BRAIN NATRIURETIC PEPTIDE AND CORTICOSTERONE DYNAMICS IN EXPERIMENTAL CHRONIC HEART FAILURE DURING PHYSICAL ACTIVITY

Dzhandarova TI[1] ✉, Tabunshchikova MO[2], Kubanov SI[1], Domenyuk DA[2]

[1] North Caucasus Federal University, Stavropol, Russia

[2] Stavropol State Medical University, Stavropol, Russia

Moderate exercise not only has a positive impact on overall health, but also can serve as a rather accessible preventive measure for maintaining health, particularly the cardiovascular system health. The study aimed to assess the cardiovascular system adaptive capacity in chronic heart failure with moderate exercise in different age groups. Moderate exercise was induced in 6- and 19-month-old rats by forced swimming in a water bath at 32–34°C. During training, chronic heart failure was induced by intraperitoneal administration of the anthracycline antibiotic doxorubicin (Teva) at a cumulative dose of 15 mg/kg, divided into 6 injections over 14 days. Serum levels of brain natriuretic peptide and corticosterone were determined by ELISA every seven days throughout the experiment in all rats. It was found that with chronic heart failure and moderate exercise, myocardial adaptation was significantly higher in both age groups. It was most pronounced in aging rats, as evidenced by the dynamic changes of serum natriuretic peptide levels throughout the experiment. In both fertile-age and aging rats, the body's adaptive capacity in the event of cardiac dysfunction with moderate exercise is higher than in the absence of training.

Keywords: physical exercise, chronic heart failure, brain natriuretic peptide, corticosterone

Author contribution: Dzhandarova TI — experimental design and procedure, material resources, editing and data analysis; Tabunshchikova MO — animal handling and enzyme-linked immunoassay, statistical processing and data analysis; Kubanov SI — design and data analysis; Domenyuk DA — material resources for the study.

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✉ **Correspondence should be addressed:** Tamara I. Dzhandarova
proezd Molodezhnyj, 17, Stavropol, Russia; djandarova@yandex.ru

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ДИНАМИКА МОЗГОВОГО НАТРИЙУРЕТИЧЕСКОГО ПЕПТИДА И КОРТИКОСТЕРОНА ПРИ ЭКСПЕРИМЕНТАЛЬНОЙ ХРОНИЧЕСКОЙ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТИ НА ФОНЕ ФИЗИЧЕСКИХ НАГРУЗОК

Т. И. Джандарова[1] ✉, М. О. Табунщикова[2], С. И. Кубанов[1], Д. А. Доменюк[2]

[1] Северо-Кавказский федеральный университет, Ставрополь, Россия

[2] Ставропольский государственный медицинский университет, Ставрополь, Россия

Умеренные физические нагрузки не только оказывают положительное влияние на общее состояние организма, но и могут выступать в качестве вполне доступного профилактического средства для сохранения здоровья, в частности, сердечно-сосудистой системы. Целью исследования было оценить адаптационные возможности сердечно-сосудистой системы при хронической сердечной недостаточности на фоне умеренных физических нагрузок в разных возрастных категориях. Умеренные физические нагрузки создавали у крыс в возрасте 6 и 19 месяцев принудительным плаванием в ванне с водой температурой 32–34 °С. На фоне тренировок хроническую сердечную недостаточность вызывали путем внутрибрюшинного введения антрациклинового антибиотика доксорубицин в кумулятивной дозе 15 мг/кг, разделенной на шесть инъекций в течение 14 дней. У всех крыс на протяжении эксперимента через каждые семь дней определяли в сыворотке крови содержание мозгового натрийуретического пептида и кортикостерона иммуноферментным методом. Установлено, что при хронической сердечной недостаточности на фоне проводимых умеренных нагрузок адаптация миокарда значимо выше в обеих возрастных группах. Наиболее ярко она проявляется у стареющих крыс, о чем свидетельствует динамика содержания натрийуретического пептида в сыворотке крови на протяжении всего эксперимента. Как у крыс репродуктивного периода, так и у стареющих крыс адаптационные возможности организма при возникновении нарушений сердечной деятельности на фоне умеренных физических нагрузок оказываются выше, чем в условиях отсутствия тренировок.

Ключевые слова: физические нагрузки, хроническая сердечная недостаточность, мозговой натрийуретический пептид, кортикостерон

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✉ **Для корреспонденции:** Тамара Исмаиловна Джандарова
проезд Молодежный, д. 17, г. Ставрополь, Россия; djandarova@yandex.ru

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It is well known that physical exercise has a positive effect on the overall body condition and can be a rather accessible preventive measure for maintaining health, particularly the cardiovascular system health.

A number of studies show the effectiveness of rehabilitation programs, in which exercise is included, based on the dynamic changes in the brain natriuretic peptide levels in healthy individuals. With the existing cardiovascular disorders, physical exercise causes a dramatic brain natriuretic peptide level increase, which can be associated with aggravation of symptoms [1, 2]. Furthermore, physical exercise is also recommended as pre-habilitation for patients, who are to undergo cardiovascular surgery aimed to improve functional capacity of the heart [3].

At the same time, there is currently no consensus about what exercises and for how long to do these to improve cardiac activity [4], and the mechanisms underlying the effects of physical exertion of varying intensity on the cardiovascular system are currently poorly understood [5–7], especially in elderly people.

Along with other signs, the age-related changes associated with natural ageing are accompanied by the major shift of the cardiovascular system neuroendocrine regulation. In particular, there are considerable functional changes in the hypothalamic-pituitary-adrenal axis. The emerging neuroendocrine dysregulation of the cardiovascular system results from the increase in basal adrenocorticotropic hormone (ACTH) and cortisol levels. Furthermore, inadequate elevation of the levels of these hormones is associated with physical stress. Such alterations result immediately in the increased risk of cardiovascular disorders, even during the short-term treatment with low-dose glucocorticoids, which affects future life, prognosis, and outcome of the underlying disease. The increase in the levels of these hormones poses a greater risk of carsiovascular events, such as myocardial infarction, stroke, coronary artery disease, chronic heart failure [8, 9]. Undoubtedly, any body's process leading to changes in the cardiovascular system activates the endocrine function of the myocardium. Atrial cardiomyocytes produce natriuretic peptides referred to as the atrial natriuretic factor (or atrial natriuretic peptide) and brain natriuretic peptide (or B-type natriuretic peptide). Natriuretic peptides that have many physiological effects are involved in numerous pathophysiological processes. Furthermore, plasma levels of natriuretic peptides, specifically brain natriuretic peptide, represent potent diagnostic and prognostic biomarkers of heart diseases [10–12].

The study aimed to assess the cardiovascular system adaptive capacity in chronic heart failure with moderate exercise in different age groups.

METHODS

The study involved 72 male Wistar rats aged 6 months (fertile age) and 19 months (senescent rats). The animals kept in natural light at the temperature of 20–22 °C and relative humidity of 60–70% had ad libitum access to drinking water and standard vivarium feed.

Animals of each age group were divided into four groups: the first group included intact rats (controls); the second one included rats getting moderate exercise; the third one included rats, in which chronic heart failure was simulated; the fourth one included rats, in which chronic heart failure was simulated with moderate exercise.

Chronic heart failure was simulated in rats by intraperitoneal administration of the cardiotoxic dose of the anthracycline antibiotic doxorubicin (Teva) at a cumulative dose of 15 mg/kg, divided into 6 injections over 14 days [13].

The controls for intraperitoneal administration we represented by the group of animals receiving intraperitoneal injections of saline. The analysis and comparison of the data obtained with the values of intact animals revealed no significant differences. That is why in the study the data of experimental animals were compared with the values of intact control animals.

Moderate exercise was induced in the animals by forced swimming in a water bath at 32–34 °C. Training was conducted daily, five days a week throughout three weeks. The cycle consisted of 15 days with training sessions. The first training session lasted for 2 min; the duration of each subsequent session to the day 21 was increased by 4 min. The animals were included in the experiment after 1, 2, and 3 weeks of training. In all rats, 1 mL of blood was collected from the tail vein into the test tubes containing clotting activator under anesthesia in due course. Blood was centrifuged at 3000 rpm for 15 min, then collected and stored at –35 °C.

Brain natriuretic peptide (NT-proBNP) was determined by sandwich ELISA using the NTBNP-ELISA-BEST kit, and corticosterone was determined using the DRG reagent kit (DRG Instruments GmbH, Germany). Optical density of the studied hormones was measured using the plate spectrophotometer equipped with the cell holder combined with the software and μDrop plate, Thermo for microvolume analysis (Multiskan SkyHigh, USA). Significance of differences in the studied indicators was determined using the Student's t-test, when the sample distribution was normal. The distribution was tested for normality using the Shapiro–Wilk test. The results were considered significant at $p < 0.05$.

RESULTS

The fertile age rats showed no differences in serum brain natriuretic peptide levels from both baseline values and values of controls within the first two weeks of training. During adaptation to training a significant decrease in serum levels of the peptide relative to the data of control rats was reported in these animals (Fig. 1).

In the group of rats of the same age, in which chronic heart failure was simulated, the considerably high serum brain natriuretic peptide levels relative to both baseline and the data of control rats were observed throughout the experiment (Fig. 1).

When modeling chronic heart failure with moderate exercise, a rather high brain natriuretic peptide concentration in blood serum was revealed in the first week of training, and in subsequent weeks of training the brain natriuretic peptide levels significantly decreased compared to the data reported for rats with chronic heart failure (Fig. 1). The changes identified suggest that with moderate exercise myocardial adaptation to possible cardiac dysfunction is significantly higher.

During adaptation to moderate exercise, a significant decrease in serum corticosterone levels relative to both baseline and values of control rats was revealed in fertile age rats in the second and third weeks of the experiment (Fig. 2). In the fertile age rats, in which chronic heart failure was simulated, serum corticosterone levels were significantly high relative to both baseline values of the same rats and the values of control rats in the beginning of the experiment. Later the adaptation processes decreased considerably in these animals, as suggested by significantly low serum corticosterone levels in the end of the third week of the study (Fig. 2).

When modeling chronic heart failure in fertile rats with training, there was a significant increase in serum corticosterone

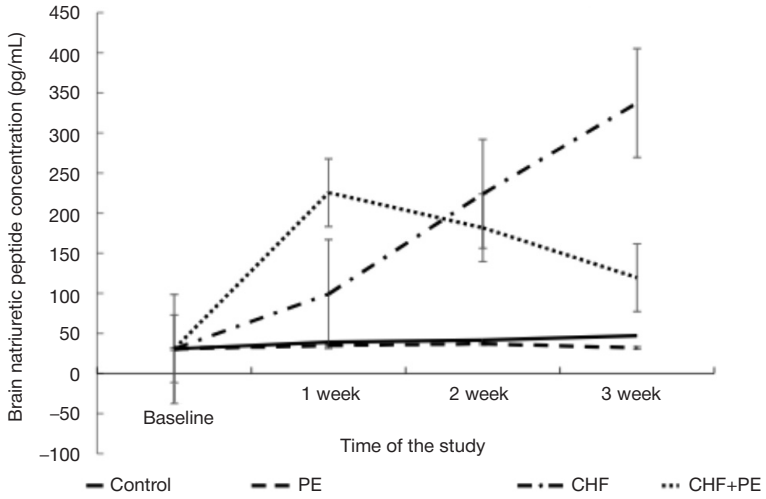

Fig. 1. Serum concentration of brain natriuretic peptide in 6-month-old rats

levels relative to baseline and the data of control rats in the beginning of the experiment. Later during the experiment serum corticosterone levels decreased to the levels of control rats, and in the end of the third week of the study serum corticosterone levels were significantly lower compared to the data of control rats, but higher, than in rats with chronic heart failure (Fig. 2). Therefore, adaptive capacity of the fertile age animals developing cardiac disorders with moderate exercise still turn out to be higher, than under conditions of no training.

As demonstrated by further findings, in the aging rats, regular moderate exercise starting from the first week of the experiment contributed to the significant decrease in serum brain natriuretic peptide levels compared to both baseline data of the same rats and the values of control rats (Fig. 3). Considering the age-related increase in the levels of this peptide in aging rats, it can be assumed that moderate exercise under conditions of no cardiovascular system dysfunction has a beneficial effect on the state of the myocardium.

In the group of aging rats, in which chronic heart failure was simulated, a significant increase in the serum levels of brain natriuretic peptide relative to the baseline values of the same animals and the values of control rats was reported throughout the experiment (Fig. 3).

When modeling chronic heart failure with moderate exercise in aging rats, the significantly high serum brain natriuretic peptide levels compared to both baseline and the values of control rats were revealed. However, after the first week of training the peptide levels decreased significantly compared to the data of rats with chronic heart failure (Fig. 3). The changes revealed suggest that regular training improves cardiovascular system function and heart functioning effectiveness in the aging body even in cases of developing cardiac dysfunction.

During adaptation to regular training the aging rats showed a significant moderate increase in serum corticosterone levels compared to both baseline corticosterone levels and the values of control rats throughout the experiment (Fig. 4). In the aging rats, in which chronic heart failure was simulated, serum corticosterone levels were significantly high relative to both baseline values of the same rats and the values of control rats in the first week of the experiment. In the next weeks of the experiment, especially in the end of the third week, these rats showed a significant decrease in serum corticosterone levels, which suggests lower adaptation against the background of cardiac dysfunction (Fig. 4).

When modeling chronic heart failure in aging rats with training, the significant increase in serum corticosterone levels compared to both baseline values and the data of control rats was reported in the beginning of the experiment. In the remaining time of the experiment, up to the end of the third week, the decrease in serum corticosterone levels to the values of control rats took place (Fig. 4). Therefore, when the aging rats develop cardiac dysfunction with moderate exercise,

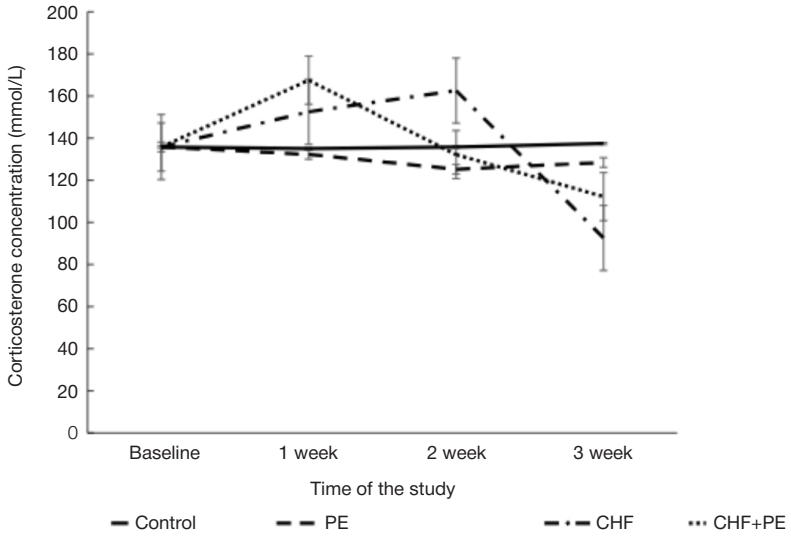

Fig. 2. Serum concentration of corticosteroids in 6-month-old rats

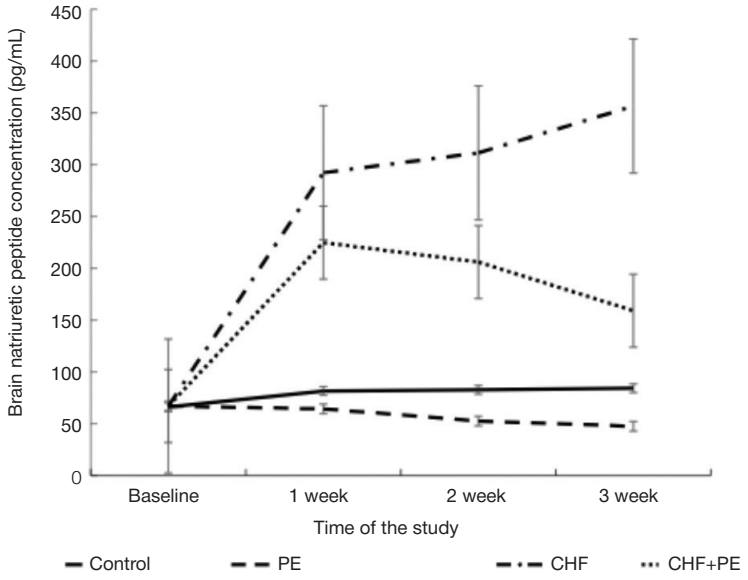

Fig. 3. Serum concentration of brain natriuretic peptide in 19-month-old rats

body's adaptive capacity turns out to be higher, than under conditions of no training.

DISCUSSION

As is well known, considerable changes in all body's system occur during aging, which results in limitation of the capability of adaptation to environmental factors and depletion of energy resources. At the same time, certainly, pathophysiological mechanisms are activated that finally lead to the development of cardiovascular and other disorders. All the above contributes to limitation of motor activity of an elderly individual, which also can enhance the increase in destructive processes in the body.

Today, the family of cardiac hormones, such as brain natriuretic peptide, the levels of which are increased with ventricular wall dilatation caused by overload or dysfunction, represent one of the widely used markers of the cardiac function status. Brain natriuretic peptide is an important biomarker for the diagnosis and monitoring of heart failure, since the increase in blood concentration of the peptide is correlated to the heart failure severity [1, 2, 10].

As is well known, heart failure results from structural and functional cardiac impairment. It is characterized by water and sodium retention, electrolyte imbalance, and kidney function deterioration. Our previous studies also showed that the experimental chronic heart failure led to the progressive increase in serum levels of aldosterone, sodium, and potassium [14]. The effect of brain natriuretic peptide is to reduce the load on the myocardium through enhancement of diuresis, increased sodium excretion. The elevated blood brain natriuretic peptide concentration indicates the decreased heart muscle contractility and allows one to judge about heart failure even without echocardiography. The main stimulus for natriuretic peptide secretion are the increase in myocardial tension with increasing blood pressure or volume in the left heart ventricle and mechanical stretching of the atria [15]. Glucocorticoids, in turn, have a multifaceted effect on the myocardium due to metabolic alterations, contribute to blood pressure increase, which represents and independent risk factor of many cardiovascular disorders [8].

The feature of our study is that we modeled moderate exercise before the emergence of any significant disorder of the cardiovascular system in the fertile period of ontogeny and during aging of the body. It was found that adaptation to moderate physical exercise was associated with the decrease in serum brain natriuretic peptide levels in both age groups.

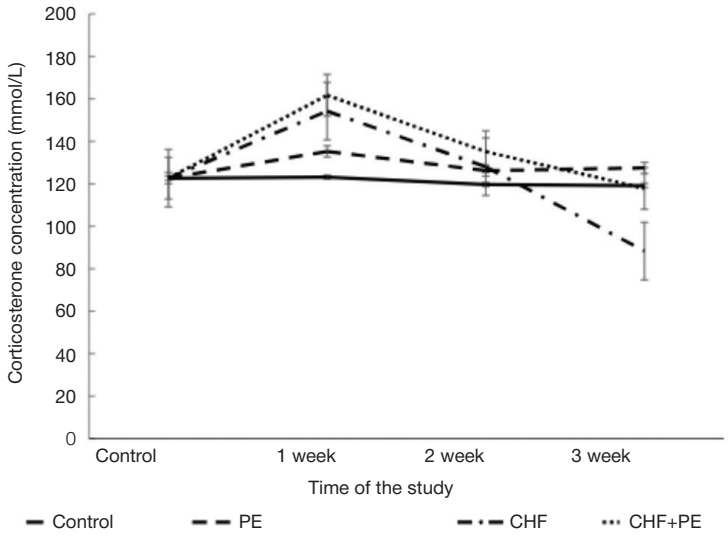

Fig. 4. Serum concentration of corticosteroids in 19-month-old rats

When creating the model of chronic heart failure with moderate exercise, adaptation of the myocardium to possible cardiac dysfunction increases considerably in both age groups, which is particularly evident in aging rats. Furthermore, in both fertile age and aging rats, body's adaptive capacity is higher with moderate exercise, than under conditions of no training, which is indicated by the dynamic changes in serum corticosterone levels throughout the experiment. Positive impact of moderate exercise on body's physiological processes has been determined by other factors. These papers report that physical activity is the source of substances possessing therapeutic effects that are produced by the body itself. Regular physical activity has a beneficial effect on the tissue homeostasis, function, and interaction [5].

However, the long-term heavy physical exertion can adversely affect the condition of cardiomyocytes, as indicated by the significantly elevated brain natriuretic peptide binding fatty acids, copeptin, troponin [16, 17]. Undoubtedly, physical exercise has a multifaceted effect on the brain natriuretic peptide levels depending on the exertion intensity and duration, as well as on the baseline cardiovascular system state [1]. As also shown by our studies, regular moderate exercise should have its place in life since young adulthood, before the emergence of the age-related cardiovascular system alterations. It will make it possible to improve the aging body's quality of life.

CONCLUSIONS

It has been found that when creating the model of chronic heart failure with moderate exercise, adaptation of the myocardium to possible cardiac dysfunction increases significantly in both age groups, which is particularly evident in aging rats. In both fertile age and aging rats, body's adaptive capacity in cases of developing cardiac dysfunction turns out to be higher with moderate exercise, than under conditions of no training, as indicated by the dynamic changes in serum corticosterone levels throughout the experiment.

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