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RESEARCH ARTICLE

Investigating the effects eight weeks of non-continuous aerobic exercise on the levels of angiopoietin2-like protein and interferon beta in rats suffering from coronary artery disease

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ABSTRACT

Background: Reviewing the previous studies reveals that the balance between stimulators and inhibitors of angiogenesis is of a great deal of importance. Among these factors, it can be pointed to the ANGPT2-like protein and the interferon (IFN)-beta. Since hypoxia is one of the most powerful stimulators of angiogenesis and considering the fact that endurance training creates a hypoxia condition. **Aims and Objectives:** The purpose of the present study was to investigate the effects of 8 weeks of non-continuous aerobic exercise on levels of angiopoietin2-like proteins and IFN beta (IFNβ) in male rats suffering from coronary artery disease. **Materials and Methods:** To this end, 32 months old rats weighting between 200 and 250 g were randomly selected. Afterward, 20 of the rats were made sick and further divided into two 10 member groups of control and experimental. The experimental group received 5 sessions of non-continuous aerobic exercises on animal per week for 8 weeks on an animal treadmill while the control group did not receive any exercises during these 8 weeks. After the period of the experiment, 5 mL of blood was taken from reach rat's lower inferior vein 72 h after the past exercise after anesthetization by expert animal surgeons. Research data have been analyzed using the ANOVA test and the SPSS v.0.24 Software. **Results:** Research findings indicate that after 8 weeks of participation in non-continuous aerobic exercises, a certain statistically significant difference was made between the control and experimental groups in terms of the level of IFNβ. However, no statistically significant difference was recorded for the level of angiopoitein-2 like proteins. **Conclusion:** In general and with respect to the obtained results it can be stated that 8 weeks of non-continuous aerobic exercises did not result in an increase in the angiopoietin-2 like proteins level while resulting in a statistically significant decrease in the level of IFNβ.

KEY WORDS: Non-continuous Exercise; Angiogenesis; Coronary Arteries

INTRODUCTION

The coronary artery disease (CAD) is the most prevalent cause of fatalities in the world.[1] Iran is not an exception to this phenomenon and this disease is also one of the most prevalent causes of fatality in Iran.[2] According to a report published by the world health organization, 46% of the fatalities resulting from non-contagious diseases in Iran are caused by cardiovascular diseases (CVD).[29] Coronary arteries are the primary veins in charge of feeding the heart. Blockage of these arteries and or reduction of the section of coronary arteries can damage certain parts of the myocardium. Previous studies have shown that exercising increases the capillary density of the damaged myocardium tissues. New capillary formation and the following increased capillary density is one of the most important changes that occur

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during exercising. The former occurrence ultimately results in more and better oxygen transfer.[9] During the specifically ordered process of natural formation of blood vessels, the endothelial cellules receive stimuli from the angiogenesis and secrete special enzymes such as matrix metalloproteinases and heparinizes. The former and latter digest outer-cellular matrices and ultimately result in a strengthened bond between the disrupted endothelial cellules.[6]

Under natural circumstances, the inhibitor factors of angiogenesis outnumber the stimulating factors, and therefore, the process of angiogenesis is impeded. Factors such as hypoxia, shear stress, dilators of vessels, muscular stretching, and contraction result in an increase in the density of angiogenesis factors in addition to a decrease in the density of factors that inhibit the former process.[7,8,9] Formation of new capillaries requires the proliferation and migration of capillary endothelial cellules.[9] Several growth factors are engaged in the process of angiogenesis. Among these factors it can be pointed to the vascular endothelial growth factor, the fibroblast growth factor (FGF), the hepatocyte growth factor, and angiopoietin.[6,8,9] Angiopoietins are human growth factors that are also especially effective on the process of angiogenesis. The gene corresponding to this protein is located on chromosome eight. At present, there are four known types of angiopoietin including ANGPT1, ANGPT2, ANGPT3, and ANGPT4.[10] The ANGPT2-like proteins are also among factors responsible for angiogenesis, however, there still a long way until mankind can identify the entire mechanisms of this protein.[12] Regarding patients of CAD, this protein has shown significant changes.[12] Similar to angiopoietins, the ANGPT2-like protein is a glycoprotein too. Furthermore, its function on the endothelial cellules may be through the autocrine and paracrine.[15] On the one hand, decreased functionality of anti-angiogenesis factors is also important in occurrence of angiogenesis. Among these factors it can be pointed to angiostatin, endostatin, vasostatin, certain interleukins (ILs) such as IL-4 and IL-12 and also alpha, beta, and gamma interferons (IFNs). The IFN family is divided into three groups, namely, as IFN Type 1, IFN Type 2, and IFN Type 3. IFN Type 1 includes IFN-alpha; IFN beta (IFNβ), IFN-ε, IFN-k, and IFN-ω. IFN Type 2 includes IFN-γ; and IFN type three includes IFN-λ1 and IFN-λ2.[14]

IFNβ is a spherical glycoprotein with a sequence of 166 amino acids 20% of which is comprised saccharine bases.[13] Several studies have shown that compared to the effects of other IFN sub-units, the IFNβ is more powerful in terms of inhibition of cellular proliferation and angiogenesis.[1] Angiogenesis is precisely controlled by a number of factors activating and inhibiting the angiogenesis and the balance between these factors.[3] Angiogenesis inhibitors can prevent diseases such as cancer, diabetes nephropathy, and joint inflammation. While the stimulators of angiogenesis are beneficial for the treatment of the CAD, heart diseases, tissue damages, etc.[22] The balances between growth factors, angiogenesis stimulators, angiogenesis inhibitors and cytokines tightly control the process of angiogenesis.[13] The factors studied in the present study include the ANGPT2-like protein and IFNβ.

Several studies have elaborated on the effects of sport and exercising on coronary angiogenesis, however, the obtained results are contradictory in some cases. Variable exercise programs in terms of time and intensity, age and other factors need to be carefully controlled.

There is no evidence regarding effectiveness of exercising on collateral vessel growth, however, there is evidence showing that collateral vessel growth in animals is accelerated when coronary arteries are blocked.[19,26] Several studies have also elaborated on the effects of continuous aerobic exercises on inhibiting and stimulating factors of angiogenesis,[6,9,26] however; there is a little information in hand regarding the effects of non-continuous aerobic exercises on the aforementioned factors.

The growth potential, or in other words, angiogenesis potential of coronary arteries is important for certain clinical conditions that result in increased coronary blood flow. For example, it is desirable during the proliferation of vessels and during responding to heart hypertrophy, collateral vessel growth with myocardial ischemia and vascular regeneration in atherosclerosis.[26]

Reviewing the previous studies reveals that the balance between stimulators and inhibitors of angiogenesis is of a great deal of importance. Among these factors, it can be pointed to the ANGPT2-like protein and the IFNβ. Since hypoxia is one of the most powerful stimulators of angiogenesis and considering the fact that endurance training creates a hypoxia condition, the present study tries to investigate the effects of non-continuous aerobic exercise on angiogenesis in rats suffering from CAD.

MATERIALS AND METHODS

The present study is an experimental research with an animal model. The present research investigates the changes resulted from administration of a non-continuous aerobic exercise program on angiogenesis stimulating and inhibiting factors of an experimental group suffering from CAD (n = 10), a control group suffering from CAD (n = 10) and a healthy control group (n = 10). All three groups were consisted of male Wistar rats. It is worth mentioning that the present research has also made use of rodent treadmills for execution of exercise protocols.

The population of the present study is consisted of Wistar male rats present in the animal laboratory of the University of Medical Sciences of Bushehr. Among the population, 30 male rates aged between 6 and 8 weeks and weighting between 200 and 250 g were randomly selected as the sample of the

study. Afterward, 20 of the rats were randomly infected with coronary CAD. Next, the 20 rats that were made sick were further divided into two 10 membered groups of experimental and control. The control groups did not receive any exercise treatments.

To adhere to ethics, the Helsinki treaty was taken into account while working with animals.[5] Each standard cage with dimensions of 30 × 15 × 15 made from clear polycarbonate by the Iranian company of Razi-Rad held 4 rats. Rats were kept in an environment with a temperature of 22 ± 2 Celsius degrees and a humidity of 50 ± 5% and, a 12 h–12 h light-darkness cycle. Air conditioners, thermometers and humidifiers were used for controlling the temperature, air condition and humidity of the environment. Sterile chips were used for collection of animals' urine and feces. It is worth mentioning that for the sake of hygiene, chips were replaced every 2 days and cages were washed and disinfected. In this study rats were provided with free access to water and food and the entire subjects were fed by identical pelleted foods containing the entire nutrients required by animals.

Afterward, the subjects of the experimental group were introduced with doing the administered activities on treadmills through doing exercise on the rodent treadmills for 1 week with a pace of 10 m per min. Previous studies have shown that this amount of activity is not followed by bold physiological changes. Afterward, 8 weeks of exercise with five sessions per week were administered for the experimental group's rats. The description of exercises is provided in Table 1.

To infect the rats with CAD, 85 mg/kg of ISO made by the Germany Sigma-Aldrich company was used. The drugs were dissolved in normal saline and were then in an intraperitoneal manner injected to the rats in 2 consequent days with 24 h intervals until the occurrence of myocardial infarction (MI). 48 h later, rats were anesthetized using ketamine + zyrosin injection, and their blood samples were taken from their tail area. Afterward, each rat's Troponin-I and MI was measured.

72 h after the last exercise session, blood samples were again taken from subjects to measure their ANGPT2-like protein and

Table 1: The 8 weeks program of non-continuous aerobic exercises

Weeks	Exercise duration (min)	Activity
Introduction 1	14	Warming up: 2 min at 5 m/min Running: 10 min at 10 m/min Cooling down: 2 min at 5 m/min
2 and 3	26	Warming up: 2 min at 10 m/min Running: 10 min at 15 m/min Active rest: 2 min at 5 m/min Running: 10 min at 15 m/min Cooling down: 2 min at 10 m/min
4 and 5	38	Warming up: 2 min at 5 m/min Running: 10 min at 20 m/min Active rest: 2 min at 5 m/min Running: 10 min at 20 m/min Active rest: 2 min at 5 m/min Running: 10 min at 20 m/min Cooling down: 2 min at 10 m/min
6 and 7	50	Warming up: 2 min at 10 m/min Running: 10 min at 23 m/min Active rest: 2 min at 5 m/min Running: 10 min at 23 m/min Active rest: 2 min at 5 m/min Running: 10 min at 23 m/min Active rest: 2 min at 5 m/min Running: 10 min at 23 m/min Cooling down: 2 min at 10 m/min
8 and 9	74	Warming up: 2 min at 10 m/min Running: 10 min at 25 m/min Active rest: 2 min at 5 m/min Running: 10 min at 25 m/min Active rest: 2 min at 5 m/min Running: 10 min at 25 m/min Active rest: 2 min at 5 m/min Running: 10 min at 25 m/min Active rest: 2 min at 5 m/min Running: 10 min at 25 m/min Active rest: 2 min at 5 m/min Cooling down: 2 min at 10 m/min

Table 2: Results of 8 weeks of non-continuous aerobic exercise on levels of ANGPT2-like protein and IFNβ

Proteins	Group	*n*	Mean ± SD	F	Significant
ANGPT2-like protein	Sick experimental	10	330.39 ± 71.38	0.844	0.443
	Sick control	10	313.97 ± 53.73		
	Healthy control	10	295.81 ± 41.8		
IFNβ	Sick experimental	10	56.55 ± 5.91	19.013	0
	Sick control	10	70.24 ± 5.69		
	Healthy control	10	54.63 ± 4.485		

IFN beta: Interferon β, SD: Standard deviation

IFNβ levels. To this end, first of all, the rats were anesthetized using respiratory isoflurane (4%). After confirming the deep anesthesia of rats, their abdomens were opened up, and 5 ccs of blood was taken from their lower inferior vein. The serums were centrifuged for 10 min at 3000 Rpm using the Iranian made centrifuge device of behdad. Afterward, the serums were poured into test tubes and kept at −80° until the time of analysis. The levels of ANGPT2-like protein and IFNβ were measured using the Elisa kits made by the American company of Eastbiopharm.

Descriptive statistics have been used for calculation of descriptive indexes such as mean and standard deviation. Nevertheless, the ANOVA test was used for analysis of research questions. It is worthy of mentioning that the software of SPSS v.24.0 was used for statistical analyses while also the GraphPad software was used for drawing diagrams.

RESULTS

Results indicated that 8 weeks of non-continuous aerobic exercise does not have any statistically significant effect on the ANGPT2-like protein levels in male rats suffering from CAD. In fact, the amount of the ANGPT-2-like protein for the sick rats did not differ from experimental groups' rats. On the other hand, results of the study have also shown that after 8 weeks of non-continuous aerobic exercise, a statistically significant difference was found between the IFNβ levels of control and experimental groups. In rats in the experimental group, the amount of IFNβ was significantly lower than rates in the sick control group; however, it has no statistically significant difference with the healthy control group. On the other hand, while comparing the healthy and sick control groups, a significant observed in the sick control group was observed (Table 2).

DISCUSSION

Results of the present study indicated that 8 weeks of non-continuous aerobic exercise result in an increase in the amount of ANGPT-s-like protein in rats suffering from CAD, however, compared to the statistics of the control group, the former increase is not statistically significant. This is while a statistically significant decrease in the amount of IFNβ was recorded between the control and experimental groups.

In consistence with the results of the present study, there are several studies that have reported no significant increases in the amount of ANGPT2-like protein after administration of exercise programs.[24,25] There are also some other studies that are inconsistent with the present findings stating that the level of ANGPT-2-like protein increases after exercising.[11,12,16,28] On the other hand, some studies have reported a significant decrease in the amount of IFNβ[21,27] while some studies have reported contradictory results stating that no difference is made in the amount of IFNβ after exercising.

Larouche *et al*. reported that after administration of given exercise programs, the level of ANGPT2-like protein increased in patients suffering from CAD.[16] 20 min after one period of high-intensity interval exercise and moderate-intensity continuous exercise (MICE) exercise, the level of ANGPT2-like protein was decreased in CAD patients, however, the results were different 24 h and 72 h after participation in exercises. In this regard, the amount of ANGPT2-like protein was decreased in the high-intensity

interval training group while it was increased for the MICE group. On the other hand, the amount of ANGPT2-like protein was low in healthy young and old people, and it was not affected by any of the intervention programs. In another study by Yildirim *et al*., it was reported that IFNβ significantly reduces the angiogenesis cellules of blood flow. The IFNβ prevents the process of vascular splitting.[30]

Juwon *et al*. reported that not only IFNβ prevents the proliferation and growth of endothelial cellules but also it results in a reduction of expression of angiogenesis molecules. In addition, there is convincing evidence stating that IFNβ is a powerful anti-angiogenesis factor.[18]

In another study by Möbius-Winkler *et al*., it was observed that the index of blood flow of collateral coronary arteries was significantly increased for two groups of CAD patients who undertook two series of high intensity and medium intensity exercise programs for 4 weeks.[20] According to research findings, 8 weeks of resistance training results in a statistically significant increase in capillary density.[4] Therefore, it seems that endurance training can result in improvement of the status of patients through angiogenesis.[4] Some evidence has shown that increased blood flow is merely enough for growth of capillaries in muscles. This is caused through hemodynamic force, pressure of walls, stretching and periodic pressurizing that proliferation, and migration patterns of endothelial cellules change. Other observations have shown that ischemia and physical activity are among the most powerful stimulators of angiogenesis. However, compared to ischemia, physical activity is a highly suitable tool for prevention and treatment of CVD.[23]

The stimulus of exercising increases the transfer capacity of coronary arteries through adaptation of coronary microcirculation that results in a change in the vasomotor reaction of coronary artery resistance.[17] De Biase *et al*. stated that physical activity plays a medicating role in CVDs through having beneficiary effects on endothelial performance and the overall cardiovascular system. Endothelial progenitor cells (EPCs) are the bone marrow derivatives that are considered as a new clinical purpose in terms of CVD. There are many stimuli that are able to increase the application of EPCs. Among the pre-angiogenesis factors, it can be referred to angiopoietins and FGF. In another study by De Biase *et al*., on CAD patients, it had been observed that, 28 days of exercise and 12 weeks of running result in an increase in angiogenesis factors.[11] On the other hand, Farhat *et al*. stated that ANGPT2-like protein is a glycoprotein of the blood cycle system with numerous expressions in the heart, fat tissues, lungs, kidneys, and skeletal muscles. Its expression is stimulated through hypoxia and ultimately results in angiogenesis and migration of endothelial cellules.[12]

In consistence with the present study, Konstantinos *et al*. carried out a study on 8 CAD patients and found out that, 60 min after a period of light intensity resistance training; significant reductions were made in the amounts of IFN.[27] In addition, Palmefors *et al*., stated that physical activity increases the amounts of cytokines and IFN-gamma while increasing the amount of EPCs and angiogenesis factors.[21] Wang *et al*. stated that ANGPT2-like protein is considered as a pathogenic pre-inflammatory factor in atherosclerosis and is secreted in high dosages in CAD patients. In addition, serum levels of the ANGPT2-like protein are considered as new biomarkers for categorization of CAD.[28] Tian *et al*. reported that expression of ANGPT-2 increases in rats and humans with altered hearts. This is while in hearts changed through execution of endurance training in rats, the expression of ANGPTL2 was decreased. Increased expression of ANGPTL2 in rats' heart shows that abnormal function of heart muscles as a result of lack of activity of AKT and Ca^{2+}-ATPase of the sarcoplasmic network and metabolism of energy.[25] Thorin-Trescases *et al*. reported that the ANGPT2-like protein improves the abnormal functionality of endothelial cells in rats and that the blood flow level of ANGPTL2 is high in patients suffering from CVD.[24] In addition, it has been also previously reported that a period of physical activity can decrease the levels of ANGOTL2 in CAD patients. After 3 months of aerobic exercise, the level of ANGPTL2 was decreased, and also it was concluded that levels of angptl2 in male patients suffering from intense coronary syndromes is sensitive against chronic exercise programs.

CONCLUSION

These results indicate that in response to long-term aerobic exercise, the amount of angiogenesis and angiostatic factors change and also the responses of the factors to exercises are dependent on various factors including intensity and length of exercise and the preparedness of subjects and their conditions. It is worthy of mentioning that ANGPT2-like protein has been one of the most important and new factors regarding CAD patients during the past few years and there is still a long way until obtaining a full recognition of the entire factors effective on this protein. In addition, IFNβ is an effective element in the process of angiogenesis and for the human body's immune system that needs more attention in the domain of cardiovascular patients. Therefore, it can be stated that non-continuous aerobic exercises can be regarded to as some ways for treatment and or rehabilitation of patients suffering from CAD.

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