Journal of Vessels and Circulation
Qom University of Medical Sciences
Autumn 2021. Volume 2. Number 4

Research Paper

The Effect of an Aerobic Exercise Course on Cardiac Tissue Apoptosis in Adult Male Rats Poisoned With Oxygenated Water

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Please cite this article as Rezaei SM, Abedi B, **Fatolahi** H. The Effect of an Aerobic Exercise Course on Cardiac Tissue Apoptosis in Adult Male Rats Poisoned With Oxygenated Water. Journal of Vessels and Circulation. 2021; 2(3):201-208. http://dx.doi.org/10.32598/JVC.2.4.97.1

http://dx.doi.org/10.32598/JVC.2.4.97.1

Article info:
Received: 11 Oct 2021
Accepted: 12 Dec 2021
Publish: 01 October 2021

Keywords:
Exercise, Apoptosis, Cardiac, Hydrogen peroxide

ABSTRACT

Background and Aim: Exercise is a strong physiological stimulus that can directly or indirectly affect the process of cardiac apoptosis by affecting some extracellular and intracellular signaling pathways. This study aimed to investigate the effect of aerobic exercise on cardiac tissue apoptosis in rats poisoned with oxygenated water.

Materials and Methods: In this experimental study, 24 male Wistar rats with a weight range of 200-220 g and a mean age of 8-10 weeks were divided into 3 groups, each group containing 8 rats: (1) healthy control (HC), (2) toxicant control (TC), and (3) toxic aerobic exercise (AE). To induce apoptosis, a 9% oxidant, with a large amount of oxygenated water was used by inhalation for 3 hours daily. Twenty-four hours after the last exercise, rats were sacrificed, and their tissue samples were isolated and kept at -80 ° C. Then, the expression of BAX, Caspase 3, and BCL2 genes in cardiac tissue was measured using RT-PCR. Kolmogorov-Smirnov statistical test and one-way analysis of variance with Tukey post hoc test in SPSS software v. 22 were used to analyze the data ($P \geq 0.05$).

Results: Exposure to oxygenated water significantly increased BAX ($P=0.001$) and Caspase 3 ($P=0.002$) and significantly decreased BCL2 gene expression ($P=0.001$) in cardiac tissue. While aerobic exercise decreased levels of BAX ($P=0.001$) and Caspase 3 ($P=0.001$) and increased BCL2 ($P=0.000$) in the cardiac tissue of rats poisoned with oxygenated water.

Conclusion: It seems that a period of aerobic exercise with significant changes in the expression of genes involved in oxygenated apoptosis can be used as a complementary therapy and other methods to modulate the apoptosis of cardiac tissue.

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1. Introduction

Apoptosis is a type of cell death that causes the death of dysfunctional, abnormal, or damaged cells and harmful cells. However, when apoptosis is excessive, it can lead to abnormal changes in the structure and function of the heart [1]. This process is carried out by many intracellular and extracellular factors that can be in four groups: damage caused by various toxins and various radiation, lack or deficiency of growth factors and hormones, activation of the ligand-receptor binding pathway, and activation through immune system cells such as T lymphocytes [2]. Any factor that can prevent the normal development of the cell creates the ground for apoptosis [2]. On the other hand, the influential role of Caspase-3 as a proapoptotic agent in the unstable reduction of cardiac function and damage to myocardial fibers has been shown [3]. Activation of Caspase-3 during apoptosis is associated with phosphatidylserine expression in apoptosis [4]. B-cell Lymphoma 2 BCL-2 molecules have also been identified as regulators of proto-oncogenic apoptosis in cellular follicular lymphoma, located in the outer mitochondrial membrane. Members of this family are divided into two groups: 1) anti-apoptotic members, including BCL-2 and BCL-XL, and 2) proapoptotic members, including BAX, etc. involved in cell apoptosis or programmed cell death [3].

Hydrogen peroxide (H_2O_2) is a mild and relatively stable oxidant widely used as a reactive oxygen species (ROS) marker to evaluate cell responses to oxidative stress [5]. There is some evidence to suggest that oxidative stress exerts its destructive impact on cells by disrupting the intracellular signaling pathways of apoptosis [6]. The results of several studies indicate that ischemia and reperfusion also cause the production of free radicals (ROS) and gradually thrombosis, cell death, and coronary artery damage in male rats [7]. Hydrogen peroxide (H_2O_2) is one of the most potent ROSs researchers use to simulate oxidative stress. The results of studies have shown that oxygenated water causes severe damage to cardiac sarcolemma [8]. On the other hand, brief exposure of cardiac cells to H_2O_2 can stimulate pathological mechanisms that lead to cell damage. It also causes the release of cytochrome C into the cytosol of cardiac cells, which can stimulate cell apoptosis [9]. Therefore, ischemia and reperfusion are likely to produce ROS and cause apoptosis by disrupting intracellular signaling pathways [6]. In this regard, H_2O_2 activates a similar pathway in apoptosis. Cytochrome C is released from the space between the two mitochondrial membranes into the cytoplasm in the internal pathway. The mitochondrial membrane permeability to Cytochrome C is determined by proapoptotic mediators such as BAX and the anti-apoptotic BCL2 [6].

Exercise is one of the most important methods for preventing and treating cardiac disease [10]. Exercise, depending on its type and intensity, can have a positive effect on the physiology and morphology of cardiac tissue, including the strength of myocardial contraction, increase in the size of the left ventricular cavity, wall thickness, and increase in cardiac mass, which is known as (athlete's heart) [11]. Studies show that exercise is associated with the modulation of programmed cell death (apoptosis) of cardiac myocytes [12].

In this regard, Habibi et al. showed that 8 weeks of swimming exercise reduces apoptosis in the cardiac tissue of rats [13]. However, Sun et al. showed that one session of swimming activity to exhaustion significantly reduces BCL-2 gene expression 6 hours after exercise but has no effect on BAX and the ratio of BAX to BCL-2 [14]. Intensity, duration, and type of exercise seem to impact apoptotic activity differently. It has also been observed that physical activity and exercise, due to the increase in cellular oxidation, cause the production of free radicals and an increase in ROS, which in the long run lead to tissue destruction. On the other hand, it has been shown that regular physical activity with moderate intensity can also increase the body's antioxidant capacity [15]. The present study aimed to investigate the effect of aerobic exercise on cardiac tissue apoptosis in rats poisoned with oxygenated water in regard to apoptosis, exercise, and the destructive impacts of H_2O_2 exposure on the body.

2. Materials and Methods

This experimental study purchased 24 male Wistar albino rats in the weight range of 200-220 g and the average age of 10-12 weeks from Pasteur Institute of Tehran, Iran, and transferred them to the sports physiology laboratory at Islamic Azad University, Mahallat Branch. The present study was performed according to the National Institute of Health (NIH) instructions and was approved and conducted by the ethics committee of the Islamic Azad University of Arak (Code: IR.IAU.ARAK.REC.1399.043). All rats were kept in clean, sterile cages under standard conditions with a 12-hour cycle of darkness and light and a temperature of 19-22°C. Animals with a standard laboratory diet of rodents (crude protein 50.20%-50.19%, fat 3.5%-4.5%, fiber 4%-4.5%, calcium 0.95%-1%, phosphorus 0.7%-0.65%, salt 0.55%-

5%, lysine 1.15%, methionine 0.33% threonine 0.72% tryptophan 0.25%, calories 16.16-16 mg/kg) and tap water with unlimited access were fed. After one week of adaptation to the laboratory environment, rats were randomly divided into 3 groups of 8 including the HC group, TC group, and AE group.

Oxygenated water toxication

For animal toxication, hydrogen peroxide prepared from Atosa Oxidant 9% (Grape Oxidant No 60, 1 mL) made by Atosa Iran was used. This product contains a large amount of H_2O_2 produced for hair coloring. For toxication, the animals had to use the oxidant by inhalation, so that 60 mg of oxidant was poured into a box with an area of 18.75 cm and a volume of 125.103 cm^3, and it was covered with a net and then placed in a cage for mice to prevent oral consumption. In this way, the rats in the TC group and the AE group inhaled the air in the cage where the oxidant box was located. At each stage of toxication, 4-5 mice were placed inside the cage containing the oxidant. Mice in the toxicant groups inhaled the oxidant-containing air inside the cage for 3 hours, 3 times a week [16].

Aerobic exercise protocol

In the first stage, rats ran on a treadmill at 5-10 meters per minute for 10 minutes to get acquainted and reduce stress. Aerobic exercises were performed on a treadmill for 2 minutes at a speed of 10 meters per minute to warm up and cool down before and after the exercise. The exercise protocol started for 8 weeks and 5 sessions per week with an intensity of 10 meters per minute for 15 minutes with a slope of 5% in the first week and gradually increased to 25 meters per minute with a slope of 5% for 30 minutes in the last week. A speed of 10 meters per minute for 15 minutes with a slope of 5% in the first 2 weeks gradually increased to 15 meters per minute for 20 minutes with a slope of 5% in the second 2 weeks. The intensity increased to 20 meters per minute for 25 minutes and a slope of 5% in the third 2 weeks and 25 meters per minute for 30 minutes with a slope of 5% in the fourth 2 weeks [17].

Tissue sampling and measurement steps

Twenty-four hours after the last intervention and after 10-12 hours of fasting, the rats were anesthetized by intraperitoneal injection of ketamine (90 mg/kg) and xylazine (10 mg/kg). The chest was then opened, and the cardiac tissue was immediately separated and frozen using liquid nitrogen to be sent to a laboratory. The frozen tissues were homogenized at 4°C in the next step. So, 50 mg of ventricular muscle was homogenized by dissolving in 1 mL of ice cell lysis buffer. It was then centrifuged at 4°C for 1 minute at 1000 rpm to separate the supernatant. It was then stored in a -80°C nitrogen tank in the refrigerator for long-term use. For molecular studies on gene expression levels, RNA was first extracted from the cardiac tissue according to the manufacturer's protocol (Signage, Iran). Then, using the light absorption property at 260 nm and with the help of the following relationship, the concentration and purity of the RNA sample were quantitatively obtained (Equation 1).

$$1.\ C\ (\mu g/\mu l)=A260\times\varepsilon\times d/1000$$

After extracting RNA with very high purity and concentration from all studied samples, cDNA synthesis steps were performed according to the manufacturer's protocol, and then the synthesized cDNA was used for reverse transcription reaction. First, the designed primers related to genes were examined, and then the expression of genes was examined using quantitative q-RT PCR. Measurement of gene expression of the desired factors from cardiac tissue was designed by real-time PCR technique, and all primers were designed by Allele IDv7.8 software, and β2m gene (beta 2 microglobulin) was used as the internal control. Gene expression values were analyzed using the formula $2^{-\Delta\Delta Ct}$.

Statistical analysis method

Kolmogorov-Smirnov test was used to evaluate the normal distribution of findings, and one-way analysis of variance with the Tukey post hoc test in SPSS software version 22 was used to analyze the data ($P\geq0.05$).

3. Results

The expression levels of BAX, Caspase 3, and BCL2b are presented in Figures 1-3. The results of one-way analysis of variance showed that there was a significant difference in BAX (P=0.001, F=16.52), Caspase 3 (P=0.002, F=14.16), and BCL2 (P=0.001, F=12.29) levels of cardiac tissue in the three research groups. The results of the Tukey post hoc test showed that the expression of BAX and Caspase 3 genes in the TC group had a significant increase compared to the HC group (P=0.001), and the levels of BAX and Caspase 3 in the EA group were significantly lower than the TC group (P=0.001) (Figures 1 and 2). BCL2 levels of cardiac tissue in the TC group were significantly lower than those in the HC group (P=0.001), while BCL2 levels in cardiac tissue in the EA group were significantly higher than those in the TC group (P=0.000) (Figure 2).

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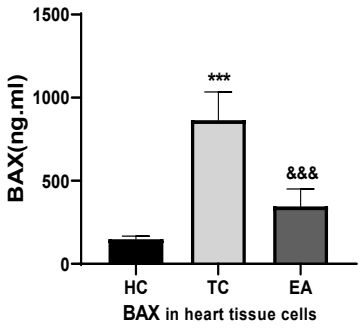

Figure 1. BAX concentration of cardiac tissue in different groups

Each group consisted of 8 rats. The data were expressed as Mean±SD.

*** Significant increase in the TC group compared to the HC group; &&& Significant decrease in the EA group compared to the TC group.

HC: healthy control group; TC: toxicant control group; EA: toxic aerobic exercise group.

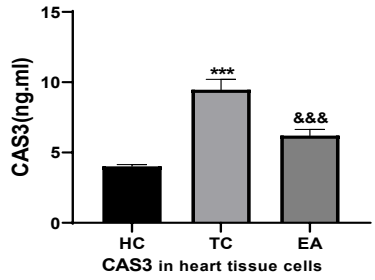

Figure 2. Caspase 3 concentrations of cardiac tissues in different groups

Each group consisted of 8 rats, and the data were expressed as Mean±SD.

*** Significant increase in the TC group compared to the HC group; &&&: Significant decrease in the EA group compared to the TC group.

HC: healthy control group; TC: toxicant control group; EA: toxic aerobic exercise group.

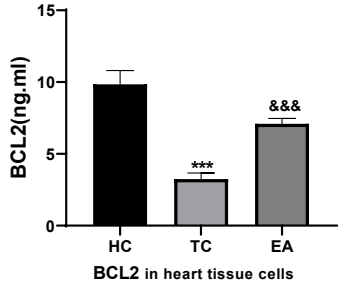

Figure 3. Concentrations of BCL2 in cardiac tissue in different groups

Each group consisted of 8 rats, and the data were expressed as Mean±SD. Symptom

*** Significant decrease in the TC group compared to the HC group; &&& Significant increase in the EA group compared to the TC group.

HC: healthy control group; TC: toxicant control group; EA: toxic aerobic exercise group.

4. Discussion

The present study results showed that exposure to oxygenated water increases apoptosis in the cardiac tissue of rats. Studies have shown that H_2O_2 causes significant changes in cell membranes, and brief exposure of cardiac cells to H_2O_2 can stimulate the pathological mechanism leading to cell damage. It also causes the release of Cytochrome C into the cytosol of cardiac cells [18]. Ischemia and reperfusion are likely to produce ROS, which causes apoptosis by disrupting intracellular signaling pathways. Studies have shown that H_2O_2 activates a similar pathway in apoptosis. Cytochrome C is released from the space between the two mitochondrial membranes into the cytoplasm in the internal pathway. The permeability of the mitochondrial membrane to cytochrome C by the ratio of proapoptotic mediators such as BAX or BAK increases the mitochondrial membrane's permeability. The pairing of proapoptotic molecules with an anti-apoptotic index (BCL2 and BAX) neutralizes their anti-apoptotic effect [19].

In this regard, Janero et al. Showed that H_2O_2 causes serious damage to cardiac sarcolemma. This disorder includes phospholipid peroxidation, thiol oxidation, and alpha-tocopherol reduction (anti-peroxidation protein and ATP depletion) [8]. Ramezani et al. also found that exposure to oxygenated water increases the apoptotic index of BAX and Caspase 3 and decreases BCL2 in lung tissue [20] which is consistent with the results of the present study. However, Safarzadeh Gargari et al. showed that exposure to oxygenated water did not significantly affect cardiac tissue apoptosis variables in toxic mice and reported the reason for these insignificant changes in BAX BCL2 proteins increasing of MIR-499 in cardiac tissue [9].

Another reason for the inconsistency of this study with the present study is the type of toxication and the amount of toxication in animals. Other results of the present study showed that aerobic exercise has a significant effect on reducing the expression of BAX and Caspase 3 genes and increasing BCL2 in the cardiac tissue of rats poisoned with oxygenated water. Studies have shown that exercise and physical activity are among the most well-known factors in preventing and treating cardiovascular disease. Studies have shown that aerobic exercise directly impacts cardiovascular and vascular vessels, including oxygen supply to the heart, endothelial function, coagulation factors, and inflammatory markers [21]. Habibi et al. showed that 8 weeks of swimming exercise reduces apoptosis in the cardiac tissue of rats [13]. Badkoubeh et al. reported a significant decrease in Caspase-3 following 8 weeks of aerobic exercise in Arsenic-poisoned rats [22] which is consistent with the results of the present study.

However, in a study, Ramezani et al. showed that aerobic exercise has no significant impact on Caspase-3 in the lung tissue of male rats poisoned with oxygenated water [20]. In a study, Kazemi et al. showed that a period of endurance training significantly increases the expression of Caspase-3 in mice with breast cancer [23]. Also, Li et al. showed that exercise increases the rate of apoptosis by increasing Caspase-3 activity in stroke mice [24], which is not consistent with the present study results. It seems that this root mismatch is in the type of subjects or exercise parameters, such as the type of exercise, intensity, duration, and the used tissue that the studies have used. Caspase-3 control is a complex process and involves several signaling pathways of apoptosis. Caspase-3 is activated by activating Caspase-12 via the calcium release pathway or by activating Caspase-9 in the internal pathway, or by increasing serum TNF-α in the external pathway [25].

Caspase-3 plays an important role in skeletal muscle changes and is essential for separating skeletal muscle cells. Thus, maintenance of Caspase-3 activity after exercise may be required for other cellular functions, such as exercise-induced state change and the separation of satellite cells [25], which have not yet been studied. The results also showed that aerobic exercise significantly reduced BAX protein and increased BCL2 after 8 weeks of aerobic exercise in the cardiac tissue of rats poisoned with oxygenated water. In this regard, Akbari et al. showed that a period of aerobic exercise in water leads to a significant decrease in BAX expression and a significant increase in BCL2 expression of cardiomyocytes in male rats treated with hydrogen peroxide [6]. Badkoubeh et al. and Arjmand et al. also showed that aerobic and resistance exercise significantly reduced BAX gene expression and increased BCL2 expression in the cardiac and endothelial tissues of mice poisoned with arsenic and anabolic steroid stanozolol [22, 26].

However, Safarzadeh Gargari showed that 8 weeks of continuous exercise did not have a significant effect on BAX and BCL2 levels and BAX/BCL2 ratio [9]. Doustar et al. also examined the effect of four weeks of resistance training on cardiac apoptosis and reported that resistance training did not affect BAX and BCL2 cardiac tissue [27] which is inconsistent with the results of the present study. Among the reasons for the inconsistency of the results of the mentioned studies

can be the studied tissues, the type of subjects, the number of exercise sessions, and the intensity of exercise. According to existing research, BAX and BCL2 proteins play an important role in modulating the process of cell death. BCL2 family members control the pathways involved in stimulating apoptotic processes. Therefore, any factor that changes the ratio of BAX to BCL2 or vice versa leads the environment to apoptosis or anti-apoptosis [23].

Normally, there is a balance between inhibitory factors and apoptotic stimuli, but this balance is always disturbed in physiological and pathophysiological situations, one of which is physical activity. It is possible that exercise activities can prevent cell death by affecting the most important factors affecting the process of apoptosis [28]. Studies have shown that increasing BCL2 as an antioxidant strengthens the mitochondrial wall and, by suppressing BAX, prevents the release of cytochrome C, increases the activity of antioxidant enzymes and cell immunity, and prevents stress-induced apoptosis by regulating glycemia and reducing the impact of ROS [29]. Due to the reduction of apoptosis in the cardiac tissue of rats following aerobic exercise, it seems that various methods of reporting cardiac function such as electrocardiography, TUNEL apoptosis test method, and measuring oxidative stress levels are among the limitations of the present study. These factors can be reported in future studies and cardiac tissue apoptosis.

5. Conclusion

Briefly, the present study results showed that oxygenated water toxication causes oxidative stress and increases cardiac tissue apoptosis. In addition, aerobic activity can mediate its protective effect on the heart against apoptosis by altering the signaling cascade pathway and negatively regulating the expression of the apoptotic gene BAX, Caspase-3 and positively regulating the expression of the anti-apoptotic BCL2 gene in cardiac tissue.

Ethical Considerations

Compliance with ethical guidelines

The current study was performed according to the National Institute of Health (NIH) instructions and was approved and conducted by the Ethics Committee of the Arak Branch, Islamic Azad University (Code: IR.IAU.ARAK.REC.1399.043).

Funding

This article was extracted from the first author's doctoral dissertation in the Department of Sports Physiology, Faculty of Physical Education and Sports Sciences, Mahallat Branch, Islamic Azad University.

Authors' contributions

Conceptualization: Bahram Abedi, Seyed Mostafa Rezaei; Methodology: Bahram Abedi, Seyed Mostafa Rezaei, and Hossein Fath Elahi; Investigation: Bahram Abedi, Seyed Mostafa Rezaei, and Hossein Fath Elahi; Writing-original draft: Seyed Mostafa Rezaei, Bahram Abedi; Data collection and Data analysis: Bahram Abedi, Seyed Mostafa Rezaei; Writing-review & editing: All authors.

Conflict of interest

There is no conflict of interest.

Acknowledgments

We would like to thank those who have contributed to the study.

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