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The Effect of Eight Weeks of Low Intensity Aerobic Exercise on Serum Levels of VIP and ET-1 Hormones in the Non-Athlete Healthy Elderly Women and Patients with Coronary Artery Disease

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Abstract

Introduction: The objective of the present study is to evaluate the effect of eight weeks of low intensity aerobic exercise on serum levels of vasoactive intestinal peptide (VIP) and Endothelin-1 (ET-1) hormones in the Non-Athlete Healthy Elderly Women and Patients with Coronary Artery Disease.

Methods: 15 females with the coronary artery disease and 15 healthy females were randomly selected for experimental and control groups, respectively. For eight weeks, the participants participated in aerobic exercises three times a week at a constant intensity of 100 ± 10 heart beats per minute. To evaluate VIP and ET-1 hormonal changes, blood samples of all participants were taken 3 times (before, immediately after the last session and 24 hours after last session). Repeated Measures ANOVA test was used to evaluate changes in the VIP, ET-1, and blood pressure. Pearson correlation coefficient Test was used to compare two variables in the control and experimental group.

Results: Data analysis did not show any significant difference in the levels of VIP and ET-1 serum before, immediately after and 24 hours after the 24th session in the control group (P=0.52 and P=0.15, respectively) and the patients group (P=0.46 and P=0.22, respectively).

Conclusion: Low intensity aerobics exercise will not change the serum VIP and ET-1 levels in the elderly women. Even though this result showed the same amount of VIP and ET-1 level in the healthy women and the patients with coronary artery diseases, the conclusion is that cardiac patients can undergo the progressive exercise programs and withstand higher intensity of exercise.

Keywords: Exercise, Endothelin-1, Vasodilator Intestinal Peptide, Coronary Artery Disease

Introduction

Vasoactive intestinal peptide (VIP) plays important roles in many biological functions, such as stimulation of contractility in the heart, vasodilation and lowering arterial blood pressure (1). VIP is mostly concentrated in the gastrointestinal, cardiac and brain nerves. VIP receptors are observed in the heart and blood vessels and also in many other tissues. Moreover, this hormone has the ability to adjust electric cardiac reactions as well as influencing the heart rate and heart contraction (2). In the central nervous system, this hormone influences the regulation of brain blood flow (3), energy metabolism and enzyme activity (4). In contrast, vessel endothelial cells play a significant role in the regulation of vessels activities through

producing active vascular substances such as Endothelin-1 (ET-1) and Nitric Oxide (NO). Endothelin-1 is a peptide produced by endothelial cells and has strong contracting effects on human endothelial cells. Endothelin-1 is a primary isoform in the human cardiovascular system and, in the human vessels, it is the most powerful and protracted constrictor ever discovered. Furthermore, endothelin-1 plays a major role in the reproduction of smooth vessel muscle cells (5). Based on the literature on this topic, exercise can be an effective factor in the changes of these hormones. Nicholls *et al.* (1992) found no significant difference in the plasma VIP levels of patients with chronic heart failure before and after the exercise session. Similarly, no significant differences were found in patients with angina pectoris after short-term exercise on ergometer bicycle (6). In addition, four weeks of high intensity exercise in Sprague Dawley male rats and their comparison with control group showed no significant difference in the plasma VIP hormone secretion at the end and 24 hours after the last exercise session (7). However, in a research by Rolandi *et al* (1987), the VIP of seven marathon runners with submaximal and maximal intensity was studied. Based on this study, there was a significant increase in VIP level of plasma after both tests (8). Maeda *et al.* (2001) investigated the effects of eight-week aerobic exercise training on plasma endothelium levels in healthy young females and found a significant decrease in the ET-1 plasma levels which turned normal in the last week of training period. Therefore, it was concluded that regular exercise training decreases the production of ET-1 in human beings and can induce positive effects on cardiovascular system (9). Aiming at determining the effects of 3-month exercise on endothelin-1 expression in the lung tissues of 20 male rats, the study conducted by Ahmadiasl *et al* (2008) showed that duration of exercise training can increase the amount of endothelin-1 in the lungs and blood flow in lungs (10). However, Cruden *et al.* (1999) stated that there was no change in the levels of blood flow endothelin-1 in healthy men after 24 hours of mountain climbing (11). It seems that few studies have been conducted to evaluate the effects of long term exercise on levels of these two hormones in coronary arterial patients. The reports of these studies show contradictory results, in which some show decrease and others show increase in the levels of these two hormones (12-15). In addition, the researcher found no studies that point to the effects of regular aerobic exercises on healthy elderly who consumed no drugs and experienced a long separation from exercise. Regular aerobic exercises decrease the prevalence of cardiovascular disease (13). One probable reaction to any kind of aerobic exercise is the diminished risk of cardiovascular diseases and observation of positive and useful effects on vasomotor function (14). Moreover, the improvement of vessels vasomotor is closely connected to the decrease of cardiovascular problems. It should be noted that in the application of intensive training plans for patients with cardiovascular problems, damage to myocardia or heart failures causes serious restrictions which points to the necessity of designing a training plan with the appropriate level of intensity. Therefore, based on the contradictory results of the abovementioned studies, and since there is no evidence on the effects of long term regular exercise in nonathletic healthy and unhealthy elderly people, the researchers of the present study seek to answer the following questions: Does eight weeks of low intensity aerobic exercise bring about significant changes in VIP and ET-1 levels in two groups of nonathletic healthy and unhealthy elderly women? Can the primary conditions of participants (being healthy or unhealthy) affect the results of the study? And finally, the major question is whether eight weeks of low intensity aerobic exercise can have significant effects on the serum levels of VIP and ET-1 hormones of elderly nonathletic healthy elderly women and those with coronary artery disease (CAD)?

Methods

This study is a quasi-experimental type. The population of the patient group consisted of patients with cardiovascular diseases who have been to Emam Reza cardiac hospital in Shiraz. Among them, 15 female patients with CAD who had referred to the cardiologist for their routine check-ups were selected as the participants of the experimental group. The population of the control group consisted of those referring to the Retiree Association of Shiraz among which 15 healthy females of the same age without any experience of cardiovascular disease were randomly selected as the participants of the control group. Since the present research was quasi-experimental and the subjects were human, the least sample size for such researches is 15 subjects as well as other similar researches (16). Before implementing the exercise protocol, all of the control participants had been checked by a cardiologist and their health had been confirmed, proving that there was no sign of cardiovascular diseases. Since all subjects participated willingly (filled out the consent form) and eligible for being non-smoking and non-athlete, the sampling procedure of the study was the targeted voluntary type. The participants did warm-up for 10 minutes at the off-set of every session and then went through the main exercise. Finally, they cooled down for ten minutes. The main exercise plan consisted of cycling on the ergometer bicycle 3 times a week, for eight weeks. In the first three sessions of the first week, participants exercised for 15 minutes with a heart rate of 100±10. From the 4th session on, the exercise period was extended for 5 more minutes. The intensity of exercise remained the same (100±10) so that until the last session of the 8th week, each participant has cycled on the bicycle for 50 minutes with the same heart rate of 100±10 table (1). The levels of serum VIP and ET-1, blood pressure, and heart rate were measured three times (before the exercise began; immediately after eight weeks of exercise; and 24 hours after eight weeks of exercise). The ELISA Laboratory method and ELISA Reader Machine, ET-1 hormone was read through Human Endothelin1 (ET-1) ELISA kit (cat. no CSBE07007h Cusabio, Japan) minimum detectable dose of human ET-1 is 0.78 pg/ml and VIP was read through Human Vasoactive Intestinal Peptide (VIP) ELISA kit (cat. no CSBE08354h Cusabio, Japan) the minimum detectable dose of human VIP is 3.9 pg/ml. Blood pressure and heart rate were measured by means of the digital manometer ALPK$_2$, K$_2$-1702 Model made in Japan while the participants were in a sitting position and their right elbow was placed parallel to their hearts. Blood samples were taken from the participants from their left elbow three times, before the exercise plan began in the first session; immediately after the end of the 24th session; and 24 hours after the end of the 24th session. The serum was immediately extracted from the blood samples in the centrifuge machine which was present at the experiment place with the speed of 4000 rounds per minute. The serums were kept in -20□C until the experiment took place. Descriptive statistics was used to calculate the mean and standard deviation and Parametric Repeated Measures ANOVA test was used to evaluate the changes in the VIP, ET-1, blood pressure and heart rate. Pearson Correlation coefficient test was used to compare the two variables in the control and experimental group. The significance level of statistical analysis was set at $P<0.05$. The data was analyzed by SPSS.16 and variable values were represented as mean ، SD.

Results

The demographic characteristics of the participants in the control and experimental groups demonstrated the age mean of 56.57±6.90 and 56.50±6.80, height mean of 160.3±6.7 and 156.20±4.10 cm, and weight mean of 69.92±10.40 and 67.15±8.15 kg respectively. All participants were nonathletic and nonsmoking (participants' demographic

characters are shown in table 2). Eventually, the results of the present study showed that there was no significant difference in the levels of serum ET-1 in patients before, immediately after the 24th exercise session, and 24 hours after the 24th exercise session (p=0.22) and there was no significant difference in three phases in the control group (p=0.15). Also there was no significant difference in 3 phase of ET1 measurements between patient and control group (p=0.147) (p=0.64), (p=0.198) (Table3). Results of the present study showed that there was no significant difference in the amount of serum VIP in patients before, immediately after the 24th exercise session, and 24 hours after the 24th exercise session (p=0.46) and there was no significant difference of 3 phase of control group (p=0.52). Also there was no significant difference in 3 phases of VIP measurements between patient and control group (p=0.162), (p=0.70), (p=0.510) (Table4). On the other hand, there was a significant difference in the healthy (P=0.001) and unhealthy (P=0.01) women's 3-cycle systolic blood pressure changes. Also it was proved that there was a significant difference in the healthy women's 3-cycle diastolic blood pressure changes (P=0.03), but there was no significant difference in unhealthy women (0.82) (Table 5). Moreover, in both control group (P=0.18) and experimental group (P=0.24), there was no relationship between serum VIP and ET-1 levels before, immediately after the 24th session, and 24 hours after the 24th session.

Discussion

In this study, the effect of eight-week low intensity aerobic exercise on the levels of serum VIP and ET-1 in nonathletic healthy elderly women and patients with CAD was evaluated. The results showed that there was no significant difference between the mean of serum VIP and ET-1 before and after eight weeks of low intensity aerobic exercise not only in elderly women with CAD, but also in healthy old women. Compared to veins, the existing VIP in the walls of coronary arteries may result in the adjustment of natural vasomotor tone and more vasodilation of coronary arteries, since density of its receptors is more in arteries. Nicholls *et al.* (1992) revealed that after following a short-term exercise plan, no significant difference was found between the plasma VIP level before and after exercise in patients with chronic heart failure and the control group (6). Similarities between the results of Nicholls' study and the present study pointed to the role of different conditions in VIP changes, as heart attacks and angina pectoris are also the consequences of the CAD. These results show that compared to healthy people, the response of VIP to exercise in patients with CAD can be different. When one session is longer than 20 minutes, VIP secretion may seemingly be stimulated. Accordingly, Opstad (1987) stated that in activities (cycling) which last longer than 20 minutes and the intensity is higher than 50% VO2max, plasma VIP increases (17). Thus, it can be concluded that periods longer than 20 minutes can be set as the time threshold of a session so that production and secretion of VIP occurs in participants (of course, exercise intensity must be high enough in one session for VIP production to be stimulated). Apparently, VIP response to exercise protocols depends on the exercise intensity and even one session of high intensity may be able to make changes in VIP levels. However, Galbo *et al.* (1979) determined that after participating in one session of cycling with maximum speed, no significant difference was found in plasma VIP levels (12) which is similar to the results of the present study. In Galbo's study, it was observed that the activity is of one-session type with maximum intensity, but no change in VIP levels could be found. Perhaps, the primary condition of participants and the type of activity can be of importance here. In Galbo's study, the participants were healthy and this shows the probability of different responses of healthy and unhealthy participants to high intensity activities. Additionally, in Galbo's study the

Table 1. The exercise protocol

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8
Session 1	15min	20min	25min	30min	35min	40 min	45 min	50 min
Session 2	15min	20min	25min	30min	35 min	40 min	45 min	50 min
Session 3	15min	20min	25min	30min	35 min	40 min	45 min	50 min

Each week 5 minutes was added to the time of exercise but the intensity of exercise remained the same heart rate (100٭10) so that until the last session of the 8th week

Table 2. Participants' demographic characteristics

	Patients (n=15)	Control (n-15)	P
Age (years)	56.51±6.83	56.57±6.92	0.984
Height (Cm)	156.21±4.12	160.31±6.71	0.150
Weight (kg)	67.13±8.15	69.92±10.40	0.572
BMI (kg/cm2)	27.72±2.81	27.55±6.05	0.325
PBF	36.70±2.54	35.92±5.43	0.731

Abbreviation: PBF (Percent Body Fat)

Table 3. Endothelin-1 in the patients and control groups

	Patients (n=15)	P [a]	Control (n=15)	P [b]	P [c]
Before	9.63±8.73	0.22	21.05±18.91	0.15	0.147
Immediately after the 24th exercise session	11.75±16.04		52.30±54.33		0.64
24 hours after the 24th exercise session	8.75±15.10		26.75±27.02		0.198

[a] Comparing 3 phase ET1 measurements in the patients
[b] Comparing 3 phase ET1 measurements in the control
[c] comparing each phase of ET1 measurements between patient and control group

Table 4. Vasoactive intestinal peptide in the patients and control groups

	Patients (n=15)	P [a]	Control (n=15)	P [b]	P [c]
Before	151.42±93.62	0.46	86.19±74.01	0.52	0.162
Immediately after the 24th exercise session	123.42±85.51		105.85±68.03		0.670
24 hours after the 24th exercise session	139.29±111.41		107.7±61.92		0.510

[a] Comparing 3 phase VIP measurements in the patients
[b] Comparing 3 phase VIP measurements in the control
[c] Comparing each phase of VIP measurements between patient and control group

Table 5. Systolic and diastolic blood pressure changes in the healthy and unhealthy women's

Group		Systolic blood pressure	P [a]	Diastolic blood pressure	P [b]
unhealthy female	Before exercise	124.37±15.71	0. 01	73.28±9.28	0.82
	After exercise	130.62±14.41		75.36±11.18	
	24 hours after the 24th exercise session	115.50±18.13		72.12±8.8	
healthy female	Before exercise	122.28±11.14	0.001	79.28±8.38	0.03
	After exercise	116.85±13.64		77.42±9.65	
	24 hours after the 24th exercise session	114±8.92		74.85±5.61	

[a] Comparing 3 phase measurements systolic blood pressure in the unhealthy and healthy female
[b] Comparing 3 phase measurements diastolic blood pressure in the unhealthy and healthy female

participants did not carry their weight (they cycled) and this may be in relation with venous return (due to gravity, compared to running, venous return and consequently stroke volume in cycling is more) and higher heart output in cyclin (18). This process caused the exercise inability to stimulate VIP secretion. In another study conducted by Rolandi *et al.* (1987) it was observed that following a maximum experiment and under maximum experiment of seven marathon runners, a significant difference of plasma VIP can be found (8) .The study revealed that when in a research an exercise protocol with longer distance and thus longer time periods were used, the VIP changes would be significant even if exercise intensities are different. However, it must be pointed out that exercise intensity must be extensive enough to produce and secrete VIP. In the present study, although the length of exercise sessions extended to 50 minutes in the 8th week, perhaps due to not reaching the desirable intensity to secrete VIP, no significant differences were observed. Based on the results of the present study, and the results of the abovementioned studies, to have significant changes in VIP, the length of each exercise session must be taken into account (at least 20 minutes). Another point to be noticed is that to initiate production and secretion of this hormone, the intensity variable must also be taken into consideration and if the intensity of the exercise protocol does not reach the intensity of stimulation threshold of VIP (that can be different for every individuality), significant differences in VIP changes may not be noticed. On the other side, ETs can be considered as the positive regulators of stress which are active in lots of organs in the form of autocrine and paracrine and play useful and important roles in mammals. Endothelial system has an essential contracting role in the vessels and is important for arteriosclerosis and heart failures. They affect inotropy and chronotropy in the hearts and regulate cardiac reconstruction in cardiac failures. In addition to their strong cardiovascular activities, ET-1 causes interaction in non-vessel smooth muscles and stimulation of the secretion of neuropeptides and hypophysis hormone (19). Genth *et al.* (1998), studying healthy people and patients with cardiac arterial failures, with mean age of 60±9 having one-session planned exercise protocol with increasing intensity till exhaustion on ergometer bicycle (the activity which lasted for two to twelve minutes starting with 30 watt intensity and every minute the intensity was increased by 10 watts until exhaustion) noticed significant difference in the plasma ET-1 of the healthy

group, but no significant difference was found in the patients' group (20). It was also observed that when the exercise protocol is only one session including intensity increasing for patients, there is a significant difference in ET-1 of the control group. The difference between Genth's study and the present study is that participants of the present study have apparently not undergone exhaustion since the exercise protocol of the present study was based on the participants' capabilities, and during the exercise protocol, the intensity was equal to 30 to 40 percent of maximum heart rate. Nonetheless, to create consistency in the inner side of vessels more time may be needed. In another research conducted on athletic men, it was observed that exercising for one session on the ergometer bicycle for 30 minutes with the intensity being 90 to 130 percent of anaerobic threshold increased the plasma ET-1 concentration. When the intensity of an exercise session is to an extent that causes ET-1 secretion, the type of participant can apparently not be a determining factor because in Maeda *et al.*'s research (on healthy people) and Genth *et al.*'s (on unhealthy people) who used one session of exercise with high intensity, significant changes had taken place in ET-1 (9,20). It may be partly due to high intensity of the exercise regardless of the fact that whether the participants are healthy or unhealthy. Ahmadiasl *et al.*'s research can also be pointed out here as the exercise protocol duration in this research was more than two months. Ahmadiasl *et al.* (2008) trained 20 male wistar rats on treadmill for 60 minutes a day with 25 meters per minute for 3 months. They found out that expression of ET-1 in the experimental group was more than the control group which was statistically a significant difference (10). Besides the three-month period, the duration of each exercise session of the study can also be mentioned as compared to the duration of exercise session of the presents study, it was lengthier. In Ahmadiasl's study, the sessions began from 60 minutes while in the present study sessions started from 15 minutes. However, it should be pointed out that the level of exercise intensity may also be effective because in former studies (namely, Genth et al. 1998) when intensity level was high, the changes of this hormone were increasing (19). Still, when the intensity is low, the changes are decreasing (15). Moreover, in Maeda et al.'s study, the sessions lasted less while in Ahmadiasl et al.'s study each session is more than 60 minutes. This may be the reason of increase of ET-1 in Ahmadiasl's study and of decrease of ET-1 in Maeda's (2003) study. Consequently, to have increasing changes in ET-1 hormone, either the duration of the protocol (more than twelve weeks), or the intensity increase of the exercise must be noticed. According to the results of the present study and studies mentioned above, to secrete this hormone, a time threshold or intensity threshold must exist because in one-session protocols the high intensity of exercise and in long term protocols, the longer duration of the protocol can affect the significant changes of ET-1 (nevertheless, intensity level must be adequate). Increasing the concentration in plasma ET-1 is correlated with aging; on the other hand, because of the relationship between this hormone and cardiovascular diseases such as hypertension, the low intensity aerobic exercise can lower the blood pressure (21). Although the results of the present study were statistically not significant, a little increase in ET-1 was observed. Because regular and aerobic exercise causes more activity of endothelium and endothelial vessels' cells, the decrease in blood pressure could be expected. In addition, the participants of this study, though they were patients with CAD, had significant improvement in terms of length of activity as in the first week, each session lasted for 15 minutes and in the 8th week each participant cycled for 50 minutes with 30 to 40 percent of their maximum heart rate each session. This improvement in terms of the length of activity period shows that the

cardiovascular adaptations are due to regular exercise and they can also be created for elderly and unhealthy people. This only occurs if the exercise protocol for this people is designed properly according to the participants' conditions. Among the limitations of the study, we can point to the lake of control of the researchers on daily activities of study subjects and consumption of medicinal drugs during the period of this study. In addition, the researchers could not implement high intensity physical activities due to the sensitive condition of patients.

Conclusion

There was no significant difference between the mean of serum VIP and ET-1 levels before and after eight weeks of low intensity aerobics exercise. Therefore, prospective researchers are suggested to select and design the intensity and duration of exercise based on the present results and evaluates the relationship between these two variables.

Ethical issues

No declared.

Authors' contributions

All authors equally contributed to the writing and revision of this paper.

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