Biphasic response of cardiodynamic adaptations to swimming exercise in rats

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Abstract. The aim of research was to assess exercise-induced changes in mechanics of hearts isolated from rats, as well as time-course of those changes. Wistar rats (n = 42) were divided into control, moderately trained (swimming 1 hour, 5 days a week for 9 or 12 weeks) and strenuously trained (swimming 2, 3 and 4 times a day for an hour in weeks 10, 11 and 12, respectively) groups. After sacrificing, hearts (weight: 1480.82 ± 145.38 mg) were isolated and perfused on a Langendorff apparatus. Coronary perfusion pressure (CPP) was gradually increased (from 40 to 120 cmH2O) in order to establish coronary autoregulation. Parameters of cardiac contractility were recorded: maximum and minimum rate of change of pressure in the left ventricle (dp/dt max and dp/dt min), systolic and diastolic left ventricular pressure (SLVP and DLVP), heart rate (HR) and coronary flow (CF). Nine weeks of moderate exercise induced slight depression of coronary function (decrease of dp/dt max, dp/dt min, SLVP and DLVP), while 3 additional weeks of moderate training improved hearts function, but not to the extent that the strenuous training program did. The results of our study add evidence about beneficial effects of regular moderate exercise on heart, and furthermore, show that exercising frequently, if the intensity stays within moderate range, may not have detrimental effects on cardiodynamics.

Key words: Rats — Swimming — Isolated rat heart — Cardiodynamics — Coronary flow

Introduction

According to the hormesis theory, the responses of biological systems to stressors in exercise training may be explained by the U-shaped curve whose two endpoints are inactivity and overtraining (Gholamnezhad et al. 2014). Both of these endpoints result in decreased physiological functions (Radak et al. 2008), while moderate exercise is proven to have numerous health benefits (Foulds et al. 2014).

In order to induce structural and functional adaptations that enable improvement of sports performance, athletes and coaches manipulate training load through adjustments in intensity, duration and frequency, or through a reduction of the regenerative period (Garcia et al. 2010; Issurin 2010; Koprivica 2012). In a well-planned and programmed training process, the training load increases stepwise and the periods of rest between the exercises bouts are sufficiently long to ensure regeneration of the muscle functions, but still short enough to not allow the regression of supercompensation (See et al. 2004). Every athletic training program includes a component of repetitive overloading, but with an inadequate recovery time or with an abrupt increase of training volume; such overloading may produce undesired effects – chronic fatigue and the absence of performance improvement (Kadaja et al. 2010). This state of underperformance, which is related to a number of physiological signs of maladaptation, is currently known
as the overtraining syndrome. Recent studies have focused on hypothetical explanations for the mechanism behind this phenomenon (Kreher and Schwartz 2012; Meuseen et al. 2013), but those theories are still speculative since there is no strong scientific evidence from human longitudinal studies. Actually, since it is unethical to train athletes in such a manner that they develop overtraining syndrome, majority of data origins from retrospective studies, and thus data are incomplete. In order to understand, prevent and treat this syndrome, development of animal models of overtraining is necessary. Using rat experimental models enables annulment of individual and external interferences that are common in human studies, enables performing of invasive analyses and consequently provides a possibility to precisely characterize adaptations that occur.

Endurance athletes perform significant volumes of exercise training. This training places a substantial demand on the heart that acts as a physiological and metabolic stimulus for adaptation in cardiac muscle phenomenon (Brown 2003; George et al. 2012). Exercise-induced remodeling is considered to be physiological and beneficial to the heart, improving cellular metabolism, left ventricular structure, coronary blood flow and ultimately function (Fenning et al. 2003). The reported studies on exercise-induced cardiac adaptations have used various protocols, so there are many arguments over the training regimes, load intensity, myocardial mass increases, gender/age differences and clinical application of findings (Fenning et al. 2003). Studies of ultra endurance activities have highlighted cardiac risks, such as the transient loss of ventricular function, increased heart tissue damage and the subsequent appearance of myocardial injury biomarkers in the blood (George et al. 2008; Scott and Warburton 2008; Gaudreault et al. 2013; Pokan et al. 2014). Unlike in skeletal muscle, the impairment of cardiac function can not only decrease performance, but also can be fatal (Ferraresso et al. 2012). Thus, the aim of our research was to assess changes in function of hearts isolated from rats that undergone different training regimes. We hypothesized that moderate intensity swimming training (60 minutes of daily swimming, 5 times a week) would induce positive changes in cardiodynamics of an isolated rat heart, while an abrupt increase of training volume (swimming 2, 3 or 4 times a day for an hour) may induce overtraining, which may also be related to adverse changes in the function of the heart.

Materials and Methods

The study was performed in the cardiovascular laboratory of the Faculty of Medical Sciences, University of Kragujevac, Serbia. It was approved by Ethical committee of the Faculty, and carried out in accordance with EU (86/609/EEC).

Subjects

Forty two Wistar albino rats (females, eight weeks old, body weight 200 ± 50 g) were subjected to the study’s protocol. The sample size was calculated based on previously published study (Ferraresso et al. 2012), using an appropriate computer program (Faul et al. 2007). Rats were housed in cages (3 rats per cage) in a room where temperature was maintained on 25°C, and 12:12 light/dark cycle. They consumed commercial rat food (20% protein rat food, Veterinary institute Subotica, Serbia) and water ad libitum.

Exercise training protocol

Rats were subjected to swimming training according to different training protocols. They were divided into 3 groups: 1) control group (n = 21), subgroups C0, C9, C12 (n = 7 for each subgroup), 2) moderately trained group (n = 14), subgroups MT9, MT12 (n = 7 for each subgroup) and 3) strenuously trained group (ST12; n = 7). ST12 group (n = 7) trained for 12 weeks according to the protocol in Table 1, which represents the recently developed overtraining animal model (Hohl et al. 2009), performed in water instead of treadmill. It is based on increasing frequency of trainings and decreasing recovery time between trainings. After completing adaptive training phase 1, MT9 (n = 7) and MT12 (n = 7) groups continued to swim once a day for 60 minutes until they were sacrificed (MT9 group was sacrificed after 9, and MT12 group after 12 weeks of training). Rats from the control group were put in water for 3 minutes a day, 5 days a week, in order to achieve the water-induced stress effect. Seven control rats were sacrificed on the very beginning of the study (C0 group), 7 after 9 weeks (C9 group), and 7 at the end of the study (C12 group). Rats swim in a specially constructed swimming pool made of glass (80 × 60 × 100 cm) in which water temperature (34°C) was maintained by an electric heater, and a pump continuously made waves in order to prevent rats from floating. The swimming was continuously supervised.

Physical capacity test

During 12 weeks of exercise training program, rats from all three groups were subjected to 6 endurance swimming tests (schedule of testing is presented in Table 1). Every physical capacity test was performed 30–32 hours after the last training session, and 30–32 hours before the next training session. The test was performed with a weight equivalent to 10% of body weight, which was attached around the waist of each rat using a rubber band (Bocalini et al. 2010). Rats from all groups were individually observed to determine swimming time until exhaustion. Exhaustion was defined as the point when the rat could not swim up to the water surface for 10 s.
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Preparation of isolated rat hearts

After a short-term ether narcosis, rats were sacrificed by decapitation. After emergency thoracotomy and rapid cardiac arrest by superfusion with ice-cold isotonic saline, the hearts were rapidly excised and retrogradely perfused in a Langendorff apparatus (Experimetria Ltd., 1062 Budapest, Hungary). The composition of the non-recirculating Krebs-Henseleit perfusate was as follows (mmol/l): NaCl 118, KCl 4.7, CaCl$_2$·2 H$_2$O 2.5, MgSO$_4$·7 H$_2$O 1.7, NaHCO$_3$ 25, KH$_2$PO$_4$ 1.2, glucose 11, pyruvate 2, equilibrated with 95% O$_2$ plus 5% CO$_2$ and warmed to 37°C (pH 7.4). After the heart perfusion started, a 30-min period was allowed for stabilization of the preparation. It was performed at basal coronary perfusion pressure (CPP) of 60 cmH$_2$O. In order to test coronary vascular reactivity, all hearts were challenged with short-term occlusions (5–30 s) and bolus injection of 5 mmol/l adenosine during the stabilization period. The hearts were discarded if the flow did not increase by 100% over the control value. After the restoration of normal heart rhythm, through the created entrance to the left atrium of the heart and damaged mitral valve, the sensor (transducer BS4 73-0184, Experimetria Ltd., Budapest, Hungary) was inserted into the left ventricle for continuous monitoring of cardiac function. Using this sensor we continuously registered following parameters of myocardial function:

1. maximum rate of left ventricular pressure development (dp/dt max)
2. minimum rate of left ventricular pressure development (dp/dt min)
3. systolic left ventricular pressure (SLVP)
4. diastolic left ventricular pressure (DLVP)
5. heart rate (HR)

CPP was gradually increased (from 40 to 120 cmH$_2$O) in order to establish coronary autoregulation. The abovementioned cardiodynamic parameters were recorded during every CPP. Furthermore, during every CPP coronary flow (CF) was measured by flowmetry.

Body weight (BW) before sacrificing, and heart weight (HW) after sacrificing were also measured, and the heart to body weight ratio (HW/BW), as an index of cardiac hypertrophy, was calculated.

Statistics

The statistical analysis was performed using SPSS 19.0 for Windows. Results in tables and in figures are expressed as means ± standard error of the mean. Due to low number of cases, nonparametric tests were used. For difference between unrelated samples Kruskall Wallis and Mann Whitney tests were used, and for difference between related samples Friedman and Wilcoxon test was used. Alpha level for significance was set to $p < 0.05$.

Results

The results of the morphometric analyses are presented in Figure 1. Groups significantly differed in BW ($p < 0.01$; Kruskal Wallis) and HW ($p < 0.01$; Kruskal Wallis), while HW/BW showed no statistically significant difference between these 6 groups. The C0 group had significantly lower BW than all other groups ($p < 0.01$; Mann Whitney), as well as lower HW when compared to the C12, MT12 and ST12 groups ($p < 0.01$; Mann Whitney). BW of the K9 and T9 groups was lower than BW of the T12 and ST12 ($p < 0.05$; Table 1.

<table>
<thead>
<tr>
<th>Week No.</th>
<th>Training phase</th>
<th>t$_s$ (min)</th>
<th>Trainings a day</th>
<th>t$_r$ (h)</th>
<th>Physical capacity test</th>
<th>Group</th>
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<td>T1</td>
<td>C0</td>
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<td>24</td>
<td>T2</td>
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</tr>
<tr>
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<td>60</td>
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<td>24</td>
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<td>2</td>
<td>T6</td>
<td>C12, MT12, ST12</td>
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AW, adaptation to water; AT1 and AT2, adaptive training phases 1 and 2; T2×, T3×, and T4×, strenuous training phase (overtraining inductive phase) in which daily training frequency is increased to two, three, and four times; t$_s$, swimming duration; t$_r$, recovery between trainings.
Mann Whitney). The MT9 group had lower HW than the MT12 group ($p < 0.05$; Mann Whitney), as well as lower HW/BW when compared to the C0 group ($p < 0.05$; Mann Whitney).

The results of the physical capacity tests are shown in Figure 2. Swimming time significantly improved in all rats when they were subjected to it for the second time ($p < 0.05$; Wilcoxon test), but no significant difference between any other two successive measurements was observed. There was no statistically significant difference between groups in results achieved on any performed test (Mann Whitney test).

Group differences in cardiodynamic parameters are presented in Figures 3–8. Dp/dt max, dp/dt min, SLVP and CF significantly changed after every increase of CPP in all groups ($p < 0.05$; Wilcoxon test). DLVP significantly changed only when CPP was increased from 40 to 60 cmH$_2$O: in the MT9 group it decreased ($p < 0.05$; Wilcoxon test), and in the ST12 group it increased ($p < 0.05$; Wilcoxon test). HR also significantly changed after initial CPP increase in all groups ($p < 0.05$; Wilcoxon test), and also in the ST12 group when CPP was increased from 60 to 80, and 100 to 120 cmH$_2$O.

Differences in values of cardiodynamic parameters during coronary autoregulation between groups (Mann Whitney test) may be summarized as follows:

1. Dp/dt max: The MT9 group had significantly lower dp/dt max levels compared to the C0 group, while when compared to the C9 group this difference was observed only when CPP was the highest. Three additional weeks of moderate training led to the moderate increase of dp/dt max values, so the difference between the MT12 group and the C0 group was obvious only when CPP had the lowest

![Figure 1. Body weight (A), heart weight (B) and heart to body weight (C) of rats. Data are means ± SE. * $p < 0.05$; ** $p < 0.01$. C0, C9, C12, control groups; MT9, MT12, moderately trained groups; ST12, strenuously trained group. For more details see Materials and Methods.](image1)

![Figure 2. Results of the physical capacity tests. Control groups: C0 (○), C9 (●), C12 (●); moderately trained groups: MT9 (●), MT12 (●) and strenuously trained group: ST12 (●). Data are means ± SE. For abbreviations see Fig. 1.](image2)
and the highest values. Three weeks of the overfrequent training led to the higher increase of dp/dt max values, so that the ST12 group had significantly higher dp/dt max levels (during CPP of 40, 100 and 120 cmH2O) compared to the MT9 group, but no significantly different than levels observed in the C12 or MT12 groups (Figure 3).

2. Dp/dt min: Dp/dt min values were also the worst in the MT9 group (statistical significance was observed between the MT9 and the C9 groups during CPP 40, 100 and 120 cmH2O), while the overfrequent training program led to its improvement, especially during the highest CPP (Figure 4).

3. SLVP: The MT9 group had lower SLVP levels compared with the C0 group (CPP 40 and 120 cmH2O), while the ST12 group had higher SLVP levels during all CPP values compared with the MT9 group. The ST12 group also had higher SLVP levels (during some CPP values) compared with the C9 and MT12 groups (Figure 5).

4. DLVP: The MT9 group had significantly lower DLVP levels (during the middle levels of CPP) compared with the C0 group (this was also observed when the C12 groups was compared with the C0 group), while when the MT9 group was compared with the C9 group this difference was observed only when CPP was the highest. The MT12 group had significantly higher DLVP levels compared with the MT9 group (CPP 100 and 120 cmH2O). The ST12 group had higher DLVP levels compared with the MT9 and MT12 groups (during all CPP values), as well as when compared with the C9 and C12 groups (Figure 6).

5. HR: Although Figure 5 shows that the C0 group had the higher and the ST12 group the lower levels of HR, there was no statistically significant difference between groups, probably due to huge variability in measured HR levels (Figure 7).

6. CF: The C0 group had lower CF (during CPP 60 to 120 cmH2O) compared with both older control groups (C9 and C12), as well as compared with MT12 and ST12 groups. The ST12 group also had higher CF when compared with the MT9 group (CPP 60, 80, 120 cmH2O) (Figure 8).

Figure 3. Values of maximum rate of left ventricular pressure development (dp/dt max) during coronary autoregulation of the isolated rat hearts after different training protocols. Data are means ± SE. CPP, coronary perfusion pressure. For more abbreviations see Fig. 2.

Figure 4. Values of minimum rate of left ventricular pressure development (dp/dt min) during coronary autoregulation of the isolated rat hearts after different training protocols. CPP, coronary perfusion pressure. Data are means ± SE. For more abbreviations see Fig. 2.

Figure 5. Systolic left ventricular pressure (SLVP) values during coronary autoregulation of the isolated rat hearts after different training protocols. Data are means ± SE. CPP, coronary perfusion pressure. For more abbreviations see Fig. 2.
The aim of our research was to assess exercise-induced changes in mechanics of hearts isolated from female Wistar rats, as well as time-course of those changes. For this purpose, we subjected rats to training regimens with different training load (9 to 12 weeks of moderate to strenuous volume of swimming). The strenuous regimen was based on a recently developed animal overtraining model, shown to be effective in overtraining induction when performed on treadmill (Hohl et al. 2009, 2012; Dong et al. 2011; Ferrareso et al. 2012), but never applied in water.

Since the only significant sign of overtraining is the fall of exercise performance, we used the results on 6 physical capacity tests to diagnose overtraining. As seen from the Figure 2, although mean value on physical capacity test is higher in all trained rats compared to untrained, there was no statistically significant difference between groups in results achieved on any performed test. Also, although it may be seen that in last three weeks the strenuously trained group of rats achieved lower mean time on the test, again no statistically significant difference between any two successive measurements in any group was observed (except 1st vs. 2nd, which is probably the result of learning and habituation to water). Based on the results of analysis of physical capacity of rats, we must deem that strenuous swimming training protocol did not manage to achieve overtraining. The explanation for these results may be found in the imperfection of the performed endurance test. Quantifying exercise intensity, because of the lack of graded workload swimming protocols, is hard. Thus, the absence of possibility to control intensity of exercise and calculate total amount of external work done by the rat both on training and testing, is a limitation of the performed protocol. Besides differences between swimming and running as forms of physical activity (Kregel et al. 2006; Seo et al. 2014), it should also be taken into account that we used female rats, while the abovementioned studies on overtraining used male rats (Hohl et al. 2009, 2012; Dong et al. 2011; Ferrareso et al. 2012). In most animal studies, females and males differ in the extent of the response to an exercise; thus, the outcomes of a given exercise intervention cannot be generalized for both sexes (Foryst-Ludwig and Kintscher 2013).

It has been suggested that training volume, rather than intensity, may be the major factor contributing to the development of overtraining syndrome (Hooper et al. 1995). Problems with recovery have been shown to occur in animal experiments when exercise training time reaches 10% within a 24 h period (Seene and Kaasik 2013). Generally, swimming 1 hour a day for 5 days a week is considered moderate exercise, while swimming more than that is classified as strenuous exercise (Seo et al. 2014). However, although our strenuously trained group of rats swam 2, 3 and 4 hours a day in last 3 training weeks (which is more than the abovementioned 10% of 24 h daily time), the above-average amount of the training load was not enough to induce a fatigue that would result in significant performance decrement. Thus, our study gives important data on development of future swimming overtraining model, as well as any rats’ swimming training regimen.
Swimming exercise recruits a large volume of muscle mass and results in high alternating loads to the cardiovascular system (Kregel et al. 2006). Thus it is able to induce physiological cardiac hypertrophy (Wang et al. 2010), which is associated with less cardiac fibrosis and better systolic and diastolic function when compared with pathological hypertrophy (McMullen and Jennings 2007). Structurally, endurance exercise in humans leads to increases in left ventricular wall thickness, left ventricular internal diameter and left ventricular mass (Douglas et al. 1997), which translates into clear functional improvements, especially with regard to left ventricular diastolic function and mitral blood flow dynamics (Claessens et al. 2001). The results of our study support those data, emphasizing the importance of the training load in occurrence of those adaptations. As it will be discussed in more details later in this chapter, those positive changes in cardiodynamics were most obvious in rats subjected to the strenuous training regimen. Knowledge of the upper limits of physiological cardiac adaptation is vital for the differentiation of the athlete’s heart from pathologies that may predispose the athletes to sudden cardiac death (George et al. 2012). Studies of ultra endurance activities have highlighted cardiac risks, such as the transient loss of ventricular function (George et al. 2008; Scott and Warburton 2008; Gaudreault et al. 2013; Pokan et al. 2014), and thus assessment of cardiodynamics in subjects who perform huge volumes of endurance training is important for the prevention of adverse events. Since it is the training volume, rather than intensity, that is considered major factor contributing to the development of overtraining syndrome (Hooper et al. 1995), we hypothesized that rats that were subjected to strenuous regimen of swimming in our research may experience some negative changes in heart function. However, since the results of the exercise test showed that we did not manage to induce overtraining with performed training protocol, we did not observe any negative effect of frequent swimming on cardiodynamics of those rats. It seems that the strenuous training protocol induced desirable changes in cardiodynamics to the greater extent than moderate training program. Generally, our results show that 9 weeks of moderate exercise induced slight depression of coronary function, while 3 additional weeks of moderate training improved hearts functions, but not to the extent that the strenuous training program did. Improvement of coronary endothelial response in MT12 subgroup, comparing to MT9 subgroup, could be result of a longer endothelium exposure to increased demand for oxygen during physical load (during 3 additional weeks). Hearts of strenuously trained rats significantly differed from hearts of rats moderately trained for 9 weeks in all measured parameters, except HR in case of which no statistically significant difference between groups was found. However, it can be seen from the Figure 7 that strenuously trained rats had the lowest HR. This bradycardia is probably a consequence of adaptation to endurance training, and only huge variations are the reason for absence of statistical significance. Lower HR (sinus bradycardia) in ST12 subgroup could be physiological response of cardiac muscle to strenuous exercise comparing to control conditions which other authors demonstrated very recently on a mice model (D’Souza et al. 2014). In more details, strenuously trained rats had significantly higher SLVP than moderately trained rats and controls, as well as higher dp/dt max value compared to rats moderately trained for 9 weeks. Those two parameters describe systolic function in our research, while diastolic function is described by dp/dt min and DLVP parameters. On the other side, although dp/dt min levels in strenuously trained rats were better than in moderately trained, DLVP of strenuously trained rats was higher than DLVP of all other groups. This does not mean that strenuous training induced impairment of diastolic function of heart, but it just follows significantly higher SLVP in those rats (SLVP in ST12 group was ~10–20 mmHg higher than in other groups, while DLVP levels were ~1–2 mmHg higher). Finally, improved heart function in strenuously trained rats is proved by the highest coronary flow. This could be a consequence of higher demand for oxygen supply and thus better perfusion in strenuously trained rats. The highest level of coronary perfusion in ST12 subgroup seems to be quite logic, having in mind that more pronounced exercise may stimulate release of another potent vasodilator, adenosine, due to lower level of ATP in the cells (the effect known as exercise-induced coronary vasodilation) (Duncker et al. 1998). During low-intensity, unfatiguing exercise the
heart activity is modified to match the increased oxygen demand by peripheral tissues as a result of their increased metabolism (Venitti et al. 2001). When analyzing our results, one can observe that hearts excised from rats, which were moderately trained for 9 weeks, functioned the worst. One may also observe that rats moderately trained for 9 weeks had the lowest BW, HW and HW/BW ratio, and thus attribute all those differences to differences in morphological parameters. Elevated left ventricular end-diastolic pressure may or may not be associated with systolic dysfunction and it can suggest diastolic dysfunction in the absence of reduced ejection fraction (Salem et al. 2006). In our experimental model, heart was retrogradely perfused through aorta, so normal cardiac output and ejection fraction were not present. In that sense, lower values of DLVP in MT9 subgroup compared to C9 subgroup could be generally discussed as either beneficial or deleterious effect of moderate physical activity, depending on other parameters. In addition, clarification for these effects can be found in decreased values of dp/dt min in this subgroup. Namely, this reduction (values of dp/dt min being less negative) speaks in favor of impaired diastolic function of the heart. This means that reduced values of DLVP in combination with more positive values of dp/dt min (as indirect indicator of lusitropic effects of the left ventricle) are harmful consequence of moderate exercise profile. However, it is important to emphasize that this adverse effect was noticed only at extreme conditions, such as the highest values of CPP.

Unfortunately, there are no studies that used training protocol similar to ours that explored cardiodynamics, except that Ferrareso and colleagues (2012), who used similar training protocol with treadmill, performed the same cardiac morphometric analysis, and found that there was no significant difference in the heart mass between groups, but that overtrained rats had higher HW/BW compared with controls. Bocalini et al. (2010) explored myocardial mechanics due to swimming training and detraining, and found that maximum rate of tension development (+dT/dt) and tension decline (–dT/dt) of isolated papillary muscle were higher in trained rats than controls and rats that stopped training. Generally, the rodent models revealed that endurance activity improved left ventricle size, diastolic and systolic functions, cardiac output, and stroke volume (Davis et al. 2013). These changes are more profound with higher intensity aerobic training (Kemi et al. 2005). In conclusion, strenuous training regimen, based on increasing volume and frequency of training, did not induce overtraining in female Wistar rats in our research, but on the contrary, it induced the most desirable changes in cardiodynamics. The results of our study add evidence about beneficial effects of regular moderate exercise on heart, and furthermore, show that exercising frequently, if the intensity stays within moderate range, may not have detrimental effects on cardiodynamics. Further research is needed to discover the elements of the training load that would induce overtraining in rats when using swimming as the chosen physical activity, and thereafter explore the relationship between structure and function the heart in this unexplained phenomenon.

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