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MODEL OF AN ISOLATED RAT HEART DURING READAPTATION AFTER HYPOKINESIA

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KEYWORDS

Isolated Heart

Hypokinesia

Rat

Left Ventricle Pressure

Heart Rate

Coronary Flow

ABSTRACT

The current study was carried out to evaluate the effect of motor activity (hypokinesia) limitation on the body and organ systems. Hypokinesia contributes to changes in the work of many adaptive systems of the body, which leads to disorders in the musculoskeletal system, respiratory, muscular, and cardiovascular systems. Of particular relevance and practical interest is the effect on the body not only of hypokinesia, but also the processes during the transition from it to an active motor regime (recovery period). The study was carried out on 2 groups of white outbred rats: group 1 - animals growing under limited motor activity for 30 days, group 2 - animals in the recovery period after 30 days of hypokinesia. The study of the functional parameters of the Langendorff heart of rats (LVP, HR, CF) was carried out on the selected groups. Results of the study revealed that after 30 days of hypokinesia and 14 days recovery period, the heart rate decreased 1.2 times and the coronary flow decreased 2 times. Further, the current study has shown a tendency to restore the heart rate parameters of an isolated heart but the restoration of the coronary flow and cardiac contractility has not been identified. The result of the study suggested that 14 days is not a full-fledged period for the restoration of the functional parameters of the body. This study devoted the effect of motor activity (hypokinesia) limitation on the body and organ systems are relevant and significant.

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1 Introduction

A decrease in muscle loads, a sedentary lifestyle is a typical feature of the life of modern people, changes in lifestyle leading to a decrease in physical activity, there is a need for the body to adapt to new conditions. In these cases, a specific adaptation has been developed, which helps in reducing structural and metabolic disorders related to the many organs and body systems function. Increased hypokinesia is a significant factor in increasing the risk of cardiovascular disease. The negative results of limiting motor activity are growth retardation of the body and internal organs against the background of disorders in differentiation and tissue regeneration (Grigoriev et al., 2004).

Adaptation of the heart to changing conditions is carried out using a single regulation with the participation of intracardiac and extracardiac mechanisms. Limited motor activity leads to disturbances in the coordinated work of the cardiovascular system, namely, the contractile function of the heart worsens, the tone of the heart muscle decreases, its minute volume decreases, and depletion of the coronary vessels is also observed (Evseeva, 2000).

It was also reported that within 7 days of hypokinesia, the absolute heart mass decreases by 7%, and by 15% in 30-days of the hypokinetic period, while the relative heart mass increases depending on the increase in the immobilization period. After 30 days of hypokinesia, the excessive relative weight increases and it reach up to 14%, this might be because of the adaptive mechanisms of the body (Maltseva & Kuznetsova, 2008).

From the first minutes of limited motor activity, a response is observed, described by a massive expansion of the coronary vessels to the stress response. After a hypokinetic period, within 7 days an increase in the volume of the structural components of the heart muscle appears by 70%. These adaptive processes were observed in the study of cardiomyocytes. With the continuation of this period, companion-adaptive mechanisms are activated that regulate the ratio of stromal-parenchymal structures. However, the inclusion of such mechanisms creates the prerequisites for the development of pathologies of the cardiovascular system (Panferova, 1977).

With a prolonged limitation of physical activity, an increase in heart rate is observed (Evseeva, 2000). At the same time, the intensity of the heart increases, reducing the efficiency of the heart (Abzalov, 2005). 30-day hypokinesia causes an increase in heart rate by 26-27 bpm (Kositskii, 1984). Besides, there are data on age-related decreases in heart rate in growing animals (Ziyatdinova et al., 2019), but still, the data remain higher than in controls (Abzalov, 2005).

There is a lot of data on the effect of restriction of motor activity on central hemodynamics, but these are always contradictory to each other. Hypokinesia reduces the stroke volume (SV); in adult rats, it

decreases by 25%, and the minute stroke volume (MSV) changes depending on age (Chinkin, 2012). It has been shown that in rat pups 10-12 weeks of age, MSV decreases by 36%, while in adult rats it remains stable (Zvonarev, 1971). It is known that limited motor activity reduces the efficiency and endurance of functional loads (Chinkin 2012; Zvonarev, 1971). The negative consequences of hypokinesia also include a decrease in the volume of circulating blood, uneconomical functioning of the myocardium, and a decrease in the contractile properties of the heart muscle (Abzalov, 2005). The authors note that during the hypokinetic period there is a negative effect on myocardial contractility, and therefore changes in the systole of the cardiac cycle occur (the period of tension increases, the period of expulsion decreases). In turn, these phenomena lead to oxygen starvation of body tissues, which is confirmed by the presence of signs of degeneration in liver cells (Kornienko et al., 1989). It should be noted that there is no consensus on the effect of limiting motor activity on central hemodynamics.

The study of metabolic regulators of systemic processes in the body with a change in the motor regime undoubtedly remains relevant. Of particular relevance and practical interest is the effect on the body not only of limitation of motor activity (MA) but also of recovery processes (during the transition from limitation to an active motor regime). The objective of this work is to study the parameters of the Langendorff heart during recovery from hypokinesia. Further, mechanisms of the adaptation in the change in the motor regime of an animal were also studied in this study.

2 Materials and Methods

The experimental study was carried out on white laboratory rats (Albino rats). To simulate the hypokinetic effect, the rats were kept in individual organic glass cages for 30 days. Abzalov's (1985) method was used for the development of hypokinesia conditions. For this, the first two days animals were subjected to hypokinesia for 1 hour, on 3 and 4 days this exposure period was two hours, after this every 2 days the time of restriction of physical activity increased by 2 hours (Abzalov, 1985). The peculiarity of this model of hypokinesia (in a horizontal position) is decreased by the influence of the stress factor, as a result of a gradual increase in the time spent by experimental animals under limited motor activity, and the likelihood of studying animals without additional changes in the hydrostatic blood pressure.

After 30 days of motor activity restriction, some of the animals remained for 14 days for the recovery period (transition to unlimited motor activity), to study the mechanisms of adaptation in the animal to a change in its motor regime. Some of the rats were taken for anesthesia (urethane intraperitoneally at a concentration of 800 mg/kg), the thorax of these anesthetized rats was opened and the heart was removed and placed in a cold working Krebs-Henseleit solution (pH=7.4).

The heart was fixed on a Langendorff cannula and perfused with a working solution. The solution was saturated with oxygen and the temperature was maintained at 37°C. Intraventricular pressure was recorded using a latex balloon, which was introduced into the left ventricular cavity. Ex vivo experiments were carried out on isolated hearts using a Power Lab 8/35 device (AD instruments); data were recorded using the LabChart Pro software. Statistical processing was carried out in Excel, the reliability was determined using the Student's t-test. The data were considered statistically significant at $p < 0.05$.

3 Results and Discussion.

Figure 1 shows the mean values of the pressure developed in the left ventricle of rats (LVP) kept in hypokinesia and rats in the recovery period after 30 days of hypokinesia. There is a tendency to decrease in this parameter, but the difference in LVP in these groups of rats was not statistically confirmed.

We observed a decrease in the heart rate (HR) in the recovered rat pups after 30 days of restriction of physical activity and it was 11 percent (Figure 2). In hypokinesized rats, the heart rate average was 161.9 ± 23.5 bpm, while in the recovered group it decreased to 141.6 ± 15.3 bpm ($p < 0.05$).

Coronary flow (CF) of the heart of rats raised in the hypokinetic period averages 5.6 ± 1 ml/min. In rats undergoing recovery after hypokinesia, CF decreases to 3.08 ± 1 ml/min. In the recovered rats, CF decreased by 45% ($p < 0.05$), in comparison with the data of the immobilized rats (Figure 3).

Prolonged limited motor activity causes violations of the contractile function of the myocardium, where a condition called "hypodynamia of the heart" is revealed (the period of tension increases and the period of expulsion decreases). These phenomena are accompanied by the development of hypoxia, in which the supply of oxygen to cells worsens and this might be because of the increase in the synthesis of nitric oxide. Researchers have found that prolonged hypokinesia leads to 2-fold increases in the content of NO in the heart tissues, which explains the presence of NO-dependent mechanisms of the body's response to limiting motor activity and immobilization stress (Zaripova et al., 2014).

The current study does not exclude the influence of immobilization stress on the functional parameters of an isolated heart with limited motor activity. In turn, immobilization stress (from the first to the fifth day of hypokinesia) is characterized by the activation of the hypothalamic-pituitary-adrenal system, which leads to a sharp increase in the production of catecholamines, glucocorticoids, and an increase in catabolic processes. An increase in the secretion of catecholamines can increase the contraction of the ventricles, but with an abrupt cessation, it can reduce myocardial contractility. On

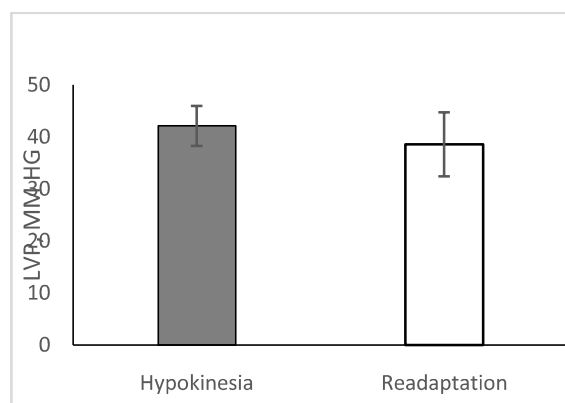


Figure 1 Average parameters of pressure developed in the left ventricle of hypokinesized rats and rats recovered within 2 weeks after hypokinesia (LVP – left ventricle pressure)

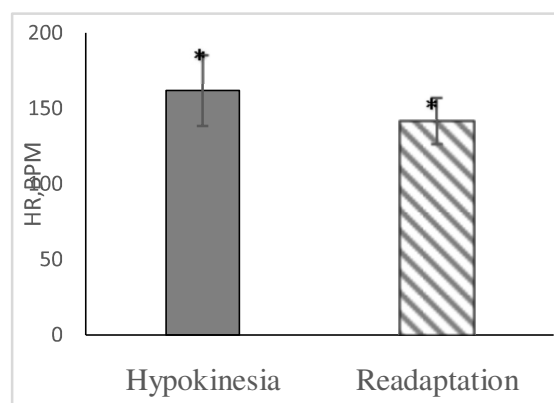


Figure 2 Average parameters of heart rate of hypokinesized rats, and rats recovered within 2 weeks after hypokinesia (HR - heart rate, "*" $p < 0.05$)

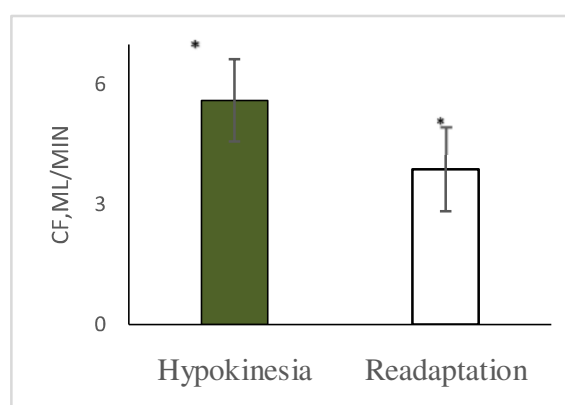


Figure 3 Average parameters of coronary flow of hypokinesized rats and rats recovered within 2 weeks after hypokinesia (CF - coronary flow, "*" $p < 0.05$)

the contrary, high levels of catecholamines can damage cardiac tissue and decrease left ventricular function due to calcium overload, and contribute to the formation of free radicals (Kozlovskaja, 2017). In the present study, after 30 days of hypokinesia, a decrease in the force of contraction is observed, however, after a 2-week recovery period, the contractility continues to decrease, which might be due to the lower value of this parameter, without any recovery observed.

It is also known that catecholamines, acting through cardiac adrenergic receptors, increase the heart rate, myocardial oxygen demand, and reduce coronary blood flow due to the contraction of vascular smooth muscle cells and platelet aggregation (Kozlovskaja, 2017). This is confirmed by our earlier studies, where, after limiting physical activity, an increase in heart rate and a decrease in CF are observed (Sungatullina et al., 2019). In this study, we compared the recovery period with the hypokinetic period and observed a continued decrease in CF after the recovery period, that is, there is no trend towards recovery. With the limitation of motor activity, an increase in the heart rate value is observed, after the recovery period this parameter decreases. Perhaps it is the frequency indicator that responds most quickly to changes in lifestyle, so we are seeing a tendency to restore this parameter.

It was also reported that prolonged limited motor activity, along with muscle atrophy, causes a rearrangement of the lipid bilayer of membranes, which indicates a violation of adaptive mechanisms. This leads to damage to the myocardial membranes, changes in the bioelectric properties of the myocardium, and a decrease in contractility and diastolic relaxation of the heart muscle. As a result, during the period of readaptation after hypokinesia, the adaptability of the heart to stress decreases. Against the background of the emerging energy deficit, simultaneously with a slowdown in the synthesis of contractile proteins, the level of cholesterol, triglycerides, and especially free fatty acids increases, which, along with lipid peroxides, disrupt the functioning of subcellular organelles and limit the adaptive capabilities of the detrained heart (Markin et al., 2009).

With the transition from hypokinesia to a normal motor regime, the load on the muscular and cardiovascular systems increases sharply. The transition of metabolism to a new level of energy requirements makes significant adjustments to the nature of metabolic processes during the recovery period. Therefore, the reaction of animals to return to free housing is complex and proceeds somewhat differently than the reaction to immobilization. The researchers studied the contractile properties of skeletal muscles in rats, with limited motor activity, and followed by a recovery period of 7 and 14 days. They showed that with a 14-day recovery period, some, but not all, parameters returned to the control values (Toader et al., 2009). Our data are consistent with these results since in our case there is a tendency to restore only heart rate parameters but contractility and CF did not recover.

4 Conclusion

Results of the study revealed that the 14-day readaptation period after 30 days of hypokinesia causes a tendency to a decrease in pressure developed by the left ventricle of an isolated heart. The recovery period after restriction of motor activity decreases the heart rate and coronary flow of the isolated rat heart. Based on the obtained results, it can be assumed that 14 days is not a full-fledged period for the restoration of the body's functional parameters. Perhaps, a longer recovery period after hypokinesia is required, which will become the object of our further research.

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Conflict Of Interest

Authors would hereby like to declare that there is no conflict of interests that could possibly arise.

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