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Research Paper

Studying the Histopathological Effects of Aerobic Training Along With Vitamin E Consumption in the Cardiac of Methamphetamine-dependent Rats

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ABSTRACT

Background and Aim: Methamphetamine abuse causes tachycardia, tachypnea (hyperventilation), high blood pressure, rupture of heart vessels, and an increase of fibrotic tissue in the human heart. This study aimed to investigate the histopathological effects of aerobic training and vitamin E consumption on the heart following the consumption of methamphetamine in male rats.

Materials and Methods: In this research, 54 adult rats weighing 200-210 g were divided into 6 groups, saline, addicted (sham), addicted+oral paraffin (AP), addicted+supplement (AS), addicted+aerobic training (AAT), addicted+aerobic training+supplement (AATS). After 23 days of methamphetamine injection, moderate-intensity aerobic training was performed for 6 weeks and 150 mg/kg of vitamin E was administered by gastric gavage. After this period, the rats were dissected and their hearts were removed. The data were analyzed using one-way ANOVA methods at $P<0.05$.

Results: The morphological investigation showed a difference between the two groups of sham and AP with the saline, AS, AAT, and AATS in the space between the endocardium, congestion, and vascular rupture. There was a difference in the hypertrophy of muscle fibers between the sham and AP with the saline, AS, AAT, and AATS in the morphometric investigation.

Conclusion: It can be said that methamphetamine causes pathological hypertrophy of cardiomyocytes and destruction and rupture of blood vessels, and aerobic training along with vitamin E consumption causes physiological cardiac hypertrophy. Regarding the effect of vitamin E alone on the type of cardiac hypertrophy and vascular changes, further studies are needed.

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Journal of Vessels and Circulation
Qom University of Medical Sciences

1. Introduction

Addiction to opioids is one of the critical issues that different countries of the world pay special attention to it annually allocating some of their budgets to prevent its production and distribution. According to the report of the United Nations Office on Narcotic Drugs, about 27 million people in the world use methamphetamine, which has made it the most widely used illegal drug after hashish [1]. Methamphetamine is a synthetic chemical stimulant of the amphetamine type, which is highly addictive and is consumed in different ways, such as injecting, swallowing, and inhalation through the respiratory tract [2]. These substances have dual properties, the properties that encourage people to use them are creating euphoria, increasing attention and concentration, reducing fatigue, and improving daily functions, but in addition to these, various destructive effects, such as tachycardia, tachypnea, high blood pressure, dilated pupils and increased temperature due to consumption of these substances have been reported [3]. In a case study, Karch (2011) showed that suffering from methamphetamine abuse causes the rupture of heart vessels and the increase of fibrotic tissue in the human heart [4]. Akhgari et al. (2017) in their research on the hearts of deceased people suffering from methamphetamine abuse, stated that the most common histopathological features observed in the hearts of these people were myocardial hypertrophy, mild to severe atherosclerosis, and necrosis [5].

Treatment and prevention of opiate addiction is a crucial issue that is addressed in world communities. Nowadays, exercise and physical activity as a treatment method is considered by researchers. But what is essential is the intensity and duration of physical activity. Shahrabadi et al. (2022) stated that intense intermittent exercise activity decreased the expression of caspase 3 in the heart of methamphetamine-dependent rats [6], but Yazdanperst et al. (2018) showed that intense activity increased Bax synthesis and caspase-3 expression and Bcl-2 synthesis decrease compared to the control group and the group with moderate activity [7]. Regarding the duration of exercise, it has been stated that in long-term aerobic exercise, adenosine triphosphate (ATP) is broken down to provide energy and support continuous muscle contractions, and the product of this continuous breakdown is adenosine diphosphate (ADP) and adenosine monophosphate (AMP). The re-degradation of AMP produces products, such as hypoxanthine and xanthine, and urea from the biochemical process of xanthine oxidase. By consuming oxygen molecules, xanthine oxidase produces peroxide species [8] and according to the results of studies, reactive oxygen species cause cell destruction [9, 10]. The body's antioxidant system is one of the crucial defense lines against free radicals and other cellular damaging factors. But in some situations, the power of destructive factors overcomes this system; therefore, people should use dietary or injectable antioxidants. Vitamin E is a fat-soluble non-enzymatic antioxidant whose isomers can control reactions based on reactive oxygen species and reduce the production of lipid peroxidation [11]. Ghafori et al., (2019) concluded that in the heart of mice addictedto ecstasy, receiving vitamin E significantly reduced therate of apoptosis compared to the group that did not receive this vitamin [11]. Xihao Du et al. (2017) investigated the protective effect of vitamin E against the destructive effect of environmental air pollution on the myocardium of male rats and concluded that compared to the hearts of rats damaged by polluted air, the rats that received vitamin E had minor injuries and pretreatment of rats with this vitamin caused a significant reduction of inflammatory cytokines in their hearts [12]. Considering the limited research in this field and the uncertainty of the combined effect of aerobic exercise and vitamin E consumption on heart tissue, this research aims to studying the histopathological effects of aerobic training along with vitamin E consumption in the cardiac of methamphetamine-dependent rats.

2. Materials and Methods

Methamphetamine drug

Methamphetamine addiction was done by intraperitoneal injection. For this purpose, methamphetamine was dissolved in 0.9% normal saline with a weight scale. The duration of the injection was 23 days, which was done as an increase in the dose relative to the weight, according to the protocol of Groman et al. (2018) [13]. The purity and authenticity of methamphetamine were determined by Fourier transform infrared spectroscopy in the chemistry laboratory of the Faculty of Basic Sciences of Qom University (Figure 1).

Animals

The present study was an empirical type with a fundamental-applied approach. In this research, 60 adult male rats (weighing 200-210 g) were purchased from Razi Vaccine and Serum Research Institute and kept in standard laboratory conditions with suitable water and food and natural light-dark rhythm conditions (12-12) and at a temperature of 23±2°C. For the saline group, 10 rats were randomly selected considering the homogeneity

of the weights. After the beginning of the addiction by injecting methamphetamine, 6 rats (out of the remaining 50 rats) died, and the number of 44 rats were divided into 6 groups as follows:

1. Intact group: They were kept in the same conditions without any intervention for 6 weeks, normal saline injection+quiet treadmill (n=10).

2. Addicted group (Sham): Methamphetamine+quiet treadmill (n=8).

3. Addicted and paraffin (AP) group: Methamphetamine+oral paraffin (n=9).

4. Addict and supplement (AS) group: Methamphetamine+vitamin E (n=9).

5. Addicted and aerobic training (AAT) group: Methamphetamine+aerobic exercise (n=9).

6. Addicted aerobic training and supplement (AATS) group.

Vitamin E

Eurovital vitamin E was purchased in the required amount from the Deputy Food and Drug, Ministry of Health and Medical Education, Qom Province, Iran. The dosage of this supplement was 150 mg/kg, which was dissolved in 1.5 mg/kg of oral paraffin and fed to rats by gastric gavage three times a week for 6 weeks [12, 14].

Exercise protocol

In the present study, 6 weeks of moderate-intensity aerobic training intervention was considered. Before starting the main training, the animals were familiarized with the treadmill for one week, and to determine the initial intensity, the exhaustive incremental test was taken on the treadmill.

Description of exhaustive test

After a 5-10 minute warm-up at a speed of 5-10 m/min, the speed of the treadmill was increased by 0.3 m/s every 2 minutes until the animal could not continue running [15, 16]. In this research, the final speed was 20 meters per minute, which was used as an exhaustive indicator. This index is used as one of the indicators to determine the intensity of exercise.

Description of aerobic training

Aerobic training was performed for 6 weeks, 6 sessions per week with 50%-60% of the determined maximum speed (10-12 meters per minute) according to Table 1 [17]. An electric shock with a voltage of 0.3 V was used to stimulate the animal to run and continue the activity on the treadmill. After finishing the activity, after 2 minutes, the animal was taken out of the treadmill chamber and moved to the cage to relax. The method used in the study is summarized in Figure 2.

Histological assay

After completing the training and treatment period for 6 weeks, the animals were anesthetized using the ketamine-xylazine mixture. Next, the animal's abdomen was opened and transcardial perfusion was performed, then the heart tissue was removed and after tissue processing and preparation of paraffin molds, incisions with a thickness of 5 µm were prepared from samples using a rotary microtome to stain hematoxylin-eosin micrometers and placed on gelatin slides. At first, the slides were placed in special colored baskets and to remove the paraffin, the baskets containing the slides were placed in three xylene containers (each container for 2 minutes). To hydrate the tissues, the samples were passed through ethanol alcohol solutions in descending order (100%, 95%, 90%, 70%, and 50%) (each container for 2 minutes). Then, to stain the nucleus, the samples were placed in hematoxylin solution (for 5 minutes) and after that, the added dyes were completely washed off with running water. Then, for color differentiation in the tissue, the samples were placed in 1% acid alcohol solution (1% HCL in 70% alcohol) for 5-10 s and immediately washed with running water. The slides were placed in a container containing distilled water and after that, to stain the cytoplasm, the slides were placed in eosin solution (for 2 minutes) and then the slides were thoroughly washed in water to wash the excess dye from the tissues. Then, to dehydrate the slides, ethanol alcohol with increasing concentration (90%, 95%, two containers of 100%) was used (each container for 2 minutes). In the end, to clarify the tissues, the samples were passed through 3 Xylene containers (each container for 2 minutes). Finally, with the help of entellan glue, the painted slides were covered with coverslips on the slides, and after the slides dried, with the help of a light microscope, the slides were quantitatively and qualitatively studied.

Journal of Vessels and Circulation
Qom University of Medical Sciences

The present study was an empirical study. This study was carried out following the ethical principles, all animal care and laboratory methods approved by the Ethics Committee of Qom University of Medical Sciences, and with the code of ethics IR.MUQ.AEC.1400.007 in the animal care center and the cellular and molecular research center of the Qom University of Medical Sciences.

In this research, SPSS software, version 26 and descriptive statistics (Mean±SEM) and inferential statistics were used for statistical analysis. First, after determining the normality of the data distribution by the Klomogrov-Smirnov test, one-way analysis of variance (ANOVA) was used to compare the differences between groups, and if the differences were significant, the LSD post hoc test was used. In all tests, a significant difference of 0.05 was considered.

3. Results

After studying the slides under the microscope, morphological examination (qualitative examination) and morphometric examination (quantitative examination) of the slides were performed. In the morphological examination, the morphological changes of heart tissue

Table 1. Program of 6 weeks of aerobic training

Week	Duration (m)	Intensity
1st	25	50% of the maximum speed (10 m per minute)
2nd	30	50% of the maximum speed (10 m per minute)
3th	30	55% of the maximum speed (11 m per minute)
4th	35	55% of the maximum speed (11 m per minute)
5th	35	60% of the maximum speed (12 m per minute)
6th	40	60% of the maximum speed (12 m per minute)

Table 2. The Mean±SEM of the diameter of the muscle fibers of the groups in terms of micrometers

Groups	Mean±SEM
Saline	314.3±37.28
Sham	410.0±37.36
AP	386.67±10.0
AS	348.0±16.85
AAT	341.70±7.92
AATS	345.0±9.57

Table 3. The results of variance analysis of the diameter of endocardium

Results	Sum Squares	d_f	Mean Squares	F	P
Between groups	45027.43	5	9005.48	2.04	0.096
Intergroup	154084.76	35	4402.42		
Total	199112.19	40			

Table 4. The results of LSD post hoc test to determine the difference between groups

Groups	Mean±SE	Sig.
Saline and sham	95.71±34.34	0.009*
Saline and AS	33.71±38.85	0.3
Saline and AP	72.38±33.43	0.03*
Saline and AAT	27.38±36.91	0.4
Saline and AATS	30.71±36.91	0.4
Sham and AS	62.00±37.82	0.1
Sham and AP	23.33±32.24	0.4
Sham and AAT	68.33±35.83	0.07
Sham and AATS	65.00±35.83	0.08
AS and AP	38.66±37.00	0.3
AS and AAT	6.33±40.17	0.8
AS and AATS	3.00±40.17	0.9
AP and AAT	45.00±34.97	0.2
AP and AATS	41.66±34.97	0.2
AAT and AATS	3.33±38.30	0.9

cells, such as the whole structure of heart cells at 4, and 10 magnification and the striated lines of heart cells were considered qualitatively at 40 magnification. In the microscopic view of Figure 3, the space between the endocardium of the fibers is marked with a black arrow, as well as the hypertrophy of the fibers and the rupture of blood vessels and muscle fibers -both- in this qualitative study. The morphometric examination of heart cells was examined with 40 magnification. Table 2 lists the Mean±SEM of the diameter of the endocardium of the groups. Figure 4 shows the difference in the diameter of the endocardium (Mean±SEM). The quantitative examination of the diameter of muscle fibers with ANOVA and LSD post hoc test showed a significant difference between the saline and the sham group, the control group, and the paraffin group ($P<0.05$). However, no significant difference was observed between other groups (Tables 3 and 4).

Table 5 presents the amount of rupture of blood vessels and endocardium in the groups as a percentage.

4. Discussion

Among the reported injuries caused by methamphetamine abuse are increased blood pressure, tachycardia, ischemia, infarction, and cardiac hypertrophy. In this research, on average, the diameter of the endocardium of the groups increased compared to the saline group, and ANOVA showed that this increase was significant between the sham and AP compared the saline group, and between the other groups, it was not significant. In their research, Kaye et al. (2009) concluded that atheroscle-

Table 5. Rate of vascular and muscle rupture in percentage

Groups	Saline	Sham	AP	AS	AAT	AATS
Vascular rupture rate (%)	0	100	80	60	20	20

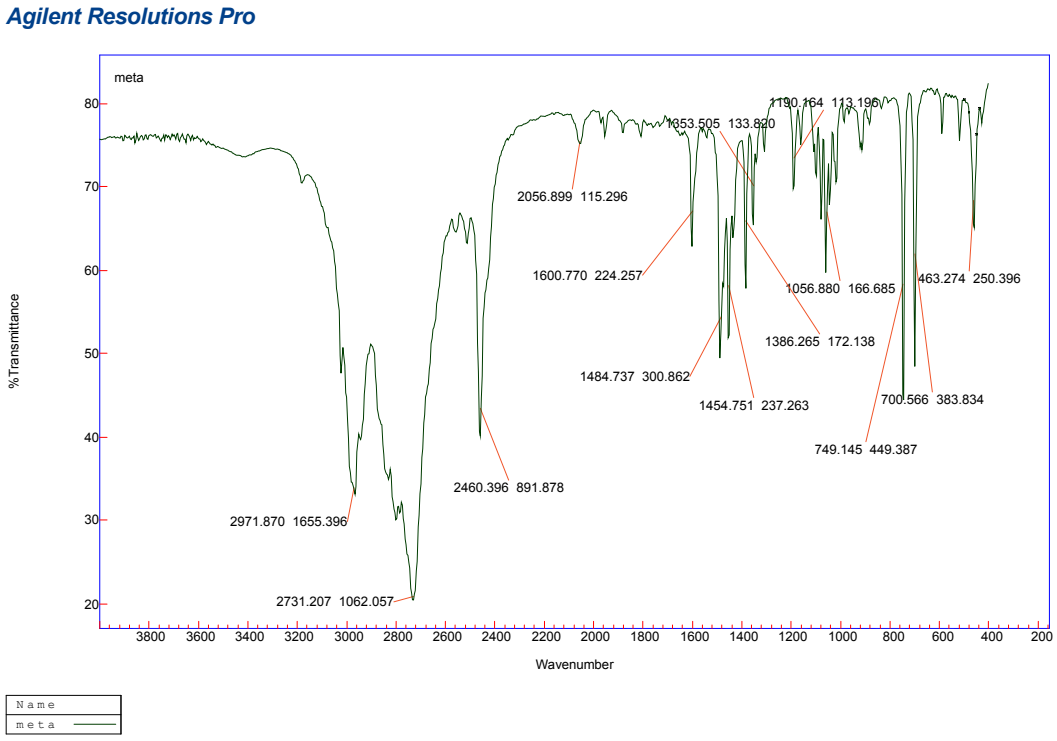

Figure 1. Determining the purity of methamphetamine by infrared spectroscopy

Journal of Vessels and Circulation
Qom University of Medical Sciences

rosis, cardiomegaly (heart enlargement), and ventricular hypertrophy develop in the hearts of ecstasy users in Australia [18]. Sun et al. (2019) stated that methamphetamine increases cardiac damage and apoptosis caused by the reduction of melusin in male rats [19]. Usually, hearts that become hypertrophied always suffer from ischemia because neosclerosis is not coordinated with the formation of new sarcomeres, and on the other hand, ischemia itself is caused by the reduction of blood flow and the transfer of nutrients to different parts of the heart. Myocardial ischemia may be caused by exercise, increased heart rate or arrhythmia [20]. Hypertrophy can be investigated in two ways, which are physiological and pathological. Both types of hypertrophies are initially created as an adaptive response to the pressures on the heart, and in both, cardiomyocytes enlarge, but a great difference exists between them in terms of molecular mechanisms. Physiological hypertrophy preserves cardiac function over time, while pathological hypertrophy is associated with cardiovascular side effects, including heart failure, arrhythmia, and death. Pathological hypertrophy heart phenotype is different and can be manifested as heart failure with a fixed ejection fraction or heart failure with a reduced ejection fraction [21]. Physiological hypertrophy has a protective effect against cardiovascular diseases caused by physical activity and adaptation to it, while pathological hypertrophy causes heart valve diseases, myocardial structural disorder, and infarction [22]. In physiological hypertrophy, the ventricular volume is increased in harmony with the thickness of the ventricular wall (eccentric hypertrophy) and cardiomyocytes grow in both width and length. In this type of hypertrophy, the dimensions of the heart return to their original state after the end of the stimulation, but in pathological hypertrophy, the ventricular volume is reduced at first and then the thickness of the wall is increased (concentric hypertrophy), which causes impaired contractile function and thickness growth (transverse) of cardiomyocytes against their longitudinal growth and reversibility of ventricular dimensions is not observed in this type. Eccentric hypertrophy is caused by endurance physical activities [21]. Petridis et al. stated that the end-diastolic volume of 15-18-year-old individuals became more prominent due to endurance training compared to other athletes [23] and Vella et al. in their research, which was conducted on 50 obese women, showed that moderate to intense physical activity reduces inflammatory markers that lead to cardiovascular risk factors [24]Similarly, Ababzadeh et al. concluded that aerobic exercise changes the muscle fibers of the rat heart which causes the compatibility of heart to the demands of this type of exercise [25]. The results of the aforementioned researchers are consistent with the results of this research. Therefore, it can be said that probably the hypertrophy created in the sham and AP groups was pathological, and the hypertrophy created in the two exercise groups was physiological, which

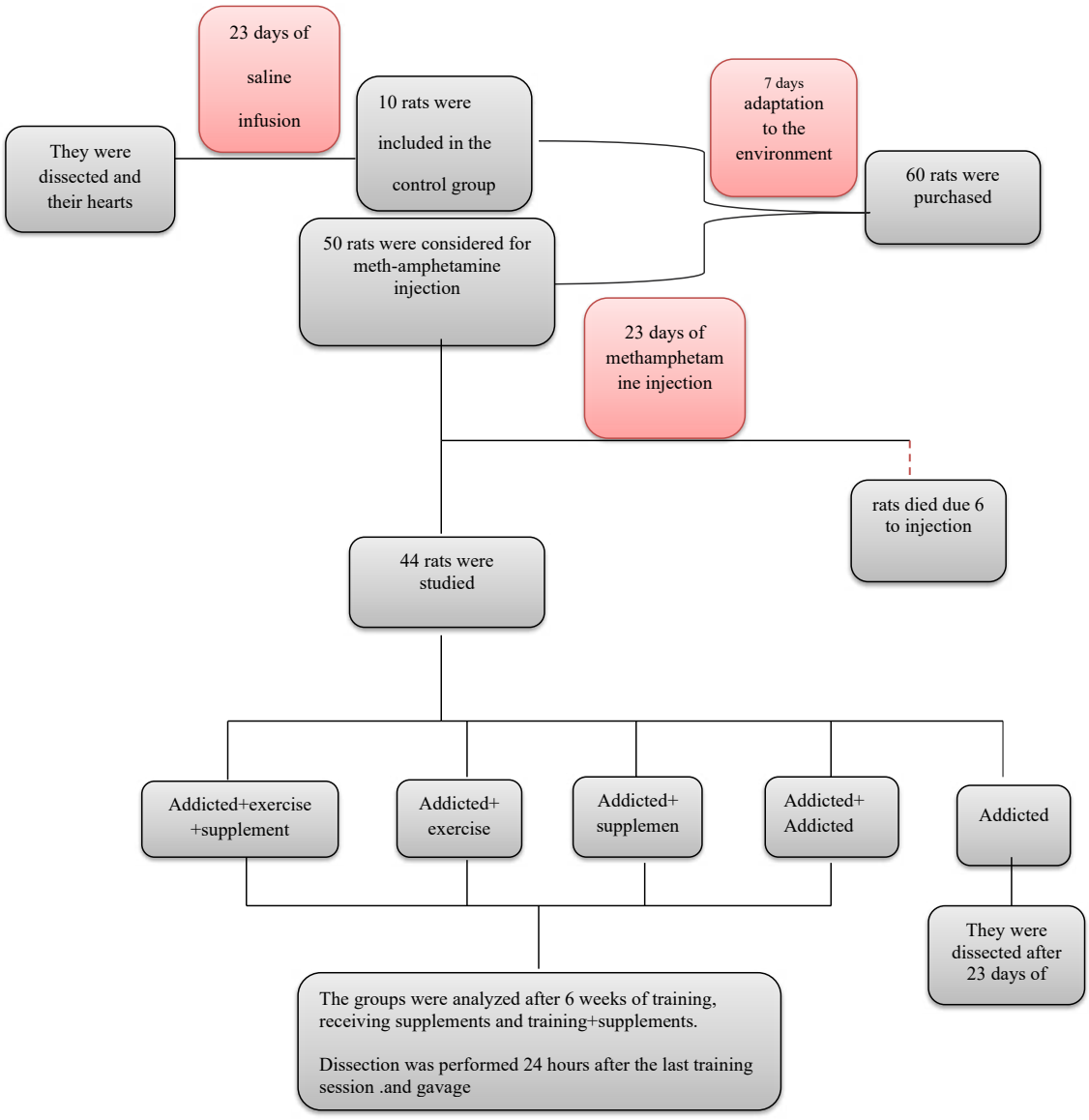

Figure 2. Summary of methods

Journal of Vessels and Circulation
Qom University of Medical Sciences

was caused by adaptation to aerobic exercise. But in the case of the AS group, due to the hypertrophy created and the distance between the membranes, it is not possible to comment with certainty about the type of hypertrophy.

As shown in Figure 3, in the sham, AP and AS groups, vascular rupture and inflammation were also observed in some parts. Studies show inflammation as a cause of vascular damage. Inflammatory factors, such as monocytes, macrophages, and inflammatory cytokines in the vessels cause the stimulation of adhesive molecules and proteases, which enter the bloodstream in a soluble form and eventually cause cardiovascular diseases [26]. The hardness of the arteries causes high blood pressure and increases the work pressure on the heart. On the other hand, it has been shown that aerobic training reduces arterial stiffness and blood pressure in people with high blood pressure. Liu et al. (2018) showed that 12 weeks of cycling activity reduces arterial stiffness in sedentary men [27]. Jenkins et al. (2010) concluded that regular endurance training improves body composition and increases the level of maximum oxygen consumption by reducing the amount of visceral fat [28]. Adaptation to aerobic exercise increases the expression of vasodilator factors, such as nitric oxide in the vascular endothelium, and on the other hand, aerobic exercise decreases sympathetic tone and increases vagal tone, and all these factors improve cardiovascular function. Regarding the role of antioxidants, it should be said that these factors reduce the destructive ef-

Journal of Vessels and Circulation
Qom University of Medical Sciences

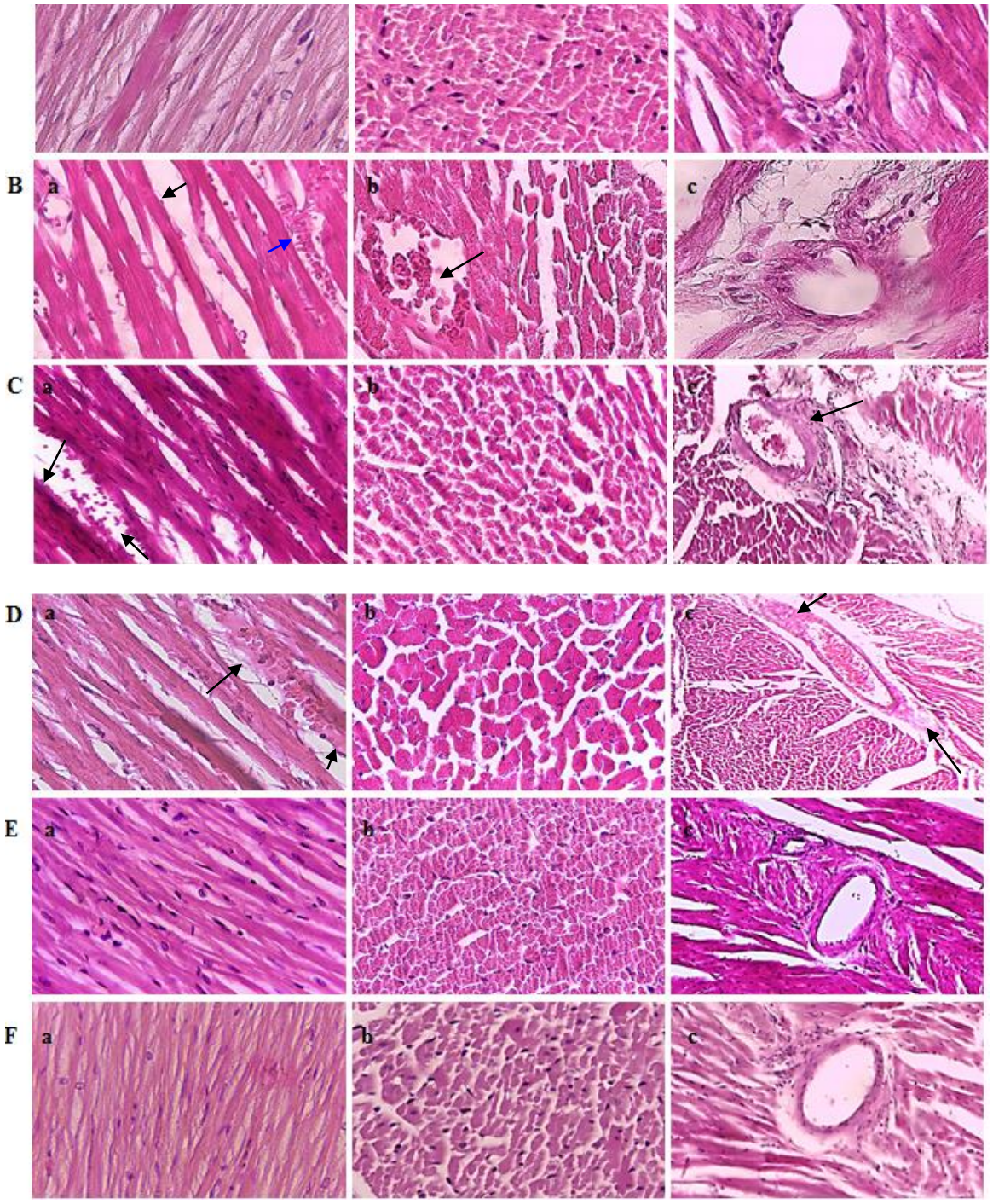

Figure 3. Microscopic view of heart tissue with 40 magnification

Journal of Vessels and Circulation
Qom University of Medical Sciences

a: Longitudinal section view, b: Transverse section view, c: Cardiovascular section view

A: Control group; B: Sham group; C: AP; D: AS; E: AAT; F: AATS.

In the Ba view, the endocardium space between the strands is marked with a black arrow and the rupture of the strands is marked with a blue arrow. In the Bb view, congestion is indicated by a black arrow. Vascular destruction and fibrosis is evident in the Bc view. In the Ca view, the endocardium space and the rupture of the fibers are marked with a black arrow. In the Cb view, more space can be seen between the endocardium of the cells. Destruction of epithelium, endothelium, and perivascular fibrosis shows the destructive effect of methamphetamine on blood vessels. It can be seen in the Cc view. In view Da, rupture of the strands is marked with a balck arrow. In the Db view, empty space can be observed between the strings. In the Dc view, inflamation and fibrossis marked with a balck arrow.

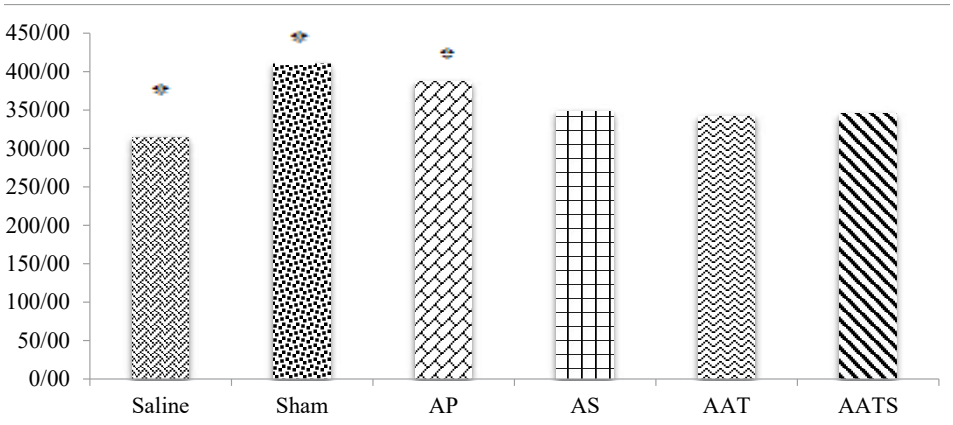

Figure 4. The difference in the diameter of endocardium (µm)

fects of reactive oxygen species in tissues, such as vascular tissue, and improve the function of the immune system, and regular exercise with low to moderate intensity improves the antioxidant defense function of glutathione peroxidase, catalase, and superoxide dismutase [29], which can be concluded that this issue promotes and improves the function of the body's immune system. In their research, Ghafori et al. (2019) investigated the effect of vitamin E on the histology of the heart of rats after taking ecstasy and concluded that vitamin E has a protective effect against the destructive effects of reactive oxygen species caused by taking ecstasy, such as the increase in collagen fibers that lead to an increase in myocardial fibrosis and also improves the increase in infiltration and the space between the cardiomyocytes that was caused by the consumption of ecstasy [11]. The result of Ghafori et al.'s research is inconsistent with the result of the present study regarding the effect of vitamin E on improving cardiovascular indicators. As can be seen in Figure 3D, the space between the endocardium is large in the AS group, like the sham and AP groups, and the consumption of vitamin E does not reduce this space and integrity, which is observed in the saline group and the AAT groups. On the other hand, the use of this vitamin did not improve and repair the damaged vessels and congestion caused by the abuse of methamphetamine.

5. Conclusion

The findings of the present study showed that methamphetamine abuse causes pathological hypertrophy and rupture of blood vessels and endocardium in the heart tissue. On the other hand, considering the lack of significant difference between the AAT and AATS groups, it can be concluded that aerobic training with moderate intensity causes physiological hypertrophy, reducing congestion, and improving the breakdown of muscle fibers and heart blood vessels; but, regarding the individual effect of vitamin E in the mentioned factors, further studies are needed.

Ethical Considerations

Compliance with ethical guidelines

This study was conducted following the ethical principles, all animal care and laboratory methods approved by the Ethics Committee of Qom University of Medical Sciences (Code: IR.MUQ.AEC.1400.007).

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Authors' contributions

Conceptualization: Amir Hossein Haghighi; Research: Hamid Reza Salimi, Amir Hossein Haghighi, Shima Ababzadeh, and Hamid Marafati; Writing–original draft: Hamid Reza Salimi; Methodology, data collection, data analysis, review & editing and finalization: Hamid Reza Salimi, Amir Hossein Haghighi, and Shima Ababzadeh.

Conflict of interest

The authors declared no conflict of interest.

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Journal of Vessels and Circulation
Qom University of Medical Sciences

References

[1] Shafiei A, Haghighi AH, Askari R, Keyhani A, Nabavizadeh MS, Asadi-Shekaari M. Effects of moderate-intensity interval training on gene expression and antioxidant status in the hippocampus of methamphetamine-dependent rats. Neurotox Res. 2022; 40(5):1455-63. [DOI:10.1007/s12640-022-00532-4] [PMID]

[2] Reddy PKV, Ng TMH, Oh EE, Moady G, Elkayam U. Clinical characteristics and management of methamphetamine-associated cardiomyopathy: State-of-the-art review. J Am Heart Assoc. 2020; 9(11):e016704. [DOI:10.1161/JAHA.120.016704] [PMID] [PMCID]

[3] Courtney KE, Ray LA. Methamphetamine: An update on epidemiology, pharmacology, clinical phenomenology, and treatment literature. Drug Alcohol Depend. 2014; 143:11-21. [DOI:10.1016/j.drugalcdep.2014.08.003] [PMID] [PMCID]

[4] Karch SB. The unique histology of methamphetamine cardiomyopathy: A case report. Forensic Sci Int. 2011; 212(1-3):e1-4. [DOI:10.1016/j.forsciint.2011.04.028] [PMID]

[5] Akhgari M, Mobaraki H, Etemadi-Aleagha A. Histopathological study of cardiac lesions in methamphetamine poisoning-related deaths. Daru. 2017; 25(1):5. [DOI:10.1186/s40199-017-0170-4] [PMID] [PMCID]

[6] Shahrabadi H, Haghighi AH, Askari R, Asadi-Shekaari M, Souza DC, Gentil P. Effect of high-intensity interval training on cardiac apoptosis markers in methamphetamine-dependent rats. Curr Issues Mol Biol. 2022; 44(7):3030-8. [DOI:10.3390/cimb44070209] [PMID] [PMCID]

[7] Yazdanparast Chaharmahali B, Azarbayjani MA, Peeri M, Farzanegi Arkhazloo P. Increased expression of bax and bcl2 apoptosis biomarkers in the heart of old female rats after interval training and curcumin consumption. Jorjani Biomed J. 2018; 6(4):40-52. [DOI:10.29252/jorjanibiomedj.6.4.40]

[8] He F, Li J, Liu Z, Chuang CC, Yang W, Zuo L. Redox mechanism of reactive oxygen species in training. Front physiol. 2016; 7:486. [DOI:10.3389/fphys.2016.00486]

[9] Nordberg J, Arnér ES. Reactive oxygen species, antioxidants, and the mammalian thioredoxin system. Free Radic Biol Med. 2001; 31(11):1287-312. [DOI:10.1016/S0891-5849(01)00724-9] [PMID]

[10] Redza-Dutordoir M, Averill-Bates DA. Activation of apoptosis signalling pathways by reactive oxygen species. Biochim Biophys Acta. 2016; 1863(12):2977-92. [DOI:10.1016/j.bbamcr.2016.09.012] [PMID]

[11] Ghafori SS, Zirak Javanmard M, Meghrazi K, Karimipour M, Peirouvi T. Protective effects of vitamin E on heart and testis histology following MDMA (Ecstasy) exposure in mice. Int J High Risk Behav Addict. 2019; 8(4):e84212. [DOI:10.5812/ijhrba.84212]

[12] Du X, Jiang S, Bo L, Liu J, Zeng X, Xie Y, et al. Combined effects of vitamin E and omega-3 fatty acids on protecting ambient PM2.5-induced cardiovascular injury in rats. Chemosphere. 2017; 173:14-21.[DOI:10.1016/j.chemosphere.2017.01.042] [PMID]

[13] Groman SM, Rich KM, Smith NJ, Lee D, Taylor JR. Chronic exposure to methamphetamine disrupts reinforcement-based decision making in rats. Neuropsychopharmacology. 2018; 43(4):770-80. [DOI:10.1038/npp.2017.159] [PMID] [PMCID]

[14] Ayinde OC, Ogunnowo S, Ogedegbe RA. Influence of vitamin C and vitamin E on testicular zinc content and testicular toxicity in lead exposed albino rats. BMC Pharmacol Toxicol. 2012; 13:17. [DOI:10.1186/2050-6511-13-17] [PMID] [PMCID]

[15] Høydal MA, Wisløff U, Kemi OJ, Ellingsen O. Running speed and maximal oxygen uptake in rats and mice: Practical implications for exercise training. Eur J Cardiovasc Prev Rehabil. 2007; 14(6):753-60. [DOI:10.1097/HJR.0b013e3281eacef1] [PMID]

[16] Sedaghat M, Choobineh S, Ravasi AA. Taurine with combined aerobic and resistance exercise training alleviates myocardium apoptosis in STZ-induced diabetes rats via Akt signaling pathway. Life Sci. 2020; 258:118225. [DOI:10.1016/j.lfs.2020.118225] [PMID]

[17] Shimojo GL, da Silva Dias D, Malfitano C, Sanches IC, Llesuy S, Ulloa L, et al. Combined aerobic and resistance exercise training improve hypertension associated with menopause. Front Physiol. 2018; 9:1471. [DOI:10.3389/fphys.2018.01471] [PMID] [PMCID]

[18] Kaye S, Darke S, Duflou J. Methylenedioxymethamphetamine (MDMA)-related fatalities in Australia: Demographics, circumstances, toxicology and major organ pathology. Drug Alcohol Depend. 2009; 104(3):254-61./ [DOI:10.1016/j.drugalcdep.2009.05.016] [PMID]

[19] Sun X, Wang Y, Xia B, Li Z, Dai J, Qiu P, et al. Methamphetamine produces cardiac damage and apoptosis by decreasing melusin. Toxicol Appl Pharmacol. 2019; 378:114543. [DOI:10.1016/j.taap.2019.03.015] [PMID]

[20] Cecchi F, Sgalambro A, Baldi M, Sotgia B, Antoniucci D, Camici PG, et al. Microvascular dysfunction, myocardial ischemia, and progression to heart failure in patients with hypertrophic cardiomyopathy. J Cardiovasc Transl Res. 2009; 2(4):452-61. [DOI:10.1007/s12265-009-9142-5] [PMID]

[21] Nakamura M, Sadoshima J. Mechanisms of physiological and pathological cardiac hypertrophy. Nat Rev Cardiol. 2018; 15(7):387-407. [DOI:10.1038/s41569-018-0007-y] [PMID]

[22] Turkbey EB, McClelland RL, Kronmal RA, Burke GL, Bild DE, Tracy RP, et al. The impact of obesity on the left ventricle: The Multi-Ethnic Study of Atherosclerosis (MESA). JACC Cardiovasc Imaging. 2010; 3(3):266-74. [DOI:10.1016/j.jcmg.2009.10.012] [PMID] [PMCID]

[23] Petridis L, Kneffel Z, Kispéter Z, Horváth P, Sidó Z, Pavlik G. Echocardiographic characteristics in adolescent junior male athletes of different sport events. Acta Physiol Hung. 2004; 91(2):99-109. [DOI:10.1556/APhysiol.91.2004.2.2] [PMID]

[24] Vella CA, Allison MA, Cushman M, Jenny NS, Miles MP, Larsen B, et al. Physical activity and adiposity-related inflammation: The MESA. Med Sci Sports Exerc. 2017; 49(5):915-21. [DOI:10.1249/MSS.0000000000001179] [PMID] [PMCID]

[25] Ababzadeh S, Iravani A, Fallahian F, Aghamiri SM. Histological and morphological studies of cardiac cells in response to aerobic trainingand rosemary extract in rat model of aging. J Morphological Sci. 2018; 35(04):266-71. [DOI:10.1055/s-0038-1676778]

[26] Packard RR, Libby P. Inflammation in atherosclerosis: From vascular biology to biomarker discovery and risk prediction. Clin Chem. 2008; 54(1):24-38. [DOI:10.1373/clinchem.2007.097360] [PMID]

[27] Liu HB, Yuan WX, Wang QY, Wang YX, Cao HW, Xu J, et al. Carotid arterial stiffness and hemodynamic responses to acute cycling intervention at different times during 12-week supervised exercise training period. Biomed Res Int. 2018; 2018:2907548. [DOI:10.1155/2018/2907548] [PMID] [PMCID]

[28] Jenkins NT, McKenzie JA, Damcott CM, Witkowski S, Hagberg JM. Endurance exercise training effects on body fatness, VO2max, HDL-C subfractions, and glucose tolerance are influenced by a PLIN haplotype in older Caucasians. J Appl Physiol (1985). 2010; 108(3):498-506. [DOI:10.1152/japplphysiol.01018.2009] [PMID] [PMCID]

[29] Mehranjani MS, Taefi R. The protective role of vitamin E on the testicular tissue in rats exposed to sodium arsenite during the prenatal stage till sex maturity: A stereological analysis. Iranian Journal of Reproductive Medicine. 2012; 10(6):571. [PMID] [PMCID]

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