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Platelet indices and function response to two types of high intensity interval exercise and comparison with moderate intensity continuous exercise among men after coronary artery bypass graft: A randomized trial

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Original Article

Abstract

BACKGROUND: It has been indicated that the acute exercise increases the thrombotic events that stem from platelet hyper-reactivity. The present randomized controlled trial study was carried out with the aim to compare high-intensity interval exercise (HIIE) with moderate intensity continuous exercise (MICE) in terms of platelet indices and function in patients who had undergone post coronary artery bypass graft (CABG).

METHODS: 30 men with a history of CABG were recruited and divided into 3 groups (MICE, HIIE-1, and HIIE-2). The MICE protocol consisted of running for 40 minutes with 65% of maximal heart rate (HR_{max}). Subjects in HIIE-1 group performed an interval exercise with work to rest ratio of 1:1 in which 10 rounds of running (95% HR_{max}) were followed by active recovery (35% HR_{max}). HIIE-2 subjects performed an interval exercise with work to rest ratio of 2:1 in which 7 rounds of running (85% HR_{max}) were followed by active recovery (45% HR_{max}). Before and immediately after the exercise protocols, blood samples were taken from subjects and analyzed to measure the variables.

RESULTS: Although platelet count (PLT) and hematocrit (HCT) were increased significantly after HIIE-1 and HIIE-2 in comparison to MICE ($P < 0.050$), the other platelet indices [mean platelet volume (MPV), platelet distribution width (PDW), plateletcrit (PCT)] were not significantly changed among groups ($P > 0.050$). The platelet aggregation and fibrinogen were further increased after HIIE-1 and HIIE-2 as compared with MICE; however, such increment were significant between HIIE-2 and MICE ($P < 0.050$).

CONCLUSION: It seems that HIIE, regardless of the type, has higher thrombotic potentials compared with MICE. Accordingly, MICE is safer than HIIE for rehabilitation in patients undergoing CABG.

Keywords: High-intensity Intermittent Exercise, Aerobic Exercise, Rehabilitation, Platelets, Fibrinogen

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Introduction

Cardiovascular diseases (CVDs), especially coronary artery disease (CAD), currently account for nearly half of non-communicable diseases (NCDs). The main cause of death in today's society has been associated with this disease (17.3 million deaths per year).[1] Coronary artery bypass grafting (CABG) surgery is a common revascularization strategy implemented for patients with intense CAD and can be performed with a low incidence of morbidity and mortality.[2] CABG is associated with a strong activation of the hemostatic system. Platelets play an important role in hemostasis and therefore thrombotic events.[3] Changes in platelet indices, such as platelet count (PLT) and mean platelet volume (MPV) are accompanied by the increase in platelet function occurring after CABG surgery.[4-6] These changes can hold patients who have undergone a CABG in a high thrombotic condition.[3,5] Other platelet indices such as platelet distribution width (PDW) and plateletcrit (PCT), which reflect platelet morphology, are important in vascular events and thrombosis.[7] Among these indices, MPV is known as a marker of platelet function in which the increased

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MPV is related to high risk of CVD such as stroke and ischemic attacks.[8]

The cardiac rehabilitation program has an important role in survival and reduction of disability among CAD patients so that a regular training has a big share in the recovery of patients who have undergone CABG.[9-11] Different types of training including traditional moderate intensity continuous training (MICT) and modern high-intensity interval training (HIIT) have been proposed for these patients. HIIT involves intermittent short bouts of high-intensity exercise with recovery periods or light exercise.[12] HIIT method has some main determinant variables such as intensity, duration, number of intervals, and work to rest ratio.[12] Both training methods have shown beneficial effects on health-related variables. However, some studies carried out among population of patients have shown that HIIT leads to the improvement in peak oxygen consumption (VO_2peak), cardiac and muscular function compared to continuous training.[13,14] Conversely, several lines of evidence indicate that an acute exercise can elevate the risk of main vascular thrombotic events and transiently increase the incidence of primary cardiac arrest.[15,16] The incidence of cardiovascular complications during the acute exercise is substantially greater among individuals afflicted with CVDs than in healthy adults.[16] Changes in platelet indices and function following an acute exercise, regardless of the exercise types, have been shown in previous investigations.[17,18] A number of studies demonstrated that moderate intensity continuous exercise (MICE) is safer than high-intensity interval exercise (HIIE) due to causing less shear stress and minimal thrombotic risk.[16,19] Contrarily, some reports have shown that HIIE is safer than MICE with intermittent periods of ischemia.[20,21]

Currently, limited and conflicting data are available about the type of exercise (MICE vs. HIIE) safety following CABG as a cardiac rehabilitation. Moreover, it is very important that patients undergoing CABG must have a cardiac rehabilitation with a minimum thrombotic risk in order to minimize the probability of ischemic events. Therefore, the main purpose in this study was to investigate the effects of a single bout of MICE and two types of HIIE on platelet indices and function in patients who have undergone CABG, in addition, comparison of the platelet parameters among patients was made to seek for the safest exercise method for the commencement of rehabilitation after CABG.

Materials and Methods

In this study, patients were recruited from cardiovascular rehabilitation department of Baqiyatallah hospital, Iran, in January-March 2016. Initially, 110 men with a history of CABG, who had at least 6 weeks passed from their surgery, were enrolled by a responsible supervisor and the researchers in the rehabilitation center. Patients were included after initial assessments, then randomly assigned into three groups of MCIE (n = 12), HIIE-1 (n = 11), or HIIE-2 (n = 11). The randomization code was developed using a computer random number generator, by another person from different unit at the hospital to ensure blinding. However, some of subjects refused to attend the test for various reasons, and the number of patients in each group reached 10 (Figure 1). The inclusion criteria for the post-CABG patients in this study were passing six weeks after the surgery and taking similar kind and dose of platelet inhibitor medications. Moreover, patients with a history of diabetes mellitus (DM) and orthopedic and neurologic limitations were excluded from the study. It is noteworthy that all qualified patients signed the informed consent form after the study process was explained to them. The present study protocols were approved by the ethics committee of Baqiyatallah University of Medical Sciences (IR.BMSU.REC.1394.41) and were conducted according to the Declaration of Helsinki (DoH).

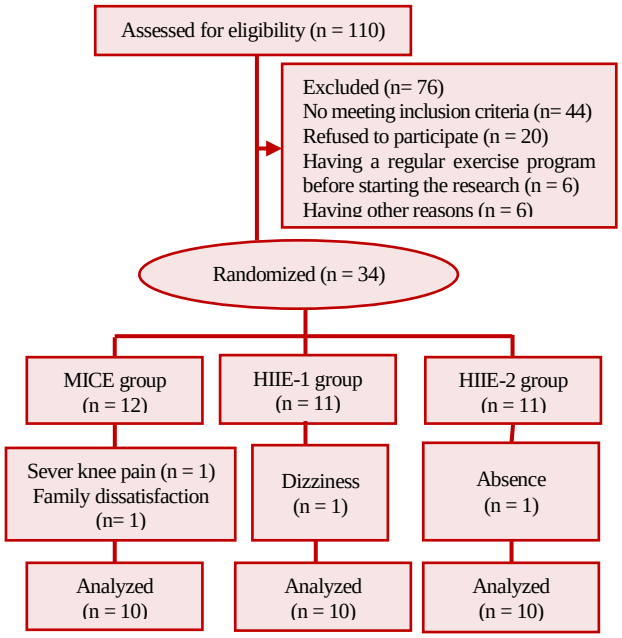

Figure 1. Flow chart of the participants throughout the study

MICE: Moderate intensity continuous exercise; HIIE: High-intensity interval exercise

Table 1. Baseline anthropometric and clinical characteristics of patients in three groups

	MICE (n = 10)	HIIE-1 (n = 10)	HIIE-2 (n = 10)	P
Anthropometric variables (mean ± SD)				
Age (years)	53.90 ± 3.45	53.70 ± 3.40	54.10 ± 4.01	0.970
Height (cm)	176.80 ± 4.02	175.60 ± 4.43	177.00 ± 4.90	0.752
Weight (kg)	82.73 ± 4.86	80.63 ± 5.36	83.47 ± 6.14	0.494
BMI (kg/m^2)	26.50 ± 1.89	26.14 ± 1.41	26.61 ± 1.13	0.771
Medications (No. of subjects) (%)				
Anti-platelets	7 (70)	5 (50)	7 (70)	0.563
β-blockers	5 (50)	5 (50)	4 (40)	0.875
Diuretics	3 (30)	5 (50)	3 (30)	0.563
ACE-inhibitors	2 (20)	4 (40)	5 (50)	0.326
Statins	5 (50)	4 (40)	4 (40)	0.873

SD: Standard deviation; MICE: Moderate intensity continuous exercise; HIIE: High-intensity interval exercise; BMI: Body mass index; Baseline levels of anthropometric and clinical variables examined by one-way ANOVA and chi-square, respectively. There were no any differences between baseline levels.

All participants were asked to present in the rehabilitation center in two separate sessions. In the first session, anthropometric variables including height, weight, and body mass index (BMI) were measured (Seca, Germany) and clinical characteristics (medications) were registered by a specialized physician (Table 1). In addition, participants got familiar with procedures. Moreover, modified Bruce protocol was used to determine the maximal heart rate (HR_{max}) in this session. For this purpose, the test was completed after appearance of exhaustion symptoms such as achieving 90% of HR_{max} by age, Perceived Exertion (Borg Rating of Perceived Exertion Scale) between 18-20, dyspnea, and signs of cardiac ischemia. Average heart rate in the final 30 s of the test was calculated as a HR_{max} for each subject. In the second session that was held after one week from the first session, MICE, HIIE-1, and HIIE-2 groups performed their protocols in the morning between 09:00 and 11:00 AM. All patients were advised to avoid intense physical activities 48 hours before the sessions. Before and immediately after exercise protocols, blood samples (10 ml) were taken from antecubital vein. It should be noted that to minimize risk of exercise, all protocols were performed under the supervision of the researchers and a cardiologist. Moreover, patients were requested to report any problems and complications, such as chest pain and breathlessness during exercise.

All participants were referred to laboratory after having a light breakfast. Baseline blood samples (10 ml) were taken, after initial preparation and 20 minutes of resting in sitting condition. A Polar S810 heart rate (HR) monitor was connected to patients' chest for measuring beat-to-beat HR during each exercise protocol. Before starting the protocols, a 5-minute period was considered for warm-up, which included walking or running with 40% of HR_{max} and stretching movements.

In this study, MICE was included 40 minutes of running on a treadmill (Technogym, Italy) with 65% of HR_{max}. Patients in HIIE-1 group performed an interval protocol with work to rest ratio of 1:1, including 10 repetitions of 2-minute running at 95% of HR_{max} and 2-minute active recovery at 35% of HR_{max}. Moreover, patients in HIIE-2 group completed an interval protocol with work to rest ratio of 2:1, including 7 repetitions of 4-minute running at 85% of HR_{max} and 2-minute active recovery at 45% of HR_{max}. Immediately after the completion of the protocols, second blood sample (10 ml) was taken from subjects. It should be noted that, the mean intensity of all protocols were similar to each other and were fixed at 65% of HR_{max}. Furthermore, HIIE-1 and HIIE-2 were considered pursuant to exercise prescription guidelines for coronary artery patients.[22]

10 ml of venous blood sample was prepared before and immediately after all protocols. 4 ml of blood sample was transferred into Ethylenediaminetetraacetic acid (EDTA) tubes for biochemical measurements. Platelet indices (PLT, MPV, PDW, and PCT) and other biochemical variables such as hematocrit (HCT) and hemoglobin (Hb) were assessed by cell counter system (Sysmex, XE-2100L, Japan). Then, in order for determining the plasma fibrinogen, EDTA tubes were centrifuged (3000 RPM, 5 minutes, 22 °C) and measured by Enzyme-linked immunosorbent assay (ELISA) methods (Stago, France).

Other portion of the sample was transferred into

tubes containing sodium citrate (100 mM) for evaluation of platelet aggregation. These tubes were immediately centrifuged at 180 g for 20 minutes at 23 °C for preparation of platelet rich plasma (PRP). Then, the PRP was separated carefully and remaining content of the tubes was centrifuged (2000 g, 15 minutes, 23 °C) for obtaining platelet poor plasma (PPP). The platelet number in PRP sample were counted and when the counts has exceeded 275 × 10^3 ml, the PRP samples were diluted by certain amount of PPP. Finally, light transmission aggregometry (APACT 4004, LABiTec, Germany) was used to determine platelet aggregation using PRP and PPP. Platelet aggregation was determined by adding 5 µM ADP (5 mM) to PRP samples at 37 °C for 5 minutes and expressed as maximal percentage.

In addition, the changes in plasma volume (ΔPV) from baseline was calculated using the Dill and Costill Formula,[23] as follows: $\Delta PV\ (\%) = 100 \times [(Hb_{pre} / Hb_{post}) \times (100 - HCT_{post}) / (100 - HCT_{pre}) - 1]$. Where, HCT is in % and Hb in g/dl.

All statistical analyses were performed using the SPSS software (version 20, IBM Corporation, Armonk, NY, USA) and the results were expressed by mean ± standard deviation (SD). The Shapiro-Wilk test was used for determining normality of data. Moreover, chi-square was used for analyzing of medications in patients. One-way analysis of variance (ANOVA) was employed to compare the baseline levels of all variables and ΔPV in three groups. To compare the changes in all research variables in three groups (MICE, HIIE-1, and HIIE-2), the differences between values before and after exercise in each groups were calculated and compared by using the independent one-way ANOVA. Moreover, when the homogeneity of variances was equal or not equal, Bonferroni and Games-Howell tests were used as a post-hoc to determine differences between groups, respectively. The level of significance in all statistical analyses was set at $P < 0.050$.

Results

The study flow chart is shown in figure 1. Briefly, 110 patients were registered and investigated in a three-month period. These patients were screened for inclusion and exclusion criteria and 76 patients were excluded. The commonest reason for exclusion from initial screening was failure to meet inclusion criteria (~ 58%). After that, the remaining 34 patients were randomly divided into three groups. However, 4 patients were excluded after randomization to 3 groups (Figure 1). The baseline characteristics of patients were examined with one-way ANOVA and chi-square test. There were no differences between baseline levels in three groups in major variables ($P > 0.050$) and medications ($P > 0.050$) (Tables 1 and 2).

Platelet indices, HCT, and fibrinogen are shown in table 2. The results of platelet indices showed that PLT, PCT, and PDW increased after all of exercise protocols (MICE, HIIE-1, and HIIE-2). However, a significant difference was found among three groups only for PLT ($P = 0.001$). PLT reduced 3.95%, 6.80%, and 6.60% after MICE, HIIE-1, and HIIE-2, respectively. Given the inequality of homogeneity of variances, Games-Howell test as a post-hoc showed that PLT increases were more significant following HIIE-1 ($P = 0.004$) and HIIE-2 ($P = 0.004$) compared to MICE.

Table 2. Values [mean ± standard deviation (SD)] of platelet indices and other variables in response to different types of exercise

Variables	MICE		HIIE-1		HIIE-2		P for baseline level	P for changes between groups
	Before	After	Before	After	Before	After		
PLT (×10^3/µl)	217.60 ± 23.25	226.20 ± 22.82*	216.30 ± 21.81	231.00 ± 22.26*#	218.10 ± 20.81	232.50 ± 20.01*#	0.982	0.030
PCT (%)	0.20 ± 0.01	0.22 ± 0.02*	0.20 ± 0.02	0.24 ± 0.02*	0.21 ± 0.02	0.24 ± 0.02*	0.627	0.280
MPV (fl)	8.96 ± 0.61	8.97 ± 0.50	8.77 ± 0.44	8.88 ± 0.38	8.71 ± 0.37	8.79 ± 0.33	0.497	0.554
PDW (fl)	11.53 ± 1.68	11.65 ± 1.60	11.71 ± 1.79	11.93 ± 1.69	11.94 ± 1.96	12.08 ± 1.78	0.880	0.762
HCT (%)	41.82 ± 2.73	46.65 ± 2.78*	43.48 ± 1.95	48.51 ± 2.06*#	42.21 ± 2.52	48.17 ± 3.28*#	0.512	0.001
Fibrinogen (mg/dl)	312.80 ± 14.76	316.70 ± 13.58*	311.70 ± 14.03	320.50 ± 14.47*	307.50 ± 12.83	317.20 ± 13.15*#	0.671	0.048

MICE: Moderate intensity continuous exercise; HIIE: High-intensity interval exercise; PLT: Although platelet count; PCT: plateletcrit; MPV: Mean platelet volume; PDW: Platelet distribution width; HCT: Hematocrit

* Indicates within group significant ($P < 0.050$) changes; # Significant differences between interval groups compared with MICE

Differences between before and after exercise values analyzed with one-way ANOVA and post-hoc test (Bonferroni or Games-Howell).

Despite a slight increase in MPV following exercise protocols, these changes were not significant among the three groups (P = 0.550). Statistical analysis through one-way ANOVA revealed that increases of fibrinogen after MICE (1.25%), HIIE-1 (2.82%), and HIIE-2 (3.15%) were significant among the groups (P = 0.048). Using Bonferroni test as a post-hoc, a significant difference was found between fibrinogen changes in HIIE-2 and MICE (P < 0.050), but not HIIE-1. Moreover, HCT increased after MICE (4.80%), HIIE-1 (5.03%), and HIIE-2 (5.96%). Statistical analyses with one-way ANOVA revealed that HCT changes were significant among the groups (P < 0.001). Based on the Bonferroni test, there was no difference between HCT changes following HIIE-1 and HIIE-2; however, HCT after HIIE-1 (P = 0.026) and HIIE-2 (P < 0.001) protocols more significantly increased compared to MICE (Table 2).

Platelet aggregation results showed an increase after MICE (8.76%), HIIE-1 (11.55%), and HIIE-2 (12.77%). Statistical investigation indicated that platelet aggregation changes were significant among three groups (P = 0.030) (Figure 2). Post-hoc test (Bonferroni) revealed that platelet aggregation changes following HIIE-2 were greater than MICE (P = 0.034), but there was no difference among other groups (P > 0.050). In employed patients with a CABG history, ΔPV reduced 8.97%, 12.85%, and 13.90% after MICE, HIIE-1, and HIIE-2, respectively.

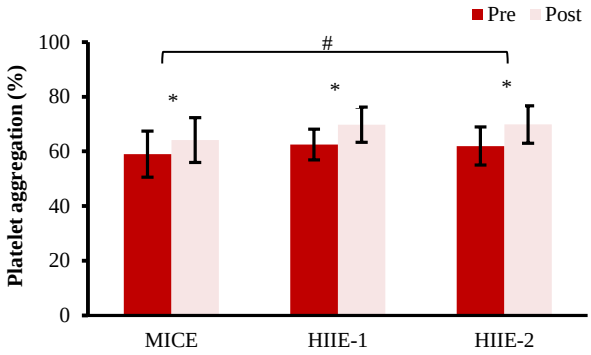

Figure 2. Values [mean ± standard deviation (SD)] of platelet aggregation before and after exercise. * Indicates within group significant (P < 0.050) changes, and significant differences between interval groups compared with MICE (P < 0.050) are denoted by #
MICE: Moderate intensity continuous exercise; HIIE: High-intensity interval exercise

In this case, a significant difference was found among the three groups (P < 0.001), where Bonferroni test as a post-hoc analysis showed significant differences between MICE group and HIIE-1 (P = 0.001) and HIIE-2 (P < 0.001) groups (Figure 3).

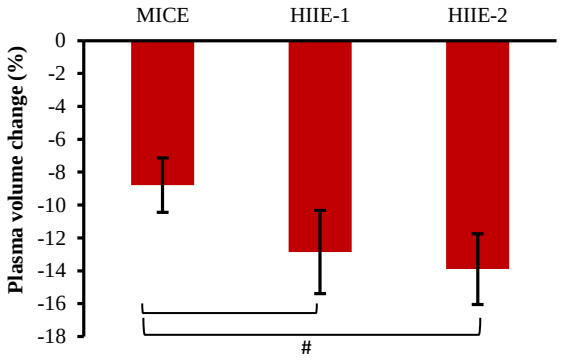

Figure 3. Values [mean ± standard deviation (SD)] of plasma volume changes after exercise. # Indicates significant differences between HIIE-1 and HIIE-2 groups compared with MICE (P < 0.010).
MICE: Moderate intensity continuous exercise; HIIE: High-intensity interval exercise

Discussion

The results indicated that PLT increased after MICE (3.95%), HIIE-1 (6.80%), and HIIE-2 (6.60%). The increase in PLT was significantly higher in HIIE-1 and HIIE-2 in comparison to MICE. The other platelet indices such as PDW, MPV, and PCT revealed that their increases were higher in HIIE-1 and HIIE-2 compared with MICE, however discrepancies in their changes were not statistically significant among the three groups. Previous studies have shown an increase in PLT following the exercise.[16,24]

Increase in PLT after an acute exercise can be attributed to release of the platelets from spleen, bone marrow, and lung vascular beds.[24] Additionally, increase in PLT can be partially associated with exercise-induced hemoconcentration.[19] Fresh platelets in circulation are larger in size and metabolically more active.[3] Since no significant change was observed in platelet size (MPV), the increase in PLT might be correlated with exercise-induced hemoconcentration instead of releasing fresh platelet from the organelles. Moreover, a significant increase in PLT after HIIE-1 and HIIE-2 in comparison to MICE can be attributed to the exercise intensity. In this regard, Wang et al. suggested that the increase in PLT after an acute exercise organelles was related to the exercise severity.[25] Furthermore, there was no significant change in the other platelet indices as it could be related to the exercise duration. In this regard, Whittaker et al. indicated that 60 minutes of

activity can alter the platelet indices,[26] however in this study, the duration was about 40 minutes in all bouts. It was also shown that the decrease in the plasma volume of patients was involved in the present study. Findings indicated that ΔPV was reduced after all protocols, but the reduction was significantly greater in HIIE-1 (-12.85%) and HIIE-2 (-13.90%) as compared to MICE (-8.79%). In addition, the increase in HCT was concomitant with the decrease in plasma volume after all types of exercises. The elevation in HCT after HIIE-1 (11.57%) and HIIE-2 (14.12%) was more pronounced when compared to MICE (8.94%). These findings are in agreement with the results of previous studies reporting the decrease in ΔPV and increase in HCT following an acute exercise.[27-29] The decrease in ΔPV following the exercise could be attributed to the increase in the blood pressure.[30] During the exercise, the blood pressure increased with the increase in the intensity.[31] The increase in blood pressure during the exercise can cause the loss of fluid from the vascular system to the interstitial space and entrapment of water into muscle cells.[32] A further decrease in ΔPV after HIIE-1 and HIIE-2 in comparison to MICE can be attributed to the intermittent activity at a higher intensity resulting in higher metabolic and physiological pressures.

Although the regular exercise training has been shown to improve the platelet function,[16,24] an acute exercise may result in the increase in the platelet reactivity and thus promoting thrombus formation.[19,26,33] In this study, it was shown that the increase in ADP-induced platelet aggregation was higher after HIIE-1 (11.55%) and HIIE-2 (12.77%) compared with MICE (8.73%), but statistical significance ($P < 0.050$) was only observed between HIIE-2 and MICE groups. There are conflicting data about the platelet responses during an acute exercise. For example, it has been shown that mean intensity exercise increases the platelet aggregation following the exercise,[19] whereas contradictory studies reported a reduction in platelet aggregation,[25] or even no change.[34] The findings in the present study are in line with those indicating that the platelet function increased following an acute exercise which was related to the intensity.[19,35] Exercise-induced platelet aggregation might pertain to some underlying mechanisms such as the increased shear stress which is due to enhancement in blood flow during the exercise,[36] increased catecholamines concentration (especially norepinephrine), and activation of α_2-adrenergic receptor on platelets,[37,38] and increased oxidative stress.[26] Furthermore, increased platelet function after the exercise has been previously attributed to the activation of Glycoprotein IIb/IIIa (GPIIb/IIIa) receptor and its agonist (fibrinogen).[33]

Fibrinogen is one of the important risk factors for the platelet aggregation. The findings of the current study revealed that the levels of fibrinogen were higher in HIIE-1 (2.82%) and HIIE-2 (3.15%) groups compared to MICE (1.25%), as the levels of fibrinogen were significantly higher in HIIE-2 in comparison to MICE.

The obtained results indicated that fibrinogen was directly associated with the platelet aggregation, ΔPV, and HCT, suggesting that the exercise-induced hemoconcentration may be involved in this phenomenon.[29] Excessive stimulation of platelet aggregation in HIIE groups compared to MICE may be owing to the bouts of exercise intensity and duration. Correspondingly, it has been shown that circulatory catecholamines are increased in the exercise intensity and duration.[39] Therefore, the differences between HIIE-2 and MICE groups may stem from performing more activity at high intensity. However, some studies showed that acute exercises with various intensities lead to the different effects on oxidative stress and shear rate.[40] Hence, it would be plausible that the higher rate of platelet aggregation in HIIE-2 group come from a longer duration of high-intensity activity and a lower duration of active recovery, which can expose that group to further increase in oxidative stress and shear rate.

However, this study had several limitations. Because of inclusion and exclusion criteria, sample size was small. Use of small sample needs great changes for statistical significance. Although 110 patients enrolled in rehabilitation department, most of them were not interested to engage in the study. Moreover, the researchers in the present study were only able to use men patients. Therefore, the effects of these exercise protocols remains unclear on women.

Conclusion

It seems that in spite of increasing the platelet function in all exercise protocols, HIIE protocols have shown remarkable thrombotic stress as compared to MICE. Therefore, it can be concluded that utilization of MICE should be carefully recommended to reduce the occurrence of acute ischemic and thrombotic events during rehabilitation program in patients undergoing CABG. However, further research is needed to

determine the gold standard protocol for patients who underwent CABG.

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Conflict of Interests

Authors have no conflict of interests.

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