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The Effect of High Intensity Interval Training on the Response of Coagulation and Fibrinolytic Factors of Hypertensive Patients to One Bout Submaximal Endurance Exercise

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Abstract

Introduction: Extensive evidence has shown that high intensity exercise triggers blood coagulation and improves blood fibrinolysis levels. The purpose of the present study was to investigate the effect of 12 weeks of high intensity interval training (HIIT) on the response of coagulation, anticoagulant and fibrinolytic factors of hypertensive cardiovascular patients to one bout submaximal endurance exercise (OBSEE).

Methods: Out of 70 men with high blood pressure, 20 men were selected based on inclusion and exclusion criteria and randomly divided into two equal groups: an experimental group (EG) and a control group (CG). First, both groups performed OBSEE. After that, the EG performed 12 weeks of HIIT. At the end, again, both groups performed OBSEE. Blood sampling was performed just before and immediately after each session of exercise. Dependent variables were categorized into three groups including 1. Coagulation: fibrinogen(FIB), factor VIII(FVIII), prothrombin time (PT), prothrombin time activity (PTA), international normalized ratio (INR), activated partial thromboplastin time (aPTT), platelet (PLT), mean platelet volume (MPV) 2. Anticoagulation: protein C (PC), antithrombinIII (ATIII) 3. Fibrinolytic: d-dimer (D-D), tissue plasminogen activator (tPA), plasminogen activator inhibitor1 (PAI-I), tPA/PAI-1. To analyze the data, Shapiro- Wilk test, Factorial repeated measures ANOVA, as well as Pearson correlation coefficient were used at significant level ($P \leq 0.05$).

Results: HIIT caused significant increase in the rate of Vo_{2max} ($p = 0.001$) and significant decrease in RHR ($p = 0.001$), SBP ($p = 0.001$) and DBP ($p = 0.001$). No significant difference was observed between the two groups in the response of FIB ($p = 0.262$), FVIII ($p = 0.248$), PT ($p = 0.396$), PTA ($p = 0.646$), INR ($p = 0.408$), aPTT ($p = 0.856$), PLT ($p = 0.678$), MPV ($p = 0.223$), D-D ($p = 0.621$), tPA ($p = 0.381$), PAI-1 ($p = 0.353$), tPA / PAI-1 ($p = 0.069$), PC ($p = 0.147$) and ATIII ($p = 0.138$) to OBSEE after 12 weeks HIIT.

Conclusion: It seems that to observation of significant positive changes in the response of coagulation, anticoagulant, and fibrinolytic factors to one OBSEE, more than 12 weeks HIIT are required.

Keywords: Training, Coagulation, Fibrinolytic, Hypertension

Introduction

It is estimated that about 30% of people over the age of 50 in the world are involved with high blood pressure (1). In patients with high blood pressure, the balance between the vasodilators and the vasoconstrictors of vessels is disturbed, which results in endothelium changes and launches a vicious cycle that can contribute to the maintenance of high blood pressure. Also, in patients with high blood pressure, activation and endothelial damage, results in changes in vascular tone,

vascular reactivity, and interruption of hemostasis (2). The hemostasis relies on a wide range of highly coordinated interactions between platelets, endothelial blood vessels, coagulation proteins, and fibrinolysis in the blood (3). In normal conditions, the blood components and endothelium are completely anti-thrombosis. This means that their operation maintains fluidity and prevents coagulation. Nevertheless, promoter thrombotic mechanisms overcome the anticoagulant mechanisms and trigger rapid and localized blood clots to respond to endothelial damage (3). Hypertension is associated with prothrombotic conditions (4). Although the symptoms of the disease are associated with high pressures, they are usually compounded by prothrombotic events, including ischemic stroke and myocardial infarction. The above is thrombotic paradox of hypertension (4). This paradox is because hypertension meets the triple Virchow's criteria for thrombosis (Virchow, a German physician, describes three categories of factors that trigger thrombosis, including hemodynamic changes, endothelial damage, and over-coagulation).These criteria include changes in blood flow due to shear stress, vascular changes with changes in endothelium and platelet activation (4). There are also many changes in the coagulation and fibrinolytic pathways of patients with hypertension (4). Previous studies have shown that there is a positive correlation between physical activity and cardiovascular health (5). Exercise has a widespread positive cardiovascular effect, including blood flow regulation, increased vasodilators of vessels, reduced resting heart rate, decreased levels of catecholamines, and decreased angiotensin II (6). Performing exercise trainings has been shown to change the processes of coagulation cascade and fibrinolysis. The effect of exercise training on the hemostasis system depends on factors such as type, intensity, duration, and initial state (7). Today, researchers have focused on high intensity interval training (HIIT) compared with moderate intensity continuous training for treating cardiovascular patients, especially those with high blood pressure (7- 9). HIIT involves repeating highly intensive training courses and active or inactive periods of rest (7). The importance of this type of training to long-term trainings is that it can be repeated for a long time at a high level. Central and peripheral adaptations have been reported in these trainings in human and animal studies. HIIT stimulates more cardiovascular adaptations in patients with moderate to severe cardiovascular disease than moderate long-term activity (8). The American Heart Association (AHA) recently recommended this kind of training in its suggestions for cardiovascular patients (8). HIITs improve speed, aerobic and anaerobic endurance, metabolism, skeletal muscle oxidative capacity, blood pressure, inflammatory markers, endothelial function, lipid oxidation, physiological changes and improve exercise performance by increasing the Vo_{2max} (10). These benefits can be achieved through changes in intensity, duration, and rest periods (10- 13). A new study on cardiovascular patients has shown that HIIT with an 80 to 95% maximal heart rate reserve (MHRR) has a positive effects on cardiovascular patients (7). It has also been shown that performing an interval training with an intensity of 85 to 95% of maximal heart rate (MHR) or VO_{2max} for 1 to 4 minutes with active recovery periods compared to a moderate continuous training improves cardiorespiratory function, endothelial function and its markers, insulin sensitivity, sympathetic activity markers, and arterial stiffness in hypertensive patients as well as those with family history of hypertension (9). On the other hand, it has been mentioned that only one session of resistance exercise can improve the fibrinolytic system in patients with coronary artery disease (14). However, the latest research suggests that it is still uncertain what type of activity and how intensely can affect fibrinolysis and

coagulation (15). Consequently, considering the non-responded questions in view of the type of activity and its effect on the homeostasis system, as well as the further mention of the researchers that HIITs can be used to improve the conditions of hemostasis in hypertensive cardiovascular patients(10, 11), this study aimed to investigate whether 12 weeks of HIIT can affect the response of coagulation, anticoagulant, and fibrinolytic factors in hypertensive cardiovascular patients following one bout submaximal endurance exercise (OBSEE).

Methods

As an applied research, the present study was semi-experimental, having pretested and post-test design with CG. In this study, the effect of 12 weeks of HIIT on the response of coagulation, anticoagulant and fibrinolytic factors in cardiovascular hypertensive patients following OBSEE was investigated. The study protocols and procedures had previously been approved by the Research Ethics Committee of Sport Sciences Research Institute of Iran with the code IR.SSRI.REC.1397.203. The sample population consisted of 20 men from 55 to 65 years of age working in the National Iranian South Oil Company. The subjects, suffering from hypertension, were selected from among 70 individuals based on inclusion and exclusion criteria. Subjects were randomly divided into two equal EG and CG. In order to observe the ethics of research, all subjects consciously completed the consent form of the participation in the research. The criteria for inclusion and selection of subjects were: 1. Participation consent; 2. Age range 50 to 65 yrs; 3. VO_{2max}> 7.5 METs; 4. Injection fraction of 50 to 70%; 5. Systolic blood pressure(SBP) ≥ 140mm Hg or diastolic blood pressure(DBP) ≥ 90 mm Hg(16,17). Exclusion criteria included: 1. Patient's discontent with continued study; 2. Ages below 50 or above 65 yrs; 3. VO_{2max}< 7.5 METs; 4. Injection fraction less than 50%; 5. SBP < 140mm Hg or DBP < 90 mm Hg; 6. Cigarette smoking; 7. Presence of other illnesses, including: coronary artery disease and diabetes. To evaluate the cardiovascular fitness of subjects, a modified Bruce protocol was used. For example, at the end of stage 5 (14 % grade and 3.4 miles/h which converts to 90 $m.min^{-1}$) VO_{2max} would be estimated as follows: $VO_{2max=}$ 0.1× ($90m.min^{-1}$) + 1.8× ($90m.min^{-1}$) × (14/100) +3.5= 35.18 $ml/kg^{-1}.min^{-1}$ (approximately 10.2 METs) (11). Determination of ejection fraction was done by echocardiography Eco Color Doppler M-Mode (Esaote MyLab Model). The resting SBP and DBP of the subjects were also determined using a digital pressure gauge. Also; anthropometric characteristics were determined by VIVENTE body composition analyzer (494-34.Banahwa-dona.aanaseo-au.seoul.korea). A week after sampling, the groups performed a OBSEE of running for 30 minutes with an intensity of 60 to 65% MHRR, following an 8-hour fasting protocol. In order to prevent the effects of pre-test activity on coagulation, anticoagulant, and fibrinolytic factors, all subjects were requested not to participate in any intensive activity 48 hours prior to OBSEE protocol (18,19). Blood samples to determine the response of 1. Coagulation: fibrinogen (FIB), factor VIII (FVIII), prothrombin time (PT), prothrombin time activity (PTA), international normalized ratio (INR), activated partial thromboplastin time (aPTT), platelet (PLT), mean platelet volume (MPV) 2. Anticoagulation: protein C (PC), antithrombinIII (ATIII) 3. Fibrinolytic: d-dimer (D-D), tissue plasminogen activator (tPA), plasminogen activator inhibitor1 (PAI-I), tPA/PAI-1 were taken from the subjects prior to and immediately after the activity. In order to determine the complete blood count (CBC), two ml of blood from brachial vein in tubes containing EDTA with a concentration of one and a half to two mg per ml was used (20). Also, five ml of blood were collected in tubes containing sodium citrate at a concentration of 0.2 ml in 1.8 ml of blood, and the tubes were centrifuged at 2500 rpm for 30 minutes in order to separate the plasma. All of

the given tests were immediately investigated and only a part of the plasma was kept for tPA and PAI-1 tests at -80 ° C (21, 22). After doing the sampling, the training group, having the same conditions with the CG, performed 3 sessions weekly exercise for 12 weeks of HIIT on the matrix model treadmill (7). The handling of exercise intensity was performed using Pollar's pulsar. During the training period, both EG and CG used medical care. After the end of 12 weeks of HIIT, again, both groups with regarding 48 hours of rest and following 8 hours fasting activity performed a 30 min submaximal endurance exercise of running with 60-65% MHRR intensity. Blood sampling was performed to examine the response of coagulation, anticoagulant and fibrinolytic factors before and immediately after the exercise. Due to sweating caused by exercise, the volume of water in the body decreases from about 900 to 1300 milliliters, depending on the severity and environmental conditions, which can lead to a decrease in plasma volume (23). Reducing plasma volume also affects the concentration of the target factors, especially fibrinogen, so the Dill and Costill formula was used to calculate plasma volume changes and modify the target factors (24, 25). Normalization of data was done using the Shapiro-Wilk test. In order to investigate the effect of training on the response of coagulation, anticoagulant and fibrinolytic factors in hypertensive patients following OBSEE, factorial repeated measures ANOVA and Pearson correlation coefficient with significant level ($P \leq 0.05$) were employed. To test the hypotheses, SPSS software (version 19) was used.

Results

Table 1 shows the descriptive information of some of the anthropometric and physiological indices of the sample.

Table 1. The anthropometric and physiological indices of EG (N = 10) and CG (N = 10)

Variables	Groups	Before 12 weeks HIIT		After 12 weeks HIIT	
		Before OBSEE M±SD	Immediately after OBSEE M±SD	Before OBSEE M±SD	Immediately after OBSEE M±SD
Height	EG	170.30±8.35	-	-	-
(cm)	CG	171.90±3.69	-	-	-
Age	EG	58.00±4.94	-	-	-
(yrs)	CG	62.50±2.99	-	-	-
Weight	EG	87.73±12.88	-	86.60±12.71	-
(kg)	CG	85.68±12.36	-	86.21±13.01	-
BMI	EG	30.23±4.03	-	29.83±3.92	-
(kg/m^2)	CG	28.91±3.37	-	29.17±3.48	-
BFP	EG	23.20±3.60	-	22.58±3.12	-
(%)	CG	22.81±2.89	-	23.93±2.10	-
PV	EG	57.39±3.51	52.68±3.87	58.02±4.23	51.67±3.85
	CG	57.33±2.09	54.28±2.54	58.19±2.59	53.98±2.69
EF	EG	56.50±2.41	-	-	-
(%)	CG	55.00±0.00	-	-	-

M±SD: mean±standard deviation, BMI: body mass index, BFP: body fat percentage, PV: plasma volume, EF: ejection fraction

Table 2 shows information on the Factorial repeated measures ANOVA of variables that any change in them can affect the physiological and homeostasis conditions of hypertensive cardiovascular patients when resting or responding to a specific exercise. Significant level (P =0.001, P <0.05) shows that 12 weeks of HIIT can improve the resting levels of Vo_{2max}, SBP, DBP and RHR of hypertensive cardiovascular patients. Table 3 shows the Pearson correlation coefficient for some of the variables in the research. The results of Table 4 show the data on the Factorial repeated measures ANOVA Δ of the response of the research variables before and after 12 weeks of HIIT.

Discussion

The results of this study showed that HIIT caused an increase (+ 46.58%) of VO_{2max} levels in cardiovascular hypertensive patients. Hilberg *et al*. found that 12 weeks of endurance training induced an evaluation of Vo_{2max} by 17% in healthy untrained males when they performed an exercise test adjusted at 80-100% individual anaerobic threshold (12).

Table 2. Factorial repeated measures ANOVA of resting levels of the variables in the EG (N = 10) and CG (N = 10)

Variables	Source	Groups	Pre resting levels M±SD	Post resting levels M±SD	Changes (%)	Effect size	F	Sig
Vo_{2max} (ml/k/min)	time × groups	EG	35.96±2.02	52.50±6.24	+ 45.99	0.75	55.48	0.001 •
		CG	33.97±1.90	34.28±1.83	+ 0.91		4	
SBP (mm Hg)	time × groups	EG	145.40±4.52	123.60±5.31	- 14.99	0.75	55.10	0.001 •
		CG	149.00±7.73	150.10±11.12	+ 0.73		4	
DBP (mm Hg)	time × groups	EG	95.20±3.29	76.80±4.73	-19.32	0.75	55.10	0.001 •
		CG	93.60±4.08	88.40±5.94	-5.55		4	
RHR (bpm)	time × groups	EG	75.30±4.02	63.50±2.83	-15.67	0.74	52.85	0.001 •
		CG	77.20±3.04	77.40±3.53	+ 0.25		5	

M±SD: mean±standard deviation, Vo_{2max}: maximal oxygen uptake, SBP: systolic blood pressure, DBP: diastolic blood pressure, RHR: resting heart rate • significant changes p≤0.05

Table 3. Results of Pearson Correlation Coefficient

First variable	Second variable	R	R^2	Sig
Vo_{2max}(ml/k/min)	SBP(mm Hg)	-0.73	0.53	0.001•
Vo_{2max}(ml/k/min)	RHR(bpm)	-0.75	0.56	0.001•
RHR(bpm)	SBP(mm Hg)	+0.71	0.50	0.001•
RHR(bpm)	DBP9mm Hg)	+0.67	0.44	0.001•
FIB(mg/dl)	Vo_{2max}(ml/k/min)	-0.55	0.30	0.001•

• Significant changes p≤0.05

Table 4. Factorial repeated measures ANOVA Δ of the response of research variables in the EG (N = 10) and CG (N = 10)

Variables	Source	Groups	Pre Δ M±SD	Post Δ M±SD	Changes (%)	Effect size	F	Sig
FIB	time ×	EG	-1.71±25.84	-9.31±58.13	-491.88	0.06	1.34	0.26
(mg/dl)	groups	CG	+8.86±24.32	-9.97±38.00	-335.39			
FVIII	time ×	EG	+25.00±10.99	+9.60±16.06	- 61.60	0.75	1.42	0.24
(%)	groups	CG	+7.20±10.99	+3.80±16.32	-47.22			
PT	time ×	EG	-0.15±0.34	-0.21±0.25	-40.00	0.04	0.16	0.39
(s)	groups	CG	-.0.17±0.41	-0.05±0.19	+70.58			
PTA	time ×	EG	+1.14±3.93	+1.27±2.57	+11.40	0.01	0.21	0.64
(%)	groups	CG	+1.32±3.70	+0.42±1.64	- 68.18			
INR	time ×	EG	-0.01±0.03	-0.02±0.02	-100	0.03	0.71	0.40
(%)	groups	CG	-0.01±0.04	+0.00±0.01	+100			
aPTT	time ×	EG	-1.02±0.78	-0.59±0.80	+42.15	0.01	0.03	.08
(s)	groups	CG	-0.99±0.70	-0.66±1.14	+33.33			
PLT	time ×	EG	+38.30±30.24	+21.90±26.81	- 42.81	0.01	0.17	0.67
(10^3/mm^3)	groups	CG	+37.30±13.40	+16.20±23.59	- 56.56			
MPV	time ×	EG	+0.06±0.24	+0.17±0.28	+183.33	0.08	1.59	0.22
(fL)	groups	CG	+0.25±0.19	+0.14±0.30	-44.00			
D-D	time ×	EG	+30.91±52.19	+57.97±67.12	+87.54	0.01	0.25	0.62
(ng/ml)	groups	CG	+10.32±70.59	+63.66±96.70	+516.86			
tPA	time ×	EG	-5.67±4.61	-1.36±6.06	+76.01	0.04	0.80	0.38
(IU/mL)	groups	CG	-6.46±7.09	+0.94±3.45	+85.44			
PAI-1	time ×	EG	-8.20±12.39	-5.39±7.06	+34.26	0.04	0.91	0.35
(AU/mL)	groups	CG	-1.71±7.09	-6.93±10.23	-305.26			
tPA/PAI-1	time ×	EG	-0.04±0.26	+0.13±0.43	+425	0.17	3.72	0.06
	groups	CG	-0.23±0.15	+0.52±0.67	+326.08			
PC	time ×	EG	+6.50±4.60	+13.80±10.21	+112.30	0.11	2.29	0.14
(%)	groups	CG	+7.90±2.88	+9.1±6.19	+15.18			
ATIII	time ×	EG	+6.68±3.38	-2.23±13.44	-133.38	0.11	2.40	0.13
(%)	groups	CG	+5.73±2.30	+4.22±4.55	-26.35			

M±SD: mean±standard deviation, FIB: fibrinogen, FVIII: factor VIII, PT: prothrombin time, PTA: prothrombin time activity, INR: international normalized ratio, aPTT: activated partial thromboplastin time, PLT: platelet, MPV: mean platelet volume, D-D: d-dimer, tPA: tissue plasminogen activator, PAI-1: plasminogen activator inhibitor1, PC: protein C, ATIII: antithrombin III

HIIT appears to be more effective than intensive continuous training in increasing Vo_{2max}. It has also been shown that there is a negative correlation between Vo_{2max} and blood pressure (26). On the other hand, Vo_{2max} has a very strong association with peripheral vascular vasodilators (27). Therefore, it can be stated that a significant increase in the levels

of Vo_{2max} in the training group resulted in favorable vascular adaptations. Correlation coefficient (R = -0.77) between Vo_{2max} and SBP in the present study is consistent with the results of many researches (26,27). Also, in this study, there was a positive and significant correlation between RHR with SBP (R = +0.71) and DBP (R = +0.67). On the other hand, there is a negative correlation between RHR and VO_{2max} (R = -0.80). Overall, the results showed that HIIT can significantly decrease the RHR, SBP, DBP and a significant increase in VO_{2max} in cardiovascular hypertensive patients. These changes due to HIIT can be considered as a treatment for hypertensive cardiovascular patients. The results of this study showed that 12 weeks of HIIT did not have a significant effect on FIB response to OBSEE. However, FIB response changes in the EG (-491.88) after 12 weeks of HIIT were significantly higher than the CG (-325.39). On the other hand, the results showed that there is a significant negative correlation coefficient between FIB and Vo_{2max} (R = -0.59). FIB is a coagulation factor and an acute phase reactant, which has been identified as a major independent risk factor for coronary artery disease (28,29). This plasma glycoprotein with a weight of 340 kDa plays a key role in coagulation. The FIB is converted to fibrin by the thrombin and ultimately becomes a form of clot. It can also play a role in hemostasis through the formation of transductive bridges between activated platelets and increasing their densities (30). It has been shown that despite high cholesterol, low FIB is associated with a lower risk of cardiovascular disease and increased plasma levels of it with an increased risk of cardiovascular disease and stroke. It has also been shown that there is a positive correlation between FIB and blood pressure (28, 31- 33). Since in this research SBP and DBP in the EG showed a significant decrease, the reduction of FIB response in the EG can be, on the one hand, attributed to the decreased SBP and DBP and, on the other hand, to the increased Vo_{2max}. Researchers have shown that increased levels of FIB are associated with arterial stiffness, target organ damage, and cardiovascular outcomes. Elastic properties of the arteries are the most important determinant of cardiovascular function and predictive of risk (34). Therefore, the significant reduction of SBP and DBP levels due to HIIT in the EG, on the one hand, and the subsequent changes in FIB response following OBSEE, on the other hand, could indicate the desired effect of HIIT on the performance of vascular dilators and FIB responses to OBSEE. It has also been shown that 12 weeks of HIIT failed to have a significant effect on the FVIII response to OBSEE. However, FVIII response changes in the EG (-61.60) after the 12 weeks of HIIT was higher than the CG (-47.22). FVIII is a necessary cofactor for the coagulation factor IXa in the internal coagulation cascade (35). When this protein is activated, it can promote the formation of thrombin and fibrin. In patients with coronary heart disease and ischemic stroke, the levels of this protein increase. It has been shown that reducing FVIII is associated with a reduction in the risk of cardiovascular disease and its increase is associated with increased risk of vascular events (36). Denuijl *et al.* showed that OBSEE resulted in a significant increase in FVIII (37). Therefore, the effective though non-significant change of the FVIII response following OBSEE, can be attributed to the increased effectiveness of HIIT in reducing the risk of thrombin formation and subsequently reduced risk of cardiovascular disease. It has been shown that 12 weeks of HIIT did not have a significant effect on PT, PT activity, INR, and aPTT response to OBSEE. Coagulation involves a series of regulated steps that cause fibrin formation and provides a framework for free platelets. A series of events including damage to the vascular wall and surrounding tissues, damage to the blood, blood transfusion, and pre-coagulation factors in the vascular wall can produce fibrin. Coagulation occurs through both intrinsic and extrinsic

pathways. Eventually, these two pathways trigger the formation of the thrombin enzyme through a common pathway. Thrombin converts FIB to fibrin and plays an important positive feedback role in several important cascade positions (3). The extrinsic pathway, measured by PT, begins with the activation of the FVII by the tissue factor (TF) and then the direct activation of the common pathway via FVIIa. The intrinsic pathway, which is measured by aPTT, begins with the activation of the XII contact factor and subsequently the cascade activation of factors XI and IX. The activated factor VIII acts as a cofactor for activating the common pathway through FIXa (38). The results of the study show that 12 weeks of HIIT did not have a significant effect on the response of intrinsic and extrinsic coagulation pathways to OBSEE. In general, however, the higher level changes of PT, PT activity and INR variation in the EG indicate that 12 weeks of HIIT have somewhat affected the response of the extrinsic pathway to OBSEE, leading to a decreased time of coagulation. TF, which is the main factor in the extrinsic coagulation pathway, seems to be increased by HIIT. However, the amount of intrinsic pathway response variation to OBSEE in the EG has been increasing and coagulation time has increased through this pathway. Studies have shown that FVIII increases immediately after exercise, which is associated with reduced aPTT time and increased PT (39, 40). The results of the study indicate an increase in the response of aPTT to OBSEE following 12 weeks of HIIT. The reason for this increase seems to be the reduction of FVIII response. As mentioned, FVIII is a necessary cofactor for the coagulation factor IXa in the intrinsic coagulation cascade (35). The reduction of which is associated with a reduction in the risk of cardiovascular disease (38). Therefore, increasing the response of aPTT, or somewhat prolonged coagulation time through the intrinsic pathway resulting from the reduction of FVIII, represents a reduction in the risk of cardiovascular disease and more effectiveness of HIIT on the response of intrinsic pathway coagulation factors to OBSEE. This finding is consistent with the study by Hilberg *et al*. (12). The results showed that 12 weeks of HIIT did not have a significant effect on the response of PLT and MPV to OBSEE. However, the MPV changes in the EG (+183.33) after 12 weeks of HIIT compared to the CG (-44.00) indicated more effectiveness of HIIT on the MPV response to OBSEE. It has been shown that there is a correlation between MPV and the rate of PLT production and turnover. As the blood platelets circulate, their size gradually decreases. Platelet activity also affects MPV size. There is strong evidence that larger platelets, reflected by increased MPV are more metabolically and enzymatically active than the small platelets. However, these large platelets have a high thrombotic potential (41). The high MPV changes in the EG indicate an increase in MPV response after 12 weeks of HIIT. It seems that this increase in the response of MPV in hypertensive cardiovascular patients is an adaptation, since increased coagulation due to platelet and MPV activity is dangerous if the fibrinolysis system loses its dynamics, while the results indicate an equilibrium of coagulation, fibrinolytic and anticoagulant system in the EG. The results showed that 12 weeks of HIIT did not have a significant effect on the response of D-D to OBSEE. D-D is a fibrin analysis product whose low concentrations indicate absence of thrombosis (42). Although HIIT did not have a significant effect on D-D response, the difference in responses in the EG (+87.56%) and CG (+516.86) indicated that HIIT was partly able to reduce the effects of thrombosis of OBSEE. Also, the results showed that 12 weeks of HIIT did not have a significant effect on the response of tPA and PAI-1 to OBSEE. The tPA is released from the endothelium and causes the plasminogen to become plasmin. This reaction is significantly accelerated in the presence of fibrin. Plasmin formation occurs

naturally only on the fibrin clot. Plasmin breaks fibrin and FIB into a number of parts and D-D. TPA is prohibited by the PAI-1 released from the endothelium (22). The change rate of PAI-1 response in the EG was increased (+34.26) and in the CG was reduced (-305.26). It seems that significant reduction in PAI-1 response and increase in D-D in the CG are due to increased thrombosis. Meanwhile, the changes in the D-D response in the EG did not significantly increase, which is indicative of lower thrombosis, and probably this is why PAI-1 somewhat imposes its inhibitory effect on the tPA, to maintain the dynamics of the fibrinolysis system. Hence, it seems that the body hemostasis system always seeks for a balance between coagulation and fibrinolysis, so that the increase in thrombosis or blood clot shows itself in the form of an increase in D-D, and, on the other hand, the reduction of PAI-1 in the thrombosis, helps the fibrinolysis system to act without any inhibitory effect. Any increase in PAI-1 when thrombosis increases can neutralize the effects of the fibrinolysis system and compromise cardiovascular health. In general, the results indicate that 12 weeks of HIIT can partly affect the response and the dynamics of the fibrinolysis system after OBSEE. The rate of changes in tPA / PAI-1 in the EG (+425) compared to the CG (+326.08) shows this dynamics. Natural coagulation inhibitors are plasma-soluble proteins that can neutralize the active coagulation factors and inhibit and control the coagulation system. ATIII and PC and S can be mentioned as the most important natural inhibitors. PC is one of the most important anticoagulants in the body. This protein is produced in the liver and has a half-life of 6 to 10 hours (43). PC, which is vitamin K-dependent serine protease, is able to disable the Va and VIIIa agents and reduce the rate of thrombin formation (43, 44).The results show that despite the fact that 12 weeks of HIIT did not have a significant effect on the response of PC to OBSEE, the rate of response change in the EG (+112.30) compared to the CG (+15.18) indicates that training slowed down the response speed of thrombin formation following the exercise, which also reduced the rate of clot formation. On the other hand, the results showed that ATIII response changes in the EG (-133.38) was higher than the CG (-26.35). ATIII is a serine protease inhibitor with a molecular weight of 58 kD, whose anticoagulant effect is mainly achieved by inhibiting IIa (thrombin) and Xa factors (44). There seems to be a certain coordination between PC and ATIII, so that initially PC with its own increase, exerts an increase in anticoagulant effect, and then ATIII, with its own decrease, allows the unbroken coagulation to pass through its natural pathway, and FIB, which acts as an acute phase reactant, can be converted to fibrin without any barrier (28, 29).

Conclusion

Although 12 weeks of HIIT did not have a significant effect on the response of any coagulation, anticoagulant, and fibrinolytic factors of hypertensive cardiovascular patients to OBSEE, different changes in D-D, PAI-1, PC and ATIII of two groups show that HIIT can likely be effective. It seems that to observe significant changes in the response of coagulation, anticoagulant, and fibrinolytic factors, more than 12 weeks of HIIT are required. Therefore, it can be stated that hypertensive cardiovascular patients' performing HIIT is likely to reduce the potential risks of thrombotic events when performing OBSEE.

Ethical issues

The study was approved by the Research Ethics Committee of Sport Sciences Research Institute of Iran with the code IR.SSRI.REC.1397.203**.**

Authors' contributions

Authors equally contributed to the writing and revision of this paper.

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References

1. Elaine NM, Katja H. Human anatomy& physiology. (9th Ed). Upper Saddle River, United States: Pearson. 2013.
2. Beevers DG, Lip G, Brien EO. ABC of hypertension. (6th Ed). Oxford, London: BMJ Books. 2015.
3. Smith DL, Fernhall B. Advanced cardiovascular exercise physiology. Human Kinetics. 2011.
4. Nadar S, Lip G. Hypertension. (2th Ed). Oxford University Press. 2015.
5. Buttar HS, Li T, Ravi N. Prevention of cardiovascular diseases: Role of exercise, dietary interventions, obesity and smoking cessation. Exp Clin Cardiol. 2005; 10 (4): 229- 249.
6. Gielen S, Schuler G, Adams V. Cardiovascular effects of exercise training molecular mechanisms. Circ J. 2010; 122: 1221- 1238.
7. Thinkham MH. Health promotion in cardiac rehabilitation patients through the use of a high- intensity interval training protocol. WJCD. 2014; 4: 493- 497.
8. Guiraud T, Nigam A, Gremeaux V, Meyer PH, Juneau M, Bosquet L. High- intensity interval training in cardiac rehabilitation. Sports Med. 2012; 42 (7): 587- 605.
9. Ciolac EG. High- intensity interval training and hypertension: maximizing the benefits of exercise?, Am J Cardiovasc Dis. 2012; 2 (2): 102- 110.
10. Biskey LM. Effects of high intensity interval training on hemostasis and fibrinolysis in healthy males: relationship to sympathetic nervous system activation. MSc thesis in University of Toronto. 2015.
11. Heyward VH, Gibson AL. Advanced fitness assessment and exercise prescription. 7th Ed. New Mexico**:** J Hum Kinet. 2014.
12. Hilberg T, Menzel K, Wehmeier UF. Endurance training modifies exercise-induced activation of blood coagulation. Eur J Appl Physiol. 2013; 113 (6): 1423-1430.
13. Graham T, Deirdre L, Douglas C, Gregory YHL. A systematic review of the effects of acute psychological stress and physical activity on haemorheology, coagulation, fibrinolysis and platelet reactivity: Implications for the pathogenesis of acute coronary syndromes. Thromb Res. 2007; 120 (6): 819- 847.
14. Nascimento DC, Neto FR, Santana FS, Silva RAS, Santos-Neto, LD, et al. The interactions between hemostasis and resistance training: a review. Int J Gen Med. 2012; 5: 249- 254.
15. Patelis N, Karaolanis G, Kouvelos GN, Hart C, Metheiken S. The effect of exercise on coagulation and fibrinolysis factors in patients with peripheral arterial disease. Exp Biol Med. 2016; 241: 1699-1707.
16. Sharief KM, Hassan HA, Osman H, Ahmed AS. Ejection fraction rate for hypertensive patients using echocardiography. Med Res Chron. 2015; 2 (3): 322- 329.
17. Jette M, Sidney K, Blumchen G. Metabolic equivalents (METS) in exercise testing, exercise prescription, and evaluation of functional capacity. Clin Cardiol. 1990; 13: 555- 565.
18. Lakhdar N, Saad HB, Denguezli M, Zaouali M, Zbidi A, Tabka Z. Effects of intense cycling training on plasma leptin and adiponectin and its relation to insulin

resistance. Neuro Endocrinol Lett. 2013; 34 (3): 229- 235.
19. Ahmadizad S, Moradi A, Nikookheslat S, EbrahiMI H, Rahbaran A, Connes PH. Effects of age on hemorheological responses to acute endurance exercise. ESCHM. 2011; 49 (1- 4): 165- 174.
20. Patel N. Why is EDTA the anticoagulant of choice for hematology use?. Tech Talk. 2009; 7 (1): 1- 7.
21. Hnasko R. Elisa methods and protocols. Humana Press. 2015.
22. Antovic JP, Blomback M. Essential guide to blood coagulation. Wiley- Blackwell. 2010.
23. Plowman SHA, Smith DL. Exercise physiology for health fitness and performance**.** (4th Ed). Philadelphia: Lippincott Williams & Wilkins. 2015.
24. Alis R, Sanchis-Gomar F, Primo-Carrau C, Lozano-Calve S, Dipalo M, Aloe R et al. Hemoconcentration induced by exercise: Revisiting the Dill and Costill equation. Scand J Med Sci Sports. 2015; 25 (6): e630- 637.
25. Dill DB, Costill DL. Calculation of percentage changes in volumes of blood plasma and red cells in dehydration. J Appl Physiol. 1974; 37 (2): 247- 248.
26. Emaus A, Wilsgaard T, Furberg AS, Thune I. Blood pressure, cardiorespiratoty fitness and body mass: Result from the Tromso Activity study. Norsk Epidemiologi. 2011; 2 (20): 189- 197.
27. Montero D. The association of cardiorespiratory fitness with endothelial or smooth muscle vasodilator function. Eur J Prev Cardio. 2015; 22 (9): 1200- 1211.
28. Eldour AAA, Khalafallah TO, Noja HM, Saad ESM, Elsayid M, Babker AMAAA. Fibrinogen levels in hypertensive and normotensive: a cross- sectional from El-obied city, sudan. J Biosci Med. 2016; 4: 28- 32.
29. Aziz CA, Omar N, Abdullah WZ, Jalil RA, Nik WW, Zakaria R. Reduced fibrinogen, fibrinolytic biomarkers, and physical parameters after a weight-loss program in obese subjects. North Am J Med Sci. 2014; 6 (8): 377- 382.
30. Cortes- Canteli M, Zamolodchikov D, Jin Ahn HA, Strickland S, Norris EH. Fibrinogen and altered hemostasis in alzheimer's disease. J Alzheimers Dis. 2012; 32 (3): 599- 608.
31. Chitsaz A, Mousavi SA, Yousef Y, Mostafa V. Comparison of changes in serum fibrinogen level in primary intracranial hemorrhage (ICH) and ischemic stroke. ARYA Atheroscler. 2012; 7 (4): 142- 145.
32. Tabak O, Gelisgen R, Uzun H, Kalender B, Balci H, Curgunlu A, et al. Hypertension and hemostatic/ fibrinolytic balance disorders. Clin Invest Med. 2009; 32 (6): E285- E292.
33. Shankar A, Wang JJ, Rochtchina E, Mitchell P. Positive association between plasma fibrinogen and incident hypertension among men. population-based cohort study. Hypertension J. 2006; 48 (6): 1043- 1049.
34. Charalambos V, Panagiota P, Konstantions A, Gregory V, Carmen V, Athanasios B, et al. Relationship of fibrinogen with arterial stiffness and wave reflections. J Hypertens. 2007; 25 (10): 2110- 2116.
35. Ikeda Y, Iwanaga S, Saito H, Katsuo S, Tanaka K, Davie EW. Recent advances in thrombosis and hemostasis. Springer. 2008.
36. Tarsia J, Chang TR, Aysenne A, Boehme AK, Sartor AE, Albright KC, et al. Elevated plasma factor VIII in patients with ischemic stroke: does it have any association with hypertensive heart disease?. J Neurol Disord Stroke. 2013; 1 (3): 1027.
37. Denuijl IEM, Groen WG, Der Net JJV, Grobbee DE, De Groot, PG, Fischer K. effects of exercise in non- severe

haemophilia patients. Blood J. 2010; 116: 545.
38. Lichtin A, Bartholomew J. The coagulation consult: a case- based guide. Springer. 2014.
39. Pan J, Dinh TT, Rajaraman A, Lee M, Scholz A, Czupalla CJ, et al. Patterns of expression of factor VIII and von Willebrand factor by endothelial cell subsets in vivo. Blood J. 2016; 128 (1): 104- 109.
40. Ribeiro J, Almeida-Dias A, Ascensao A, Magalhaes J, Oliveira AR, Carlson J, et al. Response to acute physical exercise in healthy adolescents. J Sci Med Sport. 2007; 10: 164- 169.
41. Gresele P, Fuster V, Lopez J, Page CP, Vermylen J. Platelets in hematologic and cardiovascular disorders. Cambridge University Press. 2008.
42. Longo DL. Harrison's hematology and oncology. (17th Ed). McGraw- Hill Companies. 2010.
43. Shaz BH, Hillyer CD, Abrams CS, Roshal M. Transfusion medicine and hemostasis. clinical and laboratory aspects. (2nd Ed). Elsiver. 2013.
44. Guyton AC, Hall JE. Medical physiology. 13th Ed. Philadelphia: Elsiver. 2016.