

Popov V. M. The condition of neuro-endocrine systems in acute experimental myocardial infarction against the background of various reactivity of the organism. *Journal of Education, Health and Sport*. 2020;10(7):377-388. eISSN 2391-8306. DOI <http://dx.doi.org/10.12775/JEHS.2020.10.07.040> <https://apcz.umk.pl/czasopisma/index.php/JEHS/article/view/JEHS.2020.10.07.040> <https://zenodo.org/record/4167865>

The journal has had 5 points in Ministry of Science and Higher Education parametric evaluation. § 8.2) and § 12.1.2) 22.02.2019.

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The authors declare that there is no conflict of interests regarding the publication of this paper.

Received: 19.06.2020. Revised: 09.07.2020. Accepted: 31.07.2020.

The condition of neuro-endocrine systems in acute experimental myocardial infarction against the background of various reactivity of the organism

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Abstract

The adequacy of recovery processes in myocardial infarction (MI) significantly depends on the state of reactivity of the organism, which, in turn, is determined by the adequacy of neuro-endocrine regulation, in particular, hypothalamic-pituitary-adrenocortical (HPA) and hypothalamic-pituitary-thyroid (HPT) system system.

Purpose of the study. To investigate the condition of HPA and HPT in acute experimental MI against the background of different reactivity of the organism.

Material and methods. The study was performed on 20 outbred adult dogs weighing 8-12 kg, in which MI was simulated by ligation of the anterior interventricular artery. Animals were divided into three groups (n = 5 in each group). The condition of hyperreactivity was caused by the introduction of pyrogenal (group 2), the state of hyporeactivity - the introduction of azothioprine (group 3), in group 1 drugs were not used (state of normoreactivity). In the control group used 5 falsely operated dogs with thoracopericardiotomy. In animals before surgery, on 1, 4, 7, 11 and 15 days in the blood was determined by the content of adrenocorticotrophic hormone (ACTH), thyroid-stimulating hormone (TSH), cortisol (Cr), aldosterone (Ald), thyroxine and triiodothyronine. Statistical processing was performed using license packages Statistica 5.5 (Stat Soft Rus), Statistica Neural Networks (Statsoft Inc.).

Results. Normoreactive course of myocardial infarction was characterized by primary activation of HPA, which was most pronounced for Cortisol, followed by restoration of ACTH and Aldosterone levels and duration of activation of the central link up to 4 days, peripheral - up to 7-11 days; reciprocal in relation to HPA inhibition of the functional activity of the HPT, most pronounced on the 4th day and lasting up to 15 days. Such changes caused the healing of myocardial infarction through the formation of a full-fledged post-infarction scar. The hyperreactive course of myocardial infarction was characterized by hypersecretion of ACTH with hypercorticism and hyperaldosteronism and less pronounced suppression of HPT with the restoration of its functional activity on the 7th day. The hyporeactive course of myocardial infarction was characterized by a minimally pronounced and delayed up to 4 days activation of HPA with Aldosterone hyposecretion on the 15th day; deep hypothyroidism of both central and peripheral genesis. Impaired reactivity was accompanied by an increase in the area of necrosis and a decrease in the thickness of the heart wall with the formation of postinfarction aneurysm.

Conclusions. Desynchronization of necrotic and reparative processes with a change in reactivity leads to a disruption in the relationship between necrosis and repair with the formation of postinfarction aneurysm, which is accompanied by different activities of the HPA and HPT.

Key words: myocardial infarction; reactivity; neuro-endocrine system

Introduction. Pathology of the cardiovascular system is about 63% of the overall structure of causes of death from various diseases in Ukraine and ranks first in the statistics of morbidity and mortality [1-3]. Among the most prognostically unfavorable diseases, the most dangerous is myocardial infarction (MI) [4-6]. The body's response to MI significantly depends on the state of reactivity of the body, which, in turn, is determined by the adequacy of neuro-endocrine regulation [7, 8]. Pathological reactivity (hyper- or hyporeactive) significantly complicates the course of MI, delays the recovery process, overloads or, conversely, contributes to the development of insufficiency of compensatory-adaptive reactions [9-11]. The state of hypo- or hyperreactivity in MI leads to a complicated, prolonged course of recovery, the main mechanism of which is the acceleration or deceleration of necrotic processes and delayed development of repair [10]. Inadequate regulatory effects of neuroendocrine regulation, in particular, the main adaptive systems - hypothalamic-pituitary-adrenocortical (HPA) and hypothalamic-pituitary-thyroid (HPT), cause a complicated course of MI, disrupt the mechanisms of sanogenesis [12, 13].

MI is a powerful stress factor for the body, it causes the activation of neuro-endocrine mechanisms aimed at maintaining the body's vital functions. Activation of the adrenocortical (HPA) and pituitary-thyroid (HPT) systems is aimed at maintaining blood circulation in conditions of decreased heart efficiency [14-16]. The variability of the course of the post-infarction period, the development of complications, and the duration of rehabilitation largely depend on neuro-endocrine changes in the patient's body [17-18].

A number of studies have shown that the development of acute myocardial ischemia leads to the activation of neuro-endocrine systems with vasoconstrictive effects, aimed at increasing cardiac output, blood pressure, and intensification of blood circulation [19, 20]. Activation of HPA triggers both urgent and long-term reactions in response to ischemic myocardial injury [144]. The effects of the central link - adrenocorticotrophic hormone (ACTH) and peripheral - cortisol (Cr) determine the changes in the synthesis and secretion of inflammatory mediators, growth factors, hormones and neurotransmitters. Thus, it has been found that glucocorticoids improve the survival of cardio-myocytes after MI [22, 23].

The data on the state of the HPT during the development of MI are contradictory. The experiment has shown a decrease in thyroid hormones after the development of MI and their protective role in the prevention of ischemia-induced apoptosis of border zone cardio-myocytes [24-26]. The effects of a short-term increase in thyroid hormones cause an increase in left ventricular contractility and an improvement in hemodynamics, at the same time, an excessive or prolonged increase in hormones can cause the development of complications such as arrhythmias, repeated heart attacks, and the development of heart failure [27]. Thyroid hormones increase myocardial sensitivity to catecholamines, which leads to an increase in myocardial contractility, oxygen demand, and oxidative stress [28, 29].

Thus, the study of the state of neuroendocrine systems in acute myocardial infarction against the background of different reactivity of the organism is an urgent task, the solution of which can explain the different efficiency of the repair processes after myocardial infarction.

Purpose of the study. To study the state of HPA and HPT in acute experimental MI against the background of different reactivity of the organism.

Material and methods. All studies were conducted in strict accordance with the "European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes" (Strasbourg, 1985) and in accordance with the conclusion of the Commission on Bioethics of Donetsk National Medical University. M. Gorky № 132/16 dated 25.11.2010.

The experiments were performed on 20 outbred adult dogs weighing 8-12 kg. MI was

modeled by ligation of the anterior interventricular artery in two places: in the lower and middle third. The experimental animals were divided into 3 groups of 5 dogs each. In the 1st group, the basic model of MI without changes in the reactivity of the organism was modeled. In other groups simulated healing of MI was simulated: in the 2nd group - hyperreactive condition (intramuscularly 7 days before the simulation of MI was administered daily lipopolysaccharide pyrogenal, 10 mg per 1 kg of body weight, once a day; after simulation of MI for another four days pyrogenal was administered daily in the same dose), in group 3 - hyporeactive state (intramuscularly 7 days before the simulation of MI was administered daily azothioprine, 1.5 mg per 1 kg, 1 time per day; after simulation of MI for another four days daily administered azothioprine in the same dose). In the control group used 5 falsely operated animals with thoracopericardiotomy. In animals before surgery and on the 1st, 4th, 7th, 11th and 15th day after modeling MI performed blood sampling to determine hormones: adrenocorticotropic (ACTH), cortisol (Cr), aldosterone (Ald) , thyrotropic (TSH), thyroxine (T4) and triiodothyronine (T3). Determination of their content was performed by radioimmunological (labeled radioactive isotope I125) and enzyme-linked immunosorbent assays using standard commercial reagent kits for determination of test substances in dog blood samples (DSL, USA and Immunotech, France).

Statistical processing of the results was performed using license packages Statistica 5.5 (Stat Soft Rus), Statistica Neural Networks (Statsoft Inc.).

Results and discussion. At autopsy 15 days after surgery, it was found that all animals developed transmural MI. In animals of the 1st group, the ratio of the average thickness of the intact myocardium to the minimum thickness of the heart wall in the area of MI approached one (Fig. 1). The shape and size of the ventricle corresponded to those in the norm. Signs of insignificant myocardial hypertrophy were determined.

In animals of the 2nd group (Fig. 2), the ratio of the average thickness of the intact myocardium to the minimum thickness of the heart wall in the MI zone exceeded 2.0. This made it possible to establish that the outcome of the healing of myocardial infarction was a post-infarction aneurysm with localization in the anterior wall of the left ventricle in the middle and apical sections, which was determined by the site of ligation of the anterior interventricular artery. Light pressure on the wall of the left ventricle at the site of the aneurysm led to its bending inward.

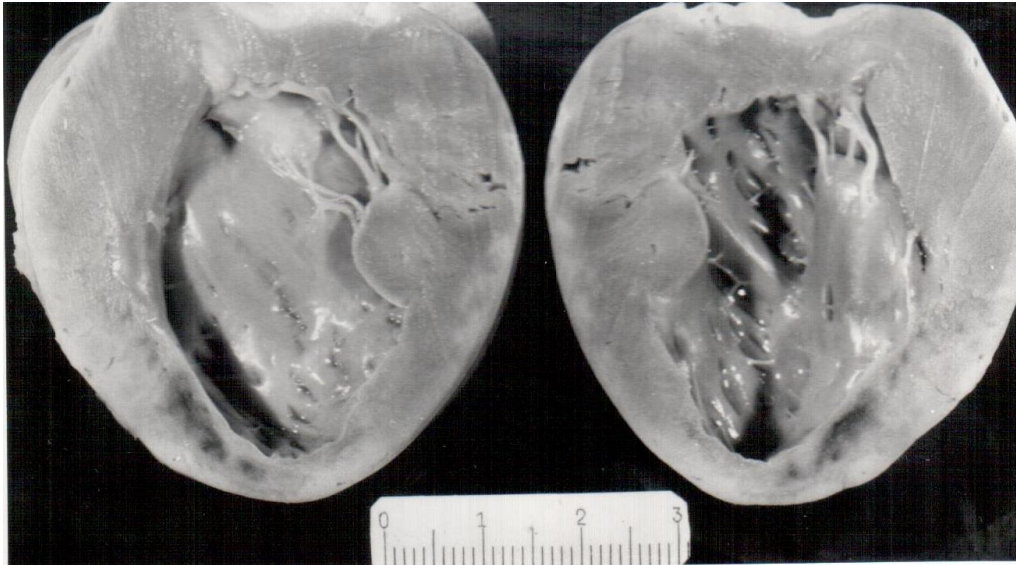


Fig. 1. Anatomical preparation of the heart of a dog of the 1st group (normoreactive course of MI). Incision through the IM area.

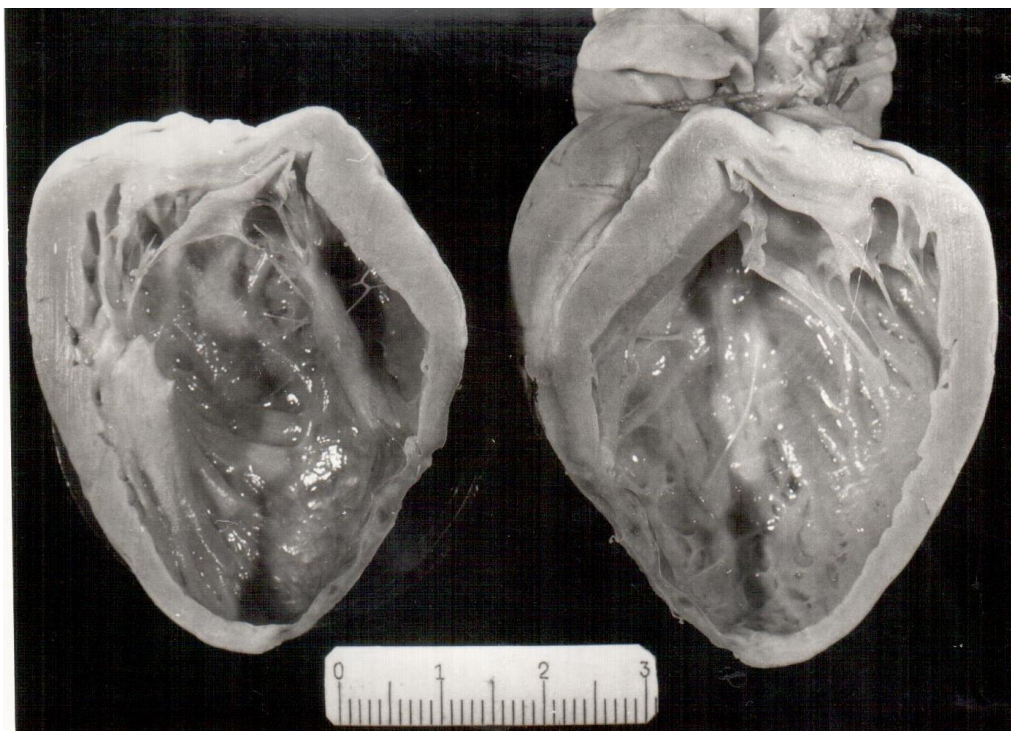


Figure: 2. Anatomical preparation of the heart of a dog of the 2nd group (hyperreactive course of MI). Incision through the MI zone.

In animals of the 3rd group, the MI zone, as in the 2nd group, healed with the formation of an aneurysm in all cases (Fig. 3).

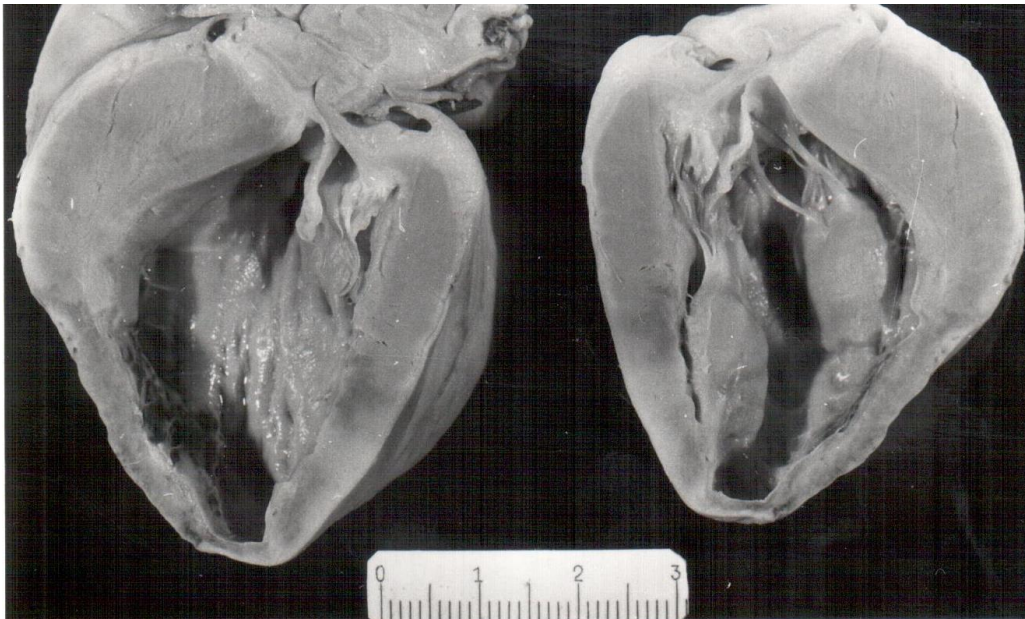


Figure: 3. Anatomical preparation of the heart of a dog of the 3rd group (hyporeactive course of MI). Incision through the MI zone.

Comparative analysis of the prevalence of aneurysm, minimum and average wall thickness of the left ventricle in the area of the aneurysm in animals of this group turned out to be smaller in surface area and more in thickness than in animals of the 2nd group.

Thus, anatomical studies have shown that in a normoreactive course, the outcome of MI healing was a full-fledged postinfarction scar. In case of impaired reactivity (hyper- and hyporeactive course of MI), healing was accompanied by an increase in the area of necrosis and a decrease in the thickness of the heart wall with the formation of post-infarction aneurysm.

In the 1st group, the level of ACTH in the blood reached its maximum value by the end of the 1st day, and then the hormone content gradually decreased to the initial level on the 15th day (Fig. 4).

Under the influence of an increased level of ACTH, the secretion of gluco- and mineralocorticoids by the adrenal cortex increased. The early reaction of the central link of HPA was parallel to the reaction of the peripheral, but the duration of the peripheral reaction was significantly longer. So the Creatinine level kept at maximum values up to 7 days, while the ACTH level - only up to 4 days. Moreover, if the secretion of ACTH normalized on the 15th day, then the level of Creatinine was higher than the control level on the 15th day.

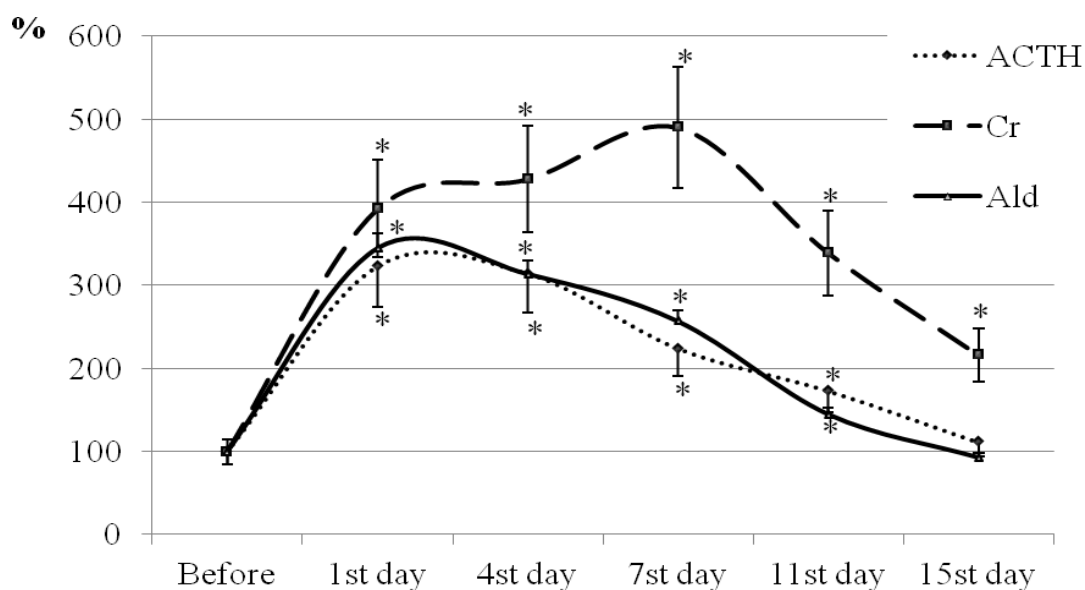


Figure: 4. Dynamics of blood levels of ACTH, Creatinine and Aldosterone in animals of the 1st group (with normoreactive course of MI). Expressed in % of the reference level, which is taken as 100%. * - $p < 0.05$ when comparing the mean values with the control level

An increase in the body's reactivity contributed to the formation of a hyperergic reaction of the central link of the HPA. Under the influence of a sharp increase in the level of ACTH in the blood, the secretion of both gluco- and mineralocorticoids increased significantly. Apparently, it was these shifts that determined the desynchronization of the recovery processes, when the necrotic processes intensified, and the reparative ones lagged behind them.

In a hyporeactive course of MI, the HPA response was generally less pronounced: the increase in ACTH content reached its maximum only on the 4th day, after which its content gradually decreased to control values on the 15th day of MI. This indicated the delayed response of the central link of the HPA. The dynamics of the content of Creatinine and Aldosterone was distinguished by the same tendency. The formation of a state of hyporeactivity against the background of experimental MI not only did not stimulate, but even inhibited Aldosterone secretion by the adrenal cortex.

The functional activity of the central link of the thyroid system in MI under conditions of normoreactivity of the organism was inhibited (Fig. 5).

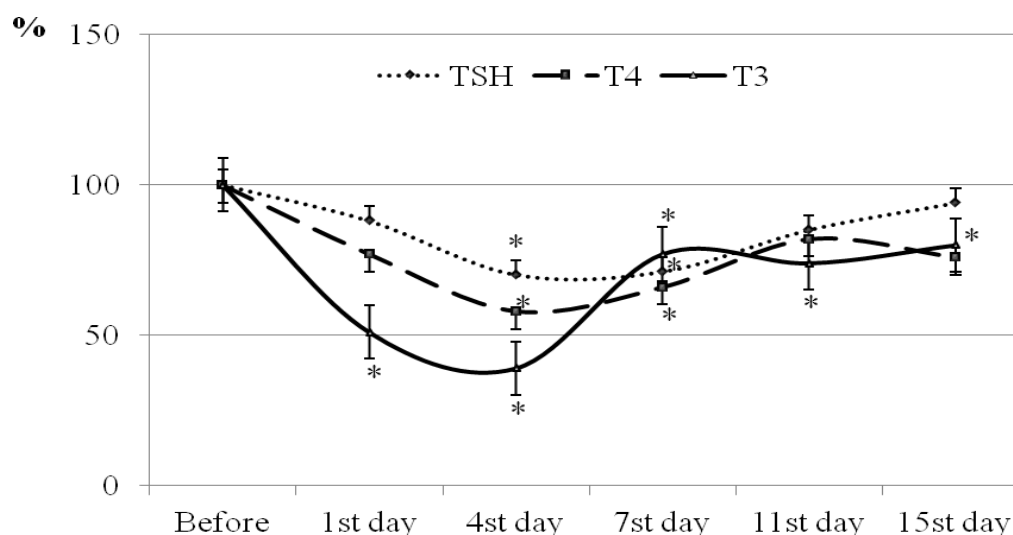


Figure: 5. Dynamics of the content of TSH, T4 and T3 in the blood in animals of the 1st group (with normoreactive course of MI). Expressed in % of the reference level, which is taken as 100%. * - $p < 0.05$ when comparing the mean values with the control level

This reaction reached its maximum expression on the 4th - 7th day. The restoration of functional activity was noted already in the subacute period from the 11th day, which determined by this period the duration of the phase reaction of the central link of the HPT: the primary inhibition of its functional activity (from day 1) and subsequent recovery (from the 11th day). According to the dynamics of TSH, the dynamics of thyroid hormones - T4 and T3 - also changed. The levels of both hormones decreased significantly: T4 with a minimum on the 4th and 7th days, and T3 - already on the 1st and, especially, on the 4th day.

Such a reciprocity of the central post-stress regulation of neuro-endocrine systems (HPA-HPT), in our opinion, could be considered a typical reaction of the neuro-endocrine system in acute stress, including MI, and the corresponding changes could be called post-infarction adaptive neuro- endocrine syndrome.

Modeling the state of hyperreactivity of the organism did not change the qualitative nature of the HPT reaction. As in the normoreactive course of myocardial infarction, there was a general trend towards a decrease in the content of both TSH and thyroid hormones with their subsequent restoration. However, the decrease in the level of hormones was the least pronounced, and already from the 7th day, the level of TSH was restored.

The hyporeactive course was characterized by the lowest values of the content of all hormones of the HPT and the lengthening of the period of the phase fluctuation of its activity, which exceeded 15 days, which indicated the formation of a deep thyroid deficit. Such

dynamics of HPT hormones indicated the development of deep hypothyroidism of both central and peripheral genesis. Apparently, it was the deep and long-term thyroid insufficiency, which was formed against the background of hyporeactivity, that could determine the later onset and slow development of the repair processes, which was the basis for the formation of a complicated outcome of MI in this group.

A summary of the obtained material on the state of neuro-endocrine systems against the background of different reactivity of the organism is presented in Table 1.

Table 1

The condition of the neuro-endocrine systems against the background of different reactivity of the organism in acute experimental myocardial infarction

System	Reactivity	Reaction characteristic
HPA	normo-	primary activation, the most pronounced for Creatinine, followed by recovery (ACTH and Aldosterone); the duration of the activation period of the central link up to 4 days, peripheral - up to 7 - 11
	hyper-	hypersecretion of ACTH with hypercorticism and hyperaldosteronism
	hypo-	primary activation is minimal and delayed up to 4 days; hyposecretion of Aldosterone on the 15th day
HPT	normo-	suppression of functional activity, most pronounced on the 4th day, lasting up to 15
	hyper-	less pronounced depression with the restoration of activity on the 7th day
	hypo-	deep hypothyroidism of both central and peripheral genesis

Thus, this study has confirmed the importance of the regulatory role of neuro-endocrine systems with different reactivity of the organism and the dependence on this of the processes of necrotization and repair in the ischemic myocardium. With MI against the background of increased reactivity of the organism, necrotic processes intensify and reparative processes are delayed in relation to them. With reduced reactivity, necrotic processes are weakened, causing a later onset and slower development of reparative processes. As a result, in both cases, desynchronization of necrotic and reparative processes occurs, as a result of which the strength of the heart wall in the infarction zone decreases.

Conclusions

1. Normoreactive course of myocardial infarction was characterized by primary activation of HPA, which was most pronounced for Creatinine, followed by restoration of ACTH and Aldosterone levels and duration of activation of the central link up to 4 days,

peripheral - up to 7-11 days; reciprocal in relation to HPA inhibition of the functional activity of the HPT, most pronounced on the 4th day and lasting up to 15 days. Such changes caused the healing of myocardial infarction through the formation of a full-fledged post-infarction scar.

2. The hyperreactive course of myocardial infarction was characterized by hypersecretion of ACTH with hypercorticism and hyperaldosteronism and less pronounced depression of HPT with restoration of its functional activity on the 7th day. The hyporeactive course of myocardial infarction was characterized by a minimally pronounced and delayed up to 4 days activation of HPA with Aldosterone hyposecretion on the 15th day; deep hypothyroidism of both central and peripheral genesis. Impaired reactivity was accompanied by an increase in the area of necrosis and a decrease in the thickness of the heart wall with the formation of postinfarction aneurysm.

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