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The effect of periodic exercise on the levels of vascular factor and functional index in patients with ischemic stroke

Kadkhodaei Khalafi M[1], Shakeri N[2✉], Ghazalian F[3], Shojaei M[4]

[1]Ph.D. student of Physiology of Exercise, Islamic Azad University, Science and Research Branch, Tehran, Iran, Email: kadkhodaei.m1350@gmail.com
[2]Ph.D. Assistant Professor of Physiology of Exercise, the Department of Sports Physiology, the Building of the Faculty of Humanities, Islamic Azad University, Science and Research Branch, Tehran, Iran, Email: nsprofsport@gmail.com
[3]Ph.D, Assistant Professor of Physiology of Exercise, the Department of Sports Physiology, the Building of the Faculty of Humanities, Islamic Azad University, Science and Research Branch, Tehran, Iran
[4]MD. Assistant Professor of Neurology, the Department of Internal Neurology, the Faculty of Medical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran

✉**Corresponding author**
Assistant Professor of Physiology of Exercise, the Department of Sports Physiology, the Building of the Faculty of Humanities, Islamic Azad University, Science and Research Branch, Tehran, Iran,
Email: nsprofsport@gmail.com

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ABSTRACT

Background: By reducing or stopping blood flow, a part of the brain suffers from cerebral ischemia with neurological deficits. Angiogenesis can play a role in repairing a damaged brain tissue, as exercise has an inductive role in the prevention of vascular disease. The aim of the research is to determine the effect of the approach of periodic exercise on the angiogenesis process from the acute phase of stroke on the vascular endothelial growth factor and the cognitive-functional index. *Materials and Methods:* 30 participants with ischemic stroke aged 45-65 years were randomly divided into two experimental and control groups (15 persons in each group). The experimental group performed periodic exercises for 3 seconds with 4 to 6 repetitions and 70 to 85% of the maximal oxygen consumption and rest for 4.5 minutes, 3 times a week. Venous blood samples of 5 cc were taken from the patients on admission and at 30th day following admission. The levels of Endothelial growth factor as the primary outcome and the motor and speech performance as the secondary outcome were assessed at the beginning and end of the study by the National Institutes of Health Stroke Scale (NIHSS) and were analyzed by one-way ANOVA and the independent t-test at the alpha level $P \leq 0.05$. *Results:* The serum levels of the vascular endothelial growth factor were significantly increased at the alpha level ($P = 0.05$) after the aerobic periodic exercise. The secondary outcome, the numerical scale of the motor and speech performance, was also significant after four weeks. *Conclusion:* Performing periodic exercises during four weeks can play a role in reducing brain damage by altering the levels of angiogenesis-related factor and performance.

Keywords: Angiogenesis, Periodic exercise, Ischemic stroke

1. INTRODUCTION

At present, stroke is the second leading cause of death and long-term disability in developing countries (Donnan et al., 2008; Kasper et al., 2016). The tissues around the penumbra are living and inactive brain cells (Longo et al., 2011; Delbari et al., 2010). The cause of the gradual death of the neuron in the penumbra area and secondary lesions after cerebral ischemia is unclear (Kasper et al., 2016). The periodic exercises in the acute phase of stroke should be performed to reduce the length of stay in the intensive care unit, even in the triage and venipuncture rooms (Freeman et al., 2011). Angiogenesis can play a role in repairing a damaged brain tissue (Ramezani & Baharara, 2014). There is evidence that regular physical activity prevents stroke (Cerebral Vascular Accident) (Sandra & Billinger et al., 2014). Also, regular physical activity plays a role in stimulating angiogenesis, enhancing the activity of aerobic enzymes (Tang et al., 2010; Samadhi, 2015), expanding the capillary network through the arteriogenesis and angiogenesis processes on the vascular bed of skeletal muscle (Tang et al., 2010; Suhr & Brixius et al., 2007). Angiogenesis refers to the formation of new blood vessels from pre-existing ones (Mansoury et al., 2012). The first step in the process of angiogenesis is the secretion and activation of angiogenic factors by binding to their receptors on endothelial cells and then dilating the stem vessels through the increased permeability by NO (Nitric oxide) and VEGF (Vascular Growth Endothelial Factor) (Sia et al., 2014; tang et al., 2010).

Regular physical activity increases the production of nitric oxide. Nitric oxide has also been suggested as a vasodilator and is likely to be broadly associated with the vascular endothelial growth factor and other key factors in the chain of angiogenic reactions. Nitric oxide as a preventive and adjunctive factor in the treatment by increasing the amount of calcium ion alters the permeability of endothelial cells by mediating the complex of the inositol triphosphate receptor and the focal membrane receptor and the phosphorylation of endothelial nitric oxide synthase. Most studies have examined the onset of rehabilitation in the chronic phase of stroke, including aerobic exercises and walking and care training (Schmidt Wolf et al., 2013). No study has not been performed in the acute phase and on the fast track in the emergency department, and in particular, about the effects of high intensity interval training (HIT) on vascular factors and human specimens. And no specific protocol has been set as a guideline for the question: When is the best time to start exercising after a stroke. But there is no doubt that exercises as a non-pharmacological and non-invasive method can be helpful in both the phases of prevention and rehabilitation (Schmidt Wolf et al., 2013; Austin Mark et al., 2014; Sundseth et al., 2012). The aim of the research is to determine the effect of the approach of periodic exercise on the angiogenesis process from the acute phase of stroke on the vascular endothelial growth factor and the cognitive-functional index.

2. MATERIALS AND METHODS

This study is an experimental study with a pre-intervention and post-intervention group and a control group with a code of ethics IR.SBMU.RETECH.REC.1397.1018 and a clinical trial registration code IRCT 30285. From the patients who referred to Loghman Hakim hospital emergency with stroke diagnosis, less than 24 hours after admission, the subjects with the definitive diagnosis of ischemic stroke were selected according to tests and results of para clinical (CT scan) by a neurologist and with the willingness and motivation to participate in an exercise program, and the level of consciousness of patients, with the Glasgow scale, between 12 and 15. 30 subjects aged 45-65 years, with ethical approval and filling out a consent form and a general profile form and a sport questionnaire, were divided into two groups, experimental and control (15 persons in each group). Patients with a history of drug abuse, coagulation disorders, cancer, advanced renal, hepatic, heart, respiratory failure, fever above 38°C, abnormalities of the musculoskeletal system, mental disorders, vascular aneurysm, previous stroke, the presence of open sores and brain concussion, and the consumption of antioxidants were eliminated.

The experimental group after familiarizing with the exercise environment, using rehabilitation bikes, performed the aerobic periodic exercise (HIT) for 30 seconds with 4 to 6 repetitions and 70 to 80% of the maximal oxygen consumption and rest for 4.5 minutes rest and cooling down for 4 minutes with stretching exercises, 3 times a week (Martini, J & Gibala et al., 2012; Jenna, B & Martin, J & Gibala, 2014) (Chart 1). Rehabilitation bikes are large and fixed or small and portable and have a handle, a television screen and a remote control out of reach of the practitioner to adjust the speed, intensity and duration of training, and the patient is able to sit on and lean the bikes. Both the control and experimental groups underwent physiotherapy and the same drug treatment regimen of stroke prescribed by the physician. All the samples were monitored with a pulse oximeter for the serial control of the blood pressure and pulse and the percentage of blood oxygen saturation. Venous blood samples of 5 cc were taken from the cubital vein in the right-hand of patients in sleep position on admission and at 30th day following admission.

Chart 1 The exercise protocol of the periodic exercise group

Variable	Exercise Group	Control Group	Physiotherapy
Protocol	30 seconds in 4-6 repetitions with 4.5 minutes rest (3 time in week)	-	+
Exercise intensity (workload)	Maximum power at least 500 watts 70 - 80% of the maximum oxygen consumption	-	+
(Weekly training)	~ 10 minutes per day (3 time in week)	-	+
Total rest per week (Time commitment)	(approximately 1.5 hours rest 3 time a week)	-	+
Exercise volume per week	~225 kJ	-	+

From Burgomaster *et al.,* (2008) $\dot{V}O_2$peak, peak oxygen uptake

The International Health Assessment Questionnaire was written in three sections of the level of consciousness, the motor function and the higher brain function, in 15 minutes (a score is given to the International Performance Scale Questionnaire with 11 items ranging from 0 to 42 (mild (0-4), moderate (5-15), moderate to severe (16-20) and severe (21-24)). After the centrifugation of blood, the patient's serum was frozen at -70°C, and the level of protein was measured by ELISA. All the steps were performed in the clinical environment of occupational therapy of Loghman Hakim hospital, with the presence of a physician and the researcher in one place in order to reduce the error and to monitor more closely the exercise, at 25°C with an air humidity between 35 and 42°C and an air pressure of 700 to 1060 Pascal (according to the Tehran Meteorological Report) between 3 and 7 pm. After analyzing the natural distribution of data by Kolmogorov-Smirnov test (K-S test), the descriptive qualitative data were analyzed by chi-square and Fisher's exact test. Before and after exercise and between the groups, the dependent variables were analyzed by one-way ANOVA and independent t-test at the alpha level equal to or less than 0.05. Spss 13 was used for drawing the tables.

3. FINDINGS

The values of mean and standard deviation of the vascular endothelial growth factor (Table 2) were changed from 498 to 703 ng / l and from 176 to 237, in the experimental group who performed periodic exercises, respectively. The serum levels of VEGF were significantly increased at the alpha level (P = 0.05) after aerobic exercises compared to on admission. In the control group, a decrease in the serum level was reported. The secondary outcome was the reduction of numerical scale of the motor and speech performance with NIHSS questionnaire from 7 to the numerical value 1 (Table 3) with P value of 0.002. Demographic and morphometric data of patients and vital signs between the two groups are shown in (Table 1).

Table 1 The descriptive characteristics of the participants in the pre-intervention study (the quantitative variables)

Variables	Periodic Exercise Group	Control Group	Significance level
	Standard deviation ± mean	Standard deviation ± mean	
Age (years)	58.33±6.20	61.46±6.47	0.49
Body Mass Index (kg / m^2)	4.28±27.93	2.46±25.06	-
Systolic Blood Pressure (mm Hg)	12.00±161.00	19.00±159.00	0.001
Diastolic Blood Pressure (mm Hg)	10.00±95.00	12.00±91.00	0.019
Heart rate (in minutes)	7.00±84.00	9.00±96.00	0.001
Breathing rate (in minutes)	2.00±18.00	2.00±18.00	0.001

Independent t-test to compare the mean of groups at baseline

Table 2 The vascular endothelial growth factor with the aerobic periodic exercise

Variable (index)	Group	mean	Standard deviation	P value
Vascular Endothelial Growth Factor (Before exercise) (Ng / l)	Periodic Exercise	498.00*	176.80	0.001
	Control	490.00	183.00	
Vascular Endothelial Growth Factor (After exercise) (Ng / l)	Periodic Exercise	703.00*	237.00	0.001
	Control	444.00	183.00	

Independent t-test results for comparison between the two groups at the alpha level (P = 0.05): * significant difference in pre-exercise and post-exercise periodic exercise group

Table 3 Functional Score Measurements

Index	Group	Mean	Standard deviation	F value	P value
Functional and Cognitive Score (After exercise)	Periodic Exercise	7.000	1.000*	7.000	0.002
	Control	11.000	4.000		

Paired t-test results to compare within-group changes at the alpha level (0.05) * Significant difference in periodic exercise group

4. DISCUSSION

The results of this study showed that the serum levels of VEGF were increased at the alpha level (P = 0.05) after the aerobic periodic exercise compared to on admission, and in the control group, the serum level was decreased. Consistent with the results of this study fig 1, in a study of Nourshahi (2011) et al., in an animal sample, about the effect of a session of extravasation on the vascular endothelial growth factor and the serum levels of endostatin in male wistar rats, the VEGF to endostatin ratio decreased immediately after exercise and increased significantly 24 h after exercise (Nourshahi et al., 2011). In a study of Zang et al. (2013), by inducing middle cerebral artery occlusion, 24 h later in rats, two weeks after exercise, the blood flow rate from the ischemic area was assessed by a laser flowmeter and the changes in the microvessel density and the tie-2 expression and the total phosphorylation of Akt (Protein Kinase B) and the infarct area volume were assessed by Western blot. They stated that early exercise after stroke increased angiogenesis, increased the vascular density, reduced the infarct area volume, and increased the cerebral blood flow (CBF) in the ischemic area of the cortex of the brain, which improves the functional prognosis (Zhang et al., 2013).

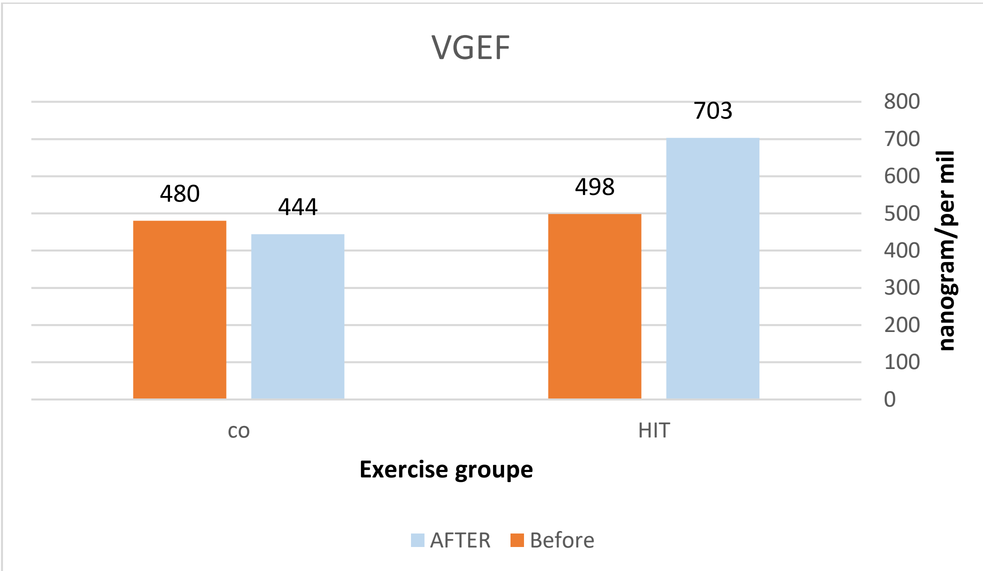

Figure 1 serum levels of VEGF

Kordi et al. (2015) investigated the effects of two types of endurance training and HIT on 18 male rats; the level of gene expression of the vascular endothelial growth factor was increased in the intense continuous and periodic aerobic exercise group compared to the control group (Kordi et al., 2015) Boyne et al. (2015) aimed to compare the responses of the intra-session exercise between three different HIT protocols for some people with chronic stroke (> 6 months). They stated that for an exercise with a higher intensity on treadmill in chronic stroke, a combination of P30 and P60 may improve the intensity threshold of aerobic exercise, the running speed on treadmill and the repetition of walking (Boyne et al., 2015). In a study by Van Craenenbroeck et al. (2010) on some patients with heart failure, it caused the repair of the endothelial wall of the heart's vessels and the cognitive performance following an acute exercise (Van et al., 2010). Sobhani Poor et al. (2016) compared the effects of endurance training and resistance training on the angiogenic inhibiting factors in elderly people with diabetes. In investigating the intra-group changes, the levels of angiostatin and the endothelial growth factor were significantly increased in both the groups, which were higher in the resistance group (Sobhanipour et al., 2016).

Sayari et al. (2015) investigated the effect of periodic exercises on the heart tissue of rats for eight weeks. There was a significant increase in the plasma VEGF level and the myocardial capillary density (Sayari et al., 2015). Review articles with different exercise protocols in animals and patients, healthy athlete and non-athlete in the form of 2, 4, 6, 8, 12 weeks or single session protocols have been done on the serum levels of factors affecting the vascular and neuronal structure (Samadhi, 2015; Chadorneshin et al., 2012). Ribeiro et al. (2017) examined a session of incremental resistance training protocol with intensities of 60, 70, and 80% of the power of a maximum repetition (including several 3-set exercises with 12 repetitions) in healthy female subjects. Their results showed that the number of the endothelial precursor cells and VEGF, hypoxia-inducible factor 1-alpha (HIF-1alpha) and erythropoietin (EPO) increased (Ribeiro et al., 2017). The study of Hemmatinafar et al. (2014) on eighteen inactive young men showed that six weeks of high intensity interval training (HIIT) reduced the levels of plasma fibrinogen and increased the hs-CRP (C -Reactive Protein) levels (Hematinafar et al., 2014). Ravasi et al. (2014) examined the effects of two types of physical activity on the non-athlete men, who used the Black and Weber test as a progressive aerobic exercise test during one session. A week later, they used the test of maximal 40-m shuttle running as an intense periodic exercise.

Their results showed that performing both the activities increased the serum levels of VEGF immediately and two hours later, and no difference in the serum levels of the vascular endothelial growth factor was observed between the groups (Ravasi et al., 2014). In this regard, Karami and Ramazani (2016) studied the adaptation response to the angiogenic stimulatory and inhibitory factors after 4 weeks of incremental resistance training three times a week in 20 male students. The values of VEGF and NO in the experimental group were significantly increased in the post-test compared to the pre-test (Karami et al., 2016). In various pathological conditions such as cerebral ischemia, traumatic brain injury, diabetes, brain tumors, multiple sclerosis and Alzheimer's disease, the blood-brain barrier is disrupted. A number of factors, such as inflammatory cytokines, nitric oxide and the endothelial vascular growth factor, increase the permeability of blood-brain barrier, thereby leading to the cerebral edema and the injury of central nervous system (Li et al., 2007). It can be said that the result of different exercises in healthy athletes and non-athletes, patients with heart failure, diabetes and brain tumors is stimulating the angiogenic factors and increasing the blood flow to the vessels. The note is that a cerebrovascular self-regulation mechanism prevents abrupt changes, and possibly several factors involve in the re-vascular formation and the redirection of ischemic cascade.

The secondary outcome was the reduction of numerical scale of the motor and speech performance with NIHSS questionnaire from 7 to the numerical value 1 (Table 3) figure 2 with P value of 0.002 at a significance level of 0.05. Each neurologic patient is assessed with a series of symptoms of a motor impairment that represents the presence of brain damage, and a score is given to the International Performance Scale Questionnaire with 11 items ranging from 0 to 42 (mild (0-4), moderate (5-15), moderate to severe (16-20) and severe (21-24). The reduction of the numerical value to less than 4 indicates an improvement of speech and motor disorders caused by stroke complications (Yong Wang et al., 2015; Singer et al., 2006). In monitoring stroke-related behaviors, the Independence Scale for Ability to Perform Daily Activities is used for comparison (Leddy et al., 2016). In line with the results of this study, in a cross-sectional study by Farzin Rad et al. (2009) based on NPI (Neuropsychiatric Inventory Questionnaire) questionnaire patients were evaluated during 1 to 12 months after stroke. The apathy, disinhibition, sleep problems, depression, anxiety and aggression were the most common mental disorders after stroke (Farzinrad et al., 2012). As a result of this report, it can be said that the release of endorphins and exercise-induced brain stimuli can reduce the effects of stroke. Jafari et al. (2014) emphasized the initiation of an appropriate planning to improve stroke-related injuries through a Quality of Life Questionnaire (SF-36) and National Health Center Stroke Assessment on 95 patients with ischemic stroke (Jafari et al., 2014).

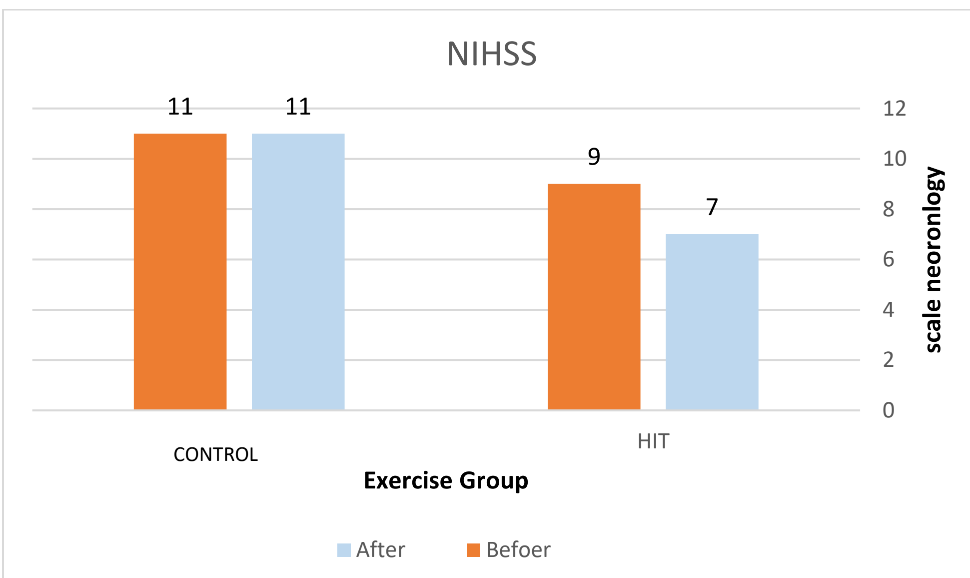

Figure 2 Health Stroke Scale

In the study of Askim et al. (2013) on 15 patients with mild to moderate stroke, a 6-week intensive Individual Army Basic Training (AIT) program was performed twice a week at an intensity of 85%. The participants achieved a significant clinical progress in walking longer and longer distances (Askim et al., 2013). Skriver et al. (2014) showed that an intense cycling aerobic exercise in healthy subjects affects the plasma levels of the brain neurological growth factor, the vascular endothelial growth factor, the insulin-like growth factor (IGF-1), and adrenergic factors and improves learning and motor skills by optimizing the long-term motor memory (Karami et al., 2016). The permeability changes of the blood-brain barrier, angiogenesis and axonal and dendritic buds using magnetic resonance imaging, quantitative imaging, focal laser scanning microscope and 3D image analysis have been studied in animal samples; these studies provide insights into the role of VEGF in maintaining the integration of the blood-brain barrier and the treatment of ischemic stroke and edema (Armoon et al., 2018; Zhang & Zheng Gang, 2018).

The aim of the present study was determining the effect of a 4-week aerobic periodic exercise approach on the serum levels of the vascular endothelial factor and angiogenic process from the acute phase of ischemic stroke in patients referred to the emergency department of Loghman Hakim hospital, and sensitizing patients with ongoing importance in the viewpoint of continuous care and effective and continuous communication between the coach and the patient in promoting daily activities of life (personal hygiene, dressing, eating, drinking and moving) by examining the performance of patients through a questionnaire. The onset of exercise in the acute phase of ischemia in the brain below 6 h and the intensity of maximal and periodic exercise stimulate the major angiogenic factors involved in the development of the capillary network in patients with ischemic stroke. Although, according to the results and the standard deviation, these serum levels changes were not significant, but teaching with a simple language on how to perform exercises using lectures, questions and answers, posters, and demonstrating how to train and introduce patients can be helpful.

5. CONCLUSION

In this study, an increase in the levels of endothelial growth factor was observed after four weeks of periodic exercise with rehabilitation bikes, and this increase is likely to alter the ischemia process in the penumbra area by stimulating the process of angiogenesis in the brain and improve the performance of patients by reducing the effects of stroke. The most important finding of this study is increasing the life expectancy and improving the daily living activities by changing the functional and speech index of patients with ischemic stroke. One of the limitations of this study was the inability to directly observe changes in brain vessels in human specimens.

Suggestions

It is recommended that high intensity exercise be performed periodically for more than four weeks, on the other hand, studies have reported that this factor is released from brain tissue and muscle cells; it is better to identify it separately, and the efficacy of the exercise be measured by the laser flow meter method or CT angiography of the cerebral arteries and with the measurement of glial and neuronal factors of the brain, and beta and apelin transduction.

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We did not receive any funds for conducting this review study.

Competing interest

The authors declare that they have no competing interests.

Ethical approval

The Ethics Committee of Shahid Beheshti University of Medical Sciences and Health Services approved the study (IR.SBMU.RETECH.REC.1397.1018).

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