | 1578 ± 103 | 1578 ± 103 | 2161 ± 216.1 | 2161 ± 216.1 | 2161 ± 216.1 | 2161 ± 216.1 |

Rel. wt. of left ventricle, mg/g
 Freq. of card. contrac. at in. before compr. of aorta
 Freq. card. contrac. during aorta compr.
 Systolic pressure in ventric. cavity
 IFS for R_{zh} in mm Hg
 Max. pressure for 5 sec. compression of aorta R_{max} 5
 Max. pressure for 15 sec. compression of aorta R_{max} 25
 Functional reserve of heart for R_{max} 5
 Average rate of increase in pressure cav. left ventricle before compression of aorta

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Table 2. Continued

| | | | | | | |
|--|------------|------------|------------|------------|--------------|-------|
| Average rate of pressure increase for aortic compression | 3324 ± 369 | 3111 ± 251 | 2944 ± 197 | 3067 ± 193 | 3324 ± 250.2 | >0.5 |
| Maximum rate of pressure increase R _{zh} | 3400 ± 216 | 2371 ± 329 | 2124 ± 171 | 2561 ± 238 | 3350 ± 206.4 | <0.1 |
| Maximum rate of pressure increase P _{max} | 6427 ± 210 | 6007 ± 481 | 5015 ± 358 | 4973 ± 474 | 6430 ± 297.5 | >0.5 |
| Functional reserve | 2.3 ± 0.30 | 2.9 ± 0.40 | 2.5 ± 0.30 | 2.3 ± 0.24 | 1.70 ± 0.20 | <0.1 |
| Opie's index before aortic contraction | 20.4 ± 7.4 | 22.1 ± 2.0 | 18.1 ± 2.0 | 18.0 ± 1.5 | 20.0 ± 6.1 | >0.5 |
| Opie's index during aortic contraction | 54.6 ± 3.7 | 47.4 ± 5.2 | 37.7 ± 4.3 | 39.4 ± 2.9 | 47.1 ± 2.7 | >0.2 |
| Contractile index (Veragut) | 57.5 ± 5.0 | 62.0 ± 5.0 | 57.0 ± 4.0 | 50.8 ± 4.8 | 60.0 ± 9.1 | >0.01 |
| Rate of relaxation of myocardium left ventricle | 47.5 ± 188 | 1007 ± 155 | 1461 ± 169 | 1087 ± 161 | 643 ± 210 | >0.5 |

ions and increases the capacity of subcellular membranes to conjugate Ca^{++} , and on the intake and association of Ca^{++} in the interfibrillary spaces, as is known, depend the strength and rate of cardiac contractions (Kukovetz, 1971).

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Supported by the fact that one of the principal reasons for the decrease in contractile function of the heart on the 5th day of hypodynamia is the decrease in the content of catecholamines in the myocardium, one has the fact that the application of small doses of thyroindin leads to the increase of the content of catecholamines in the heart, and, along with this, its contractile function increases also.

Our suggestion that thyroindin acts on the contractile function of the myocardium principally mediated by NA is proved by the fact that at normal content of NA thyroindin does not increase its level and the contractile function of the heart almost does not change (15th day of hypodynamia). However, the mediated influence is not the only mechanism which leads to an increase in contractile function of the myocardium. It is known that for a physical load the absorption by the heart of unesterified fatty acids decreases, while the fraction of carbohydrates as substrates of oxidation, utilized by the heart, increases. At the foundation of this phenomenon lies the increase in activity of several ferments of the myocardium, responsible for the intracellular transport of hydrogen, and in particular of glycerine-1-phosphatoxidase and succinate dehydrogenase (Kraus; Kirsten, 1970). As Reker observes (1967), the functioning of the alpha-glycerophosphate cycle is in conjunction with the Krebs cycle -- this is precisely that which is necessary for the rapid development of energy. Having temporary predominance in the utilization of $NAD-H_2$, the alpha-glycerophosphate cycle plays the part of a powerful competitor of lactate dehydrogenase and in the same way facilitates the maintenance of a stationary concentration of pyruvate, necessary for the oxidation and development of energy in the Krebs cycle. As a result of this the possibility increases

for the myocardium to utilize carbohydrates in the role of substrate of oxidation. The increase in activity of glycerine-1-phosphatoxidase in the heart is observed also upon the administration of thyroid hormones in animals. In connection with this it is suggested that the rate of decomposition of carbohydrates in the heart is regulated by scutellate iron and that physical training (hypodynamia leads to detrenification) and thyroid hormones act on the metabolism of the heart unidirectionally (Krauss, Kirsten, 1970).

In such a way the contractile function of the heart and the content of catecholamines in the myocardium under hypodynamia is characterized by phasal changes. In the first 5 days the content of catecholamines, contractile function of the myocardium and tolerance of the heart for a physical load are reduced. The administration of thyroïdin in small doses increases the content of catecholamines, the contractile function of the heart and its tolerance. On the 15th day of hypodynamia the content of NA in the heart approaches the norm, the fundamental properties, characterizing the strength and rate of contraction of myocardial tissue, certainly are not to be distinguished from the controls. The administration of thyroïdin in this period did not turn out to have a significant influence on the content of catecholamines in the heart and its contractile function. On the 30th day of the experiment the content of NA, the strength and rate of contraction of the myocardium of the left ventricle were not to be distinguished from the normal magnitudes. In the mechanism of cardiac disturbances under hypodynamy in the subsequent stages of its development are included additional factors, which constitute the subject of our investigations.

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Vitebsk State Medical Institute

Article received by editors 1 December, 1972