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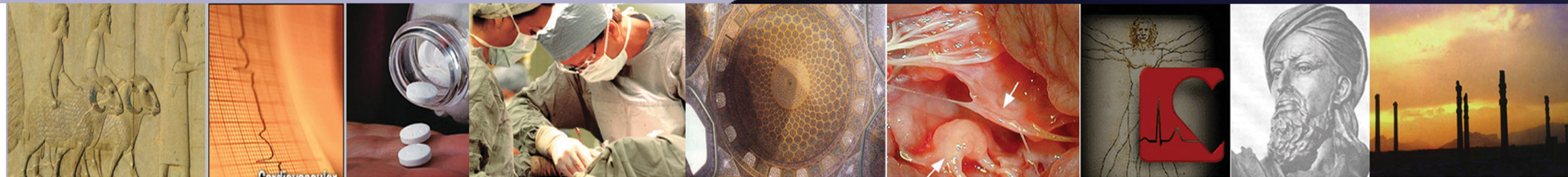

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* All the words of the article containing the references; each table is considered as 300 words.

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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

Vahid Sobhani(1), Mahmoudreza Taghizadeh(2), Maryam Moshkani-Farahani(3)

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

Date of submission: 25 Apr. 2018, ***Date of acceptance:*** 23 July 2018

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).

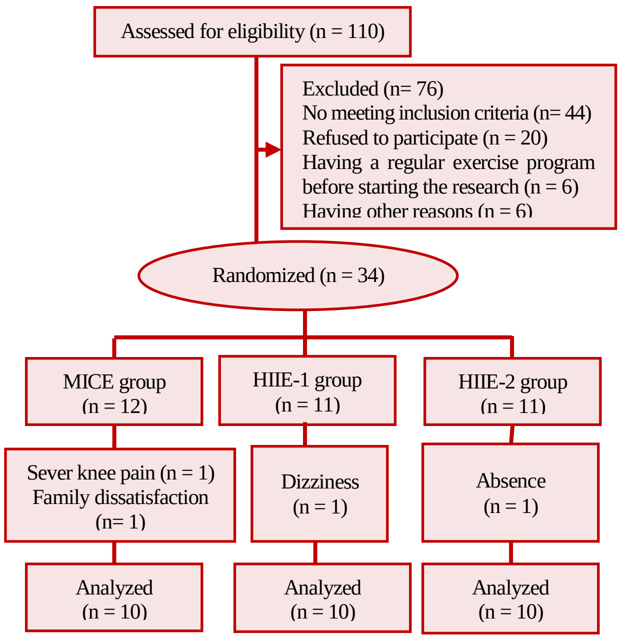

Figure 1. Flow chart of the participants throughout the study

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 ($\times 10^3/\mu l$)	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.

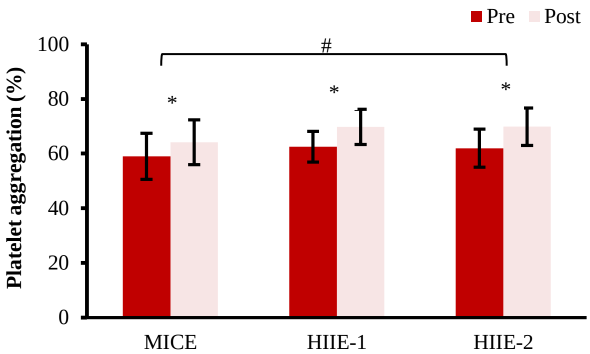

Figure 2. Values [mean ± standard deviation (SD)] of platelet aggregation before and after exercise. * Indicates within group significant (P < 0.050) changes, and significant differences between interval groups compared with MICE (P < 0.050) are denoted by #

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).

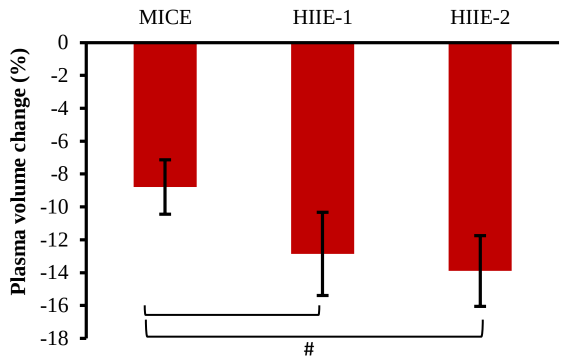

Figure 3. Values [mean ± standard deviation (SD)] of plasma volume changes after exercise. # Indicates significant differences between HIIE-1 and HIIE-2 groups compared with MICE (P < 0.010).

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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Patient competence in relation with medical and psychosocial characteristics in cardiology context: A cross-sectional study

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Original Article

Abstract

BACKGROUND: Growth of cardiovascular disease (CVD), variation in provision of medical services, rising costs, and increasing information availability through the media are making patients more actively involved in decision-making process of their treatment. The aim of this study was to better understand the components of patient competence in the context of coronary artery disease (CAD) and to further evaluate their relations with medical, demographic, and psychosocial characteristics.

METHODS: In this cross-sectional study, 148 patients with at least one year diagnosis of acute coronary syndrome (ACS) were enrolled in the study from April to June 2014. Data on demographic characteristics, depression, anxiety, quality of life (QOL), social support, and drug adherence were collected from participants. Pearson correlation, one way analysis of variance (ANOVA), and multiple linear regression tests were performed for analyzing data.

RESULTS: The mean age of patients was 53.63 ± 5.15. Of the participants, 58 (39.5%) and 61 cases (41.5%) were found to be depressed and anxious, respectively. Higher levels of self-regulation correlated with higher education years and social support, and also with lower depression and anxiety ($P < 0.050$). Stress management and confronting the threat were linked to education years, depression, anxiety, QOL, and social support ($P < 0.050$).

CONCLUSION: The patients with CAD, in order to be involved in the proper treatment process and manage their emotions during this process, need to have the required competencies. Patient competence as a whole and its components have been related to medical, demographic, and psychosocial characteristics.

Keywords: Patient Competence, Decision-Making, Characteristics, Cardiology

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Introduction

Chronic diseases, because of their nature, have a high burden and extreme impact on patients and their families in everyday life.[1] Beside the effective treatments for chronic diseases, patients' knowledge as well as their abilities in making decisions and encountering challenges can markedly influence the treatment process.[2,3] Moreover, in the treatment of chronic diseases, patients appear to be true partners to the medical team in the treatment process.[4]

Chronic diseases, especially cardiac diseases, are a matter of great concern due to their high prevalence, mortality, and morbidity in both the developed and developing countries.[5] The demise of "single best treatment", growth of cardiovascular disease (CVD), variation in provision of medical services, rising costs, and increasing information availability through the media are making patients more actively involved in decision-making process of their treatment.[6] Involving patients in treatment decisions creates new challenges for both the patients and physicians and requires special skills. In order to reach this goal, patients need sufficient abilities to control their emotions, understand the

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nature of treatment, search for information, confront the related threats, concentrate on and solve illness problems, find out the consequences of accepting or refusing a treatment, and understand the likely benefits and risks of each given option.[7] In addition, they should be able to solve the arising tasks in the context of their illness and related treatments. These abilities are known as "patient competence" that consists of cognitive, behavioral, and emotional components.[8] Based on some studies, the patient competence is influenced by many demographic and social factors and the severity of illness.[9,10]

The combination of disease severity and the level of education can lead to increased intention to start therapy.[11] Patients with limited education level or minimal experience in the medical setting may not entirely understand all the alternatives to or all the major risks of a proposed treatment.[12] Therefore, patient education may offer further information as well as technical and problem-solving skills.[13]

Patients with depression can experience low energy levels, feelings of worthlessness or guilt, and difficulty in thinking and concentrating or making decisions.[14] Due to these psychosocial characteristics, patients cannot be competent to make proper decisions and deal with stress properly in disease situations.

Quality of life (QOL) is an important patient-centered outcome and predictor of mortality in cardiac disease.[15,16] There is some evidence showing that patients who have a better control on their will report a better health-related QOL following treatment, compared with those with less control on their decisions.[3] Accordingly, patients with high QOL are those who can take care of themselves having an effective decision-making skill and sufficient competency to their disease.

Appropriate knowledge about a disease leads to better self-care, adherence, and realization of disease. Adherence is the degree to which a particular treatment has been followed. Effective delivery of the treatment requires both adherence and competence, but it is not possible to have the competent delivery of a specific treatment without adherence to that treatment. Thus, although adherence does not guarantee competence, it is a necessary factor for competence.[17]

In this study, we attempted to get a better understanding of the components of cardiac patient competence (CPC) and their relations with medical, demographic, and psychosocial characteristics in the context of coronary artery disease (CAD).

Materials and Methods

A cross-sectional design was used to investigate patient competence in patients with CAD who referred to Isfahan Cardiovascular Research Institute, Isfahan, Iran, from April to June 2014. 148 patients were enrolled in the study. They had been diagnosed with acute coronary syndrome (ACS) for at least one year. ACS was defined as acute myocardial infarction (AMI) and unstable angina (UA) based on the World Health Organization (WHO) expert committee, and was confirmed by a cardiologist through typical chest pain and dynamic electrocardiography (ECG) changes.[18-20] The inclusion criteria were: being in the range of 30-60 years of age, having no evidence of pregnancy or being in post-partum period in the past 3 months, no past history of diabetes mellitus, cardiac arrhythmias, cardiac pacemaker implantation, or heart failure. The study was approved by the Institutional Review Board (IRB) and Ethical Committee of Isfahan University of Medical Sciences (grant number: 191177), and an informed written consent was obtained from each participant. Data collection was administrated by a trained interviewer through the face-to-face interview method. For this purpose, the interviewer had been trained well, so that she was familiar with the process of filling out the questionnaires in a uniform way and also with the proper steps of interviewing to avoid some common biases.

Demographic characteristics such as age, sex, marital status, and education level were collected from participants. Lifestyle status such as smoking status (at least 1 cigarette per day), adequate physical activity (half an hour per day) as well as disease status such as disease duration, number of hospitalization, number of general practitioner and cardiologist visit, and ejection fraction of patients were recorded. CPC questionnaire is a 63-item scale with eight domains (search for information, self-regulation, being assertive, independent decision-making, looking for social services, stress management, confronting the threat, and avoidance) that is rated on a five-point Likert scale with scores ranging from 1 (not true at all) to 5 (completely true). For each domain, individual scores were calculated by summing across all items defining a domain and then dividing by the respective number of items. Validity and reliability of this questionnaire were examined in Roohafza et al. study.[8]

Hospital Anxiety and Depression Scale (HADS) was used to assess patients' depression and anxiety level. It consists of fourteen items (7 items for anxiety and 7 items for depression) with scores ranging from 0 to 21 for either depression or anxiety. In both parts, scores > 7 indicate that participants are likely to be depressed or suffer from anxiety. Cronbach's alpha coefficient (to test reliability) has been found to be 0.78 for the HADS anxiety sub-scale and 0.86 for the HADS depression sub-scale. Validity showed satisfactory results as well.[21,22]

Self-administered EQ-5D instrument[23] was used for detecting the contributors' QOL. Mobility, self-care, usual activity, pain/discomfort, and anxiety/depression were evaluated by this instrument. Three distinct levels of severity were presented for each domain as 1 (no problems), 2 (some problems), and 3 (extreme problems). Global QOL score of participants was defined by the sum of dimensions' scores. Higher EQ-5D scores indicated poor QOL. The second part of the scale is a Visual Analogue Scale (EQ-VAS) that allows respondents to score their current health status from 0 to 100. Saffari et al. showed cronbach's alpha of 0.83 and 0.78 for the EQ-5D and EQ-VAS, respectively.[24]

Social support was assessed by the Multidimensional Scale of Perceived Social Support (MSPSS).[25] This scale is intended to measure the extent to which an individual perceives social support from three sources including significant others (SO) (items 1, 2, 5, and 10), family (items 3, 4, 8, and 11), and friends (items 6, 7, 9, and 12). The MSPSS is rated on a five-point Likert-type scale with scores ranging from 1 (very strongly disagree) to 5 (very strongly agree). A higher score indicates increased levels of perceived social support (PSS). Cronbach's alpha coefficient was 0.84 in the Farsi version of the MSPSS for the whole scale, and for friend, SO, and family subscales was 0.90, 0.93, and 0.85, respectively.[26]

Drug Adherence Questionnaire (DAQ)[27] is a structured four-item self-reported adherence measurement that has dichotomous response categories with yes or no. The failure to adhere to a medication regimen could occur because of several factors such as problems with taking medications on time: "Do you sometimes have problems remembering to take your medication?", "Do you sometimes forget to take your medication?", and problems with the complexity of the medical regimen: "Do you ever feel hassled about sticking to your treatment plan?". The questions are phrased to avoid the "yes-saying" bias by moving backward the wording of the questions about the way patients might practice failure in following their prescription regimen. Each item measures a specific medication-taking behavior and not a element of adherence behavior. Individuals who scored in the high adherence range had a significantly better treatment outcome.

Data were illustrated as mean ± standard deviation (SD) for continuous variables and frequencies and percentages for categorical variables. Pearson correlation test was used for assessing the relations between CPC dimensions and psychological characteristics, social support, drug adherence, rehospitalization, and demographic data. Association between CPC dimensions and different subgroups including sociodemographics, depression, anxiety, and adherence were analyzed using independent t-test. To determine variables potentially predicting CPC dimensions, multiple linear regressions were performed. Each of CPC dimensions was considered as a dependent variable. Data were analyzed using the SPSS software (version 15, SPSS Inc., Chicago, IL, USA). All tests were two-sided. Statistical significance was defined as $P < 0.050$.

Results

148 cardiac patients were enrolled in the study. The mean age of patients was 53.63 ± 5.15 years. About 79 cases (53.4%) were men and 123 cases (83.1%) were married. The mean of education years was 7.18 ± 5.71 years. Among all participants, 58 (39.5%) and 61 cases (41.5%) were depressed and anxious, respectively. Other clinical and psychological characteristics and dimensions of CPC are shown in table 1. As illustrated in table 2, some dimensions of CPC significantly correlated with demographic, clinical, and psychological characteristics. Higher levels of self-regulation associated with higher education years and social support, and also with lower depression, anxiety, and QOL scores.

Findings of qualitative data in table 3 showed that depression was associated with search for information, self-regulation, stress management, and confronting the threat. Anxiety was related to self-regulation and stress management. Additionally, adherence to treatment was associated with looking for social services. Relations among scores of CPC dimensions and demographic, clinical, and psychological variables are detailed in table 3.

Table 1. Basic, clinical, and psychological characteristics and dimensions of cardiac patient competence (CPC)

Variables	Range	n = 148
Age (year) (mean ± SD)	30-60	53.63 ± 5.15
Educational years	0-18	7.18 ± 5.71
Duration of disease (year) (mean ± SD)	1-37	10.42 ± 7.96
Hospitalization (mean ± SD)	0-5	0.43 ± 0.88
Visit to general practitioner (mean ± SD)	2-50	8.12 ± 5.99
Visit to cardiologist (mean ± SD)	1-15	3.54 ± 2.14
Ejection fraction (mean ± SD)	15-65	51.73 ± 10.79
Depression score (mean ± SD)	0-21	7.01 ± 4.67
Anxiety score (mean ± SD)	0-21	6.95 ± 4.93
Quality of life score (mean ± SD)	5-15	7.74 ± 2.30
Walking score (mean ± SD)	1-3	1.55 ± 0.53
Self-care score (mean ± SD)	1-3	1.27 ± 0.57
Daily activity score(mean ± SD)	1-3	1.43 ± 0.61
Pain score (mean ± SD)	1-3	1.77 ± 0.70
Anxiety/depression score (mean ± SD)	1-3	1.72 ± 0.71
Total social support score (mean ± SD)	12-60	43.49 ± 11.13
Family social support score (mean ± SD)	4-20	17.01 ± 3.94
Friend social support score (mean ± SD)	4-20	10.61 ± 5.75
Other social support score (mean ± SD)	4-20	15.96 ± 4.34
Search for information (mean ± SD)	11-55	29.01 ± 9.95
Self-regulation (mean ± SD)	14-70	54.14 ± 8.25
Being assertive (mean ± SD)	7-35	20.49 ± 4.93
Independent decision-making (mean ± SD)	7-35	18.84 ± 5.47
Looking for social services (mean ± SD)	2-10	6.09 ± 2.35
Stress management (mean ± SD)	10-50	37.52 ± 8.80
Confronting the threat (mean ± SD)	6-30	22.54 ± 4.74
Avoidance (mean ± SD)	6-30	18.07 ± 4.22
Smoking (current smoker) [n (%)]	-	10 (7.0)
Sex (male) [n (%)]	-	79 (53.4)
Marriage (married) [n (%)]	-	123 (83.1)
Adherence to treatment (low and moderate) [n (%)]	-	67 (45.3)
Depression [n (%)]	-	58 (39.5)
Adequate physical activity [n (%)]	-	57 (40.4)
Anxiety [n (%)]	-	61 (41.5)

SD: Standard deviation

No links between the CPC dimensions and adequate physical activity, duration of disease, and visit of cardiologist were identified. Self-regulation, stress management, and confronting the threat were related to depression and anxiety.

Table 2. Correlations between dimensions of cardiac patient competence (CPC) and demographic, clinical, and psychological characteristics

Variables	Problem-focused task					Emotion-focused task		
	Search for information	Self-regulation	Being assertive	Independent decision-making	Looking for social services	Stress management	Confronting the threat	Avoidance
Age	-0.291**	-0.017	-0.123	-0.120	0.051	0.082	0.022	-0.110
Education years	0.513**	0.220**	0.279**	0.392**	0.153	0.029	0.204*	0.048
Duration of disease	-0.002	-0.003	-0.007	-0.020	-0.105	0.017	0.018	0.019
Hospitalization	0.041	-0.044	-0.224**	-0.042	0.003	-0.200*	-0.089	0.096
Visit to general practitioner	-0.084	0.008	0.064	-0.077	-0.044	0.251**	-0.025	-0.026
Visit to cardiologist	-0.017	0.095	0.058	-0.028	-0.072	-0.081	-0.059	0.082
Ejection fraction	0.180*	-0.043	0.027	0.215**	-0.153	0.184*	-0.102	-0.160
Depression score	-0.174*	-0.296**	-0.049	-0.111	-0.203*	-0.515**	-0.225**	0.019
Anxiety score	0.072	-0.227**	0.053	-0.105	-0.074	-0.630**	-0.215**	0.181*
Quality of life score	-0.169*	-0.176*	-0.054	-0.097	-0.091	-0.397**	-0.211*	-0.015
Total social support score	0.241**	0.543**	0.036	0.279**	0.053	0.335**	0.234**	-0.119

* P < 0.050; ** P < 0.010

Table 3. Association between scores of cardiac patient competence (CPC) dimensions and demographic, clinical, and psychological characteristics

Variables		Problem-focused task					Emotion-focused task		
		Search for information	Self-regulation	Being assertive	Independent decision-making	Looking for social services	Stress management	Confronting the threat	Avoidance
Sex	Male	31.24 ± 10.38	55.01 ± 8.13	20.81 ± 4.80	20.13 ± 5.20	6.59 ± 2.21	39.82 ± 7.54	23.10 ± 4.20	17.77 ± 4.36
	Female	26.53 ± 8.87	53.15 ± 8.32	20.12 ± 5.09	17.35 ± 5.42	5.52 ± 2.39	34.89 ± 9.44	21.89 ± 5.26	18.43 ± 4.05
	P	0.004	0.170	0.390	0.002	0.005	0.001	0.130	0.350
Marital status	Married	29.57 ± 10.11	54.73 ± 7.95	22.32 ± 4.67	18.88 ± 5.29	6.09 ± 2.41	38.22 ± 8.16	22.74 ± 4.59	18.29 ± 4.13
	Single	26.36 ± 8.82	51.17 ± 9.19	20.11 ± 4.92	18.64 ± 6.34	6.08 ± 2.10	34.17 ± 10.99	21.54 ± 5.46	17.04 ± 4.55
	P	0.140	0.053	0.040	0.840	0.970	0.040	0.260	0.180
Adequate physical activity	Yes	31.14 ± 10.37	54.87 ± 7.99	20.55 ± 4.85	19.42 ± 5.76	6.32 ± 2.33	38.38 ± 8.82	23.05 ± 4.36	18.85 ± 4.12
	No	26.40 ± 9.07	53.12 ± 8.30	20.61 ± 4.94	18.04 ± 5.06	5.67 ± 2.36	36.00 ± 8.65	21.30 ± 5.12	17.50 ± 4.33
	P	0.006	0.220	0.940	0.150	0.110	0.130	0.030	0.140
Current smoker	Yes	30.22 ± 11.34	51.60 ± 7.04	22.00 ± 4.39	20.30 ± 4.71	6.40 ± 2.59	36.44 ± 9.86	22.51 ± 4.79	16.20 ± 5.09
	No	29.05 ± 10.02	54.38 ± 8.18	20.41 ± 4.92	18.74 ± 5.55	6.03 ± 2.34	37.51 ± 8.72	20.67 ± 4.36	18.27 ± 4.13
	P	0.740	0.290	0.320	0.390	0.630	0.730	0.260	0.140
Adherence to treatment	High	28.27 ± 9.71	53.60 ± 8.82	20.83 ± 4.83	18.75 ± 5.40	6.40 ± 2.16	37.89 ± 8.88	22.90 ± 4.28	18.41 ± 3.94
	Moderate	29.90 ± 10.48	54.90 ± 7.19	20.09 ± 5.22	19.25 ± 5.62	6.07 ± 2.44	34.12 ± 8.86	22.16 ± 5.24	17.51 ± 4.65
	Low	30.23 ± 9.61	54.50 ± 8.62	19.92 ± 4.59	17.69 ± 5.42	4.35 ± 2.46	36.76 ± 8.64	21.78 ± 5.45	18.14 ± 4.16
	P	0.590	0.680	0.640	0.650	0.010	0.850	0.590	0.480
Depression	Yes	26.91 ± 9.83	51.26 ± 8.94	40.31 ± 5.40	18.14 ± 5.40	5.91 ± 2.58	31.96 ± 9.30	21.24 ± 5.17	18.64 ± 4.27
	No	30.44 ± 9.85	55.94 ± 7.23	30.65 ± 4.63	49.30 ± 5.51	6.17 ± 2.18	40.96 ± 6.33	23.35 ± 4.27	17.76 ± 4.15
	P	0.038	0.001	0.690	0.210	0.500	< 0.001	0.009	0.220
Anxiety	Yes	28.81 ± 10.34	52.23 ± 8.91	20.90 ± 5.33	18.47 ± 5.30	5.73 ± 2.52	32.83 ± 8.97	21.84 ± 5.19	18.73 ± 4.34
	No	29.27 ± 9.51	55.58 ± 7.48	20.17 ± 4.66	19.34 ± 5.68	6.39 ± 2.16	40.17 ± 6.90	23.16 ± 4.19	17.68 ± 4.07
	P	0.790	0.010	0.380	0.340	0.090	< 0.001	0.090	0.140

Table 4. Predictive factors for cardiac patient competence (CPC) dimensions: multivariate analysis (age and sex-adjusted)

Variables		Problem-focused task					Emotion-focused task		
		Search for information	Self-regulation	Being assertive	Independent decision-making	Looking for social services	Stress management	Confronting the threat	Avoidance
Marriage	β	-0.017	0.243	0.265	-0.115	0.081	-0.110	-0.056	-0.144
	P	0.850	0.016	0.003	0.197	0.365	0.222	0.476	0.115
Education years	β	0.500	0.251	0.332	0.367	0.083	0.275	0.231	0.091
	P	< 0.001	0.017	0.001	< 0.001	0.414	0.001	0.027	0.385
Adequate physical activity	β	-0.117	-0.073	0.059	-0.027	-0.095	-0.085	-0.180	-0.145
	P	0.175	0.433	0.513	0.764	0.286	0.345	0.051	0.111
Smoking	β	0.014	-0.204	-0.090	-0.063	-0.022	-0.227	-0.223	0.156
	P	0.875	0.031	0.332	0.483	0.807	0.013	0.019	0.094
Duration of disease	β	0.092	0.021	0.020	0.044	0.072	0.084	0.044	0.019
	P	0.267	0.805	0.813	0.596	0.390	0.329	0.612	0.826
Hospitalization	β	0.095	-0.024	-0.215	0.006	0.043	-0.158	-0.068	0.089
	P	0.240	0.779	0.010	0.937	0.604	0.058	0.423	0.290
Visit to general practitioner	β	-0.048	0.028	0.076	-0.040	-0.008	0.217	0.007	0.039
	P	0.551	0.740	0.364	0.624	0.919	0.008	0.940	0.639
Visit to cardiologist	β	-0.025	0.094	0.057	-0.037	-0.080	-0.087	-0.064	0.085
	P	0.753	0.261	0.490	0.646	0.320	0.286	0.447	0.305
Ejection fraction	β	0.165	-0.024	0.030	0.183	-0.110	0.215	-0.080	-0.191
	P	0.031	0.780	0.724	0.009	0.181	0.030	0.347	0.052
Adherence to treatment	β	0.110	0.078	-0.071	-0.013	0.188	0.010	-0.069	-0.080
	P	0.169	0.358	0.393	0.861	0.020	0.903	0.419	0.339
Depression	β	-0.105	-0.314	0.029	0.001	-0.121	-0.486	0.212	-0.029
	P	0.242	0.001	0.756	0.996	0.189	< 0.001	0.025	0.762
Anxiety	β	0.131	-0.225	0.074	-0.223	0.026	-0.605	-0.204	0.150
	P	0.132	0.013	0.419	0.011	0.773	< 0.001	0.026	0.096
Quality of life score	β	-0.012	-0.166	0.000	0.071	0.028	-0.378	-0.212	-0.055
	P	0.899	0.095	> 0.999	0.464	0.774	< 0.001	0.032	0.576
Total social support score	β	0.175	0.563	0.012	0.220	0.012	0.280	0.223	-0.107
	P	0.035	< 0.001	0.888	0.009	0.887	0.001	0.011	0.217

Dimensions such as searching for information, self-regulation, independent decision-making, stress management, and confronting the threat were linked to social support. Results of predictive factors for CPC dimensions are summarized in table 4.

Discussion

As it has been observed, the competency helps patients arise their tasks on confronting the disease, making desirable decisions about the treatment process, and managing the effects of disease on everyday life. One notable point about patient competence is that the idea of active patient–physician interaction corresponds closely with the aims of patient empowerment[28] and self-management.[29] Thus, the patients are capable of managing symptoms, treatment, and the consequences of a disease condition. Furthermore, physicians can positively encourage this behavior.[30] Involving patients in treatment deciding and the perceptions of control over treatment decisions lead to health-related QOL. It was showed that patients who more actively used consultations to decide about the treatment would perceive more decision-control, which in turn leads to a better health-related QOL following treatment. Additionally, emotions as an intact part of a person's internal state, have profound influence on the choices one makes and the abilities one has.[31]

Based on what have been observed, some sociodemographic factors such as education and marriage were effective on CPC. We found it most plausible that education may protect against disease development by influencing lifestyle behaviors, problem-solving abilities, knowledge, and coping capabilities;[32] thus, it may enable the patients to live with the best possible QOL given their chronic conditions.[13] Accordingly, higher educational attainment brings about more tendencies to search information about the treatment process, self-regulation, assertiveness, independent decision-making, confronting the threat, and higher self-management. In contrast, patients with limited education or with minimal prior experience in the medical setting may not completely understand all the alternatives to or all the major risks of a proposed treatment.[12] Moreover, we have some evidence in hand suggesting that less-educated individuals may experience more severe stress and report greater distress and physical symptoms compared to higher-educated ones.[33]

As seen in some studies, social support can moderate negative effect of stressful conditions that cardiac patients might encounter during their disease and treatment process.[34] Moreover, individuals who perceive social support can modify the situations based on problem and emotion-focused coping strategies related to CAD.[35] Family members especially the patients' spouse could have positive effect on CAD self-care maintenance and management.[36] In addition, the provision of support by physicians has been linked to greater knowledge, life satisfaction, and perceived health as well as reduced anxiety and depression.[34] Therefore, visit to general practitioner would help patients manage and cope with the stress raised from the disease.

Depressed and anxious patients are incapable to manage their stress and cannot concentrate on and solve illness problems properly. There is some evidence suggesting that depression is associated with a decrease in exercise capacity and poor health perception in patients with CAD.[37,38] It has been observed that patients with CAD and concurrent depression were 2.5 times more likely to develop a functional disability than nondepressed ones.[38,39] Anxiety and depression can largely influence specific decision components. The everyday decisions made by individuals suffering from anxiety or depression disorders to avoid perceived threats are substantially affected, which in turn can have a great impact on their ability to function adaptively in the context of CAD.[40] Thus, anxious and depressed individuals cannot have an appropriate self-care and properly respond to the challenges they encounter during their cardiac disease. Depressed patients may underestimate the benefits of a treatment or overestimate its risks. Moreover, some patients with depression may even prefer a high-risk medical treatment and consider the potential risk as a desirable outcome and a tool to end their misery.[9] Additionally, anxiety increases the sensitivity to negative choice options, the likelihood that ambiguous options be construed negatively, and the tendency to avoid potentially negative options, even if the outcomes have great gains.[40] According to our results, cardiac patients who were anxious were more under stress and had problems in dealing with and making decisions about their illness.

We found that components of stress management and confronting the threat had negative relation with smoking. The devastating impact of smoking on heart disease is known to everybody.[41] Smokers report that smoking will relieve their negative moods when they are stressed out, angry, anxious, or sad.[42] Therefore, smokers use maladaptive coping strategy in dealing with stressful life situations and lack appropriate stress control skills. It has been extracted that stress control skills can be upgraded and promoted by proper cognitive behavioral approaches.[42,43]

Being under stress can alter the way the body behaves and can have negative effects on heart health. Accordingly, with a high-intensity cardiac disease, patients will need more information about their illness and the ways of coping with it. Recent evidence indicates that patients who adhere to treatment have better health outcomes than poorly adherent patients.[44] In this study, we found that being adherent to the treatment was associated with using social services. In fact, economic incentives and using of health insurance were effective in securing good medical adherence.[45]

One of the limitations of this study, that is important to be borne in mind, is that we investigated the relation of only some of the medical, demographic, and psychosocial characteristics with CPC, and it is imperative that the influence of other social and personality factors also be taken into account. Another limitation to consider is the cross-sectional design of the study.

Conclusion

The patients with CAD, in order to be involved in the proper treatment process and manage their emotions during this process, need to have the required competencies. Patient competence as a whole and its components such as seeking information, self-regulation, assertiveness, independent decision-making, stress management, and confronting the treat have been related to medical, demographic, and psychosocial characteristics.

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Conflict of Interests

Authors have no conflict of interests.

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Comparison of cardiovascular risk factors among coronary artery bypass graft patients in 2010 and 2016: A single-center study in Guilan province, Iran

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Original Article

Abstract

BACKGROUND: There has been a change in the risk factor profile of patients with coronary artery disease (CAD) in the western world. We sought to compare the risk factor profile of patients undergoing coronary artery bypass graft (CABG) surgery in northern part of Iran in 2010 and 2016.

METHODS: In a cross-sectional study, medical records of 296 CABG patients in 2010 and 500 patients in 2016 were collected from a referral university hospital in Guilan province, Iran. We compared the risk factor profile using chi-square test or independent t-test as needed in the two time points, 2010 and 2016.

RESULTS: The age of CABG patients significantly decreased from 62.49 ± 8.05 to 58.09 ± 9.20 over time. The frequency of hypertension (HTN) (66.2% vs. 59.1%, P = 0.045), diabetes mellitus (DM) (51.8% vs. 43.6%, P = 0.025), smoking (35.6% vs. 28.0%, P = 0.028), and patients with multimorbidity (31.8% vs. 26.7%, P = 0.001) increased in the second period compared to the first period of study. Whereas, the prevalence of hypercholesterolemia and positive family history of coronary heart disease (CHD) remained stable over time (49.6% vs. 49.0%, P = 0.870; 10.5% vs. 11.1%, P = 0.810, respectively).

CONCLUSION: We observed a dramatic increase in DM, HTN, and cigarette smoking as well as the multimorbidity prevalence in 2016 compared to 2010. Even with considering all study limitations, primary and secondary prevention program to decrease cardiovascular disease is required.

Keywords: Coronary Artery Bypass Grafting, Risk Factors, Diabetes Mellitus, Hypertension, Smoking

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Introduction

Cardiovascular disease (CVD) is known as an important leading global health burden.[1] The worldwide burden of disease has changed from communicable disease to non-communicable disease specially CVD.[2,3] The frequency of all causes of mortality related to non-communicable disease (NCD) increased approximately by 10% from 1990 to 2010 in Iran as a developing country.[4] CVDs including coronary artery disease (CAD), stroke, and vascular diseases are the important components of NCD burden in Iran like the rest of the world.[5] According to the World Health Organization (WHO), by 2050, Iran will encounter an aging population problem.[6] Recent evidence estimated that the burden of CVD will increase by 2025 due to aging phenomenon among Iranian population.[6] As a result of increased frequency of metabolic risk factors like unhealthy diet, low physical activity, and smoking[7] as well as aging population, CVD has become an important health problem in Iran. The Global Burden of Disease Study 2013 (GBD 2013) showed that total disability-adjusted life years (DALYs) related to diabetes increased by more than 100% from 1990 to 2013 in the eastern Mediterranean region.[8] Interestingly, findings of the

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Caspian III Study points to the considerable prevalence of cardiometabolic risk factors such as body mass index (BMI), triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and fasting blood sugar (FBS) even in Iranian adolescents.[9] On the other hand, older population suffer from coexistence of more than one disease in the same person, defined as multimorbidity.[10] Previous studies mentioned the effect of coexistence of more than one disease in the same person known as multimorbidity on acceleration of disability and mortality[11] as well as higher cost of care.[12] Prevalence of multimorbidity in a large Iranian population was substantial[13] and was similar to Canadian population.[14] Every year, many coronary artery bypass graft (CABG) surgeries are conducted in Guilan province, Iran. Accordingly, we sought to compare the frequency of cardiovascular risk factors and number of multimorbidity among CABG patients in 2010 and 2016.

Materials and Methods

This was a cross-sectional study based on data records of a university referral hospital in Guilan province, the northern part of Iran. The medical records of 296 patients undergoing isolated CABG in 2009-2010 and 500 patients in 2015-2016 were included by convenience sampling method. All data collection was retrospectively conducted at the end of 2016. Any record of cardiac surgery for valvular disease, concomitant operations, those undergoing re-operative CABG, and incomplete medical data were excluded from the study.

Demographic data and medical history were derived by reviewing hospital records. A standardized checklist was completed by a trained research assistant to collect cardiovascular risk factors for each patient. Data on the diagnosis of diabetes mellitus (DM), hypertension (HTN), hypercholesterolemia, smoking, and family history of CAD were extracted from patients' history taken by cardiology residents in both phases of the study. Serum factors like FBS, TC, HDL, low-density lipoprotein (LDL), and TG related to the first day of admission for each patient were included in the study. Multimorbidity was defined as the presence of two or more chronic conditions in one patient. We categorized multimorbidity into four groups based on simultaneous presence of CAD plus other morbidity such as DM, HTN, and hypercholesterolemia including 1) CAD without any other disease, 2) CAD plus one chronic condition, 3) CAD plus two chronic conditions, and 4) CAD plus three chronic conditions.

Design and protocol of the study was approved and funded by Vice-Chancellor for Research of Guilan University of Medical Sciences and Cardiovascular Disease Research Center (research number: IR.GUMS.REC.1394.282). Informed consent was not feasible because of retrospective data gathering. But researchers ensured that all medical records were used only for medical research.

Data analyses were conducted using SPSS software (version 16, SPSS Inc., Chicago, IL, USA). Categorical variables and continues variables were described as frequencies (percentages) and mean ± standard deviation (SD), respectively. To compare the frequency of DM, HTN, hypercholesterolemia, smoking, male sex, and family history of CAD between two periods of study, we used chi-square test. Independent t-test was used to compare the mean of continuous factors like age and serum factors. Univariate analysis of covariance (ANCOVA) was conducted to examine the effect of age on the serum laboratory factors. All tests were two-sided and $P < 0.050$ was considered statistically significant.

Results

The baseline characteristics and frequency of risk factors are reported in table 1. A total of 296 patients with CABG in first period (2009-2010) and 500 patients in second period (2015-2016) were included in the present study. Several patients were excluded in the first period of study due to incomplete data records ($n = 12$), repeated CABG ($n = 18$), and other cardiac surgery ($n = 28$). In the second period, 24 patients were excluded for other cardiac surgery and 17 patients for repeated surgery.

As shown in table 1, the number of patients undergoing CABG in second period increased from 296 surgery to 500 surgery. There was a significant decrease in the mean age of CABG patients (58.09 ± 9.20 vs. 62.49 ± 8.05, $P = 0.010$). The frequency of patients in various age groups were significantly different ($P = 0.001$), as the rate of CABG among patients aged 50 and younger increased from 5.4% in the first period to 16.4% in the second period. Although the number of female patients in the second period (34.8%) was greater than that in the first period (32.4%), there was no significant difference between two points of study ($P = 0.400$).

Table 1. Prevalence of cardiovascular risk factors in two periods of study

Variables	2009-2010 (n = 296)	2015-2016 (n = 500)	P*
Age (year) (mean ± SD)	62.35 ± 8.07	60.88 ± 9.10	0.024#
BMI (kg/m^2) (mean ± SD)	27.70 ± 4.20	28.10 ± 4.30	0.310#
Age category (year) [n (%)]			< 0.001*
< 50	16 (5.4)	73 (14.6)	
50-70	238 (80.4)	359 (71.8)	
> 70	42 (14.2)	68 (13.6)	
Sex (male) [n (%)]	200 (67.6)	326 (65.2)	0.400*
Smoking [n (%)]	83 (28.0)	178 (35.6)	0.028*
Diabetes [n (%)]	129 (43.6)	259 (51.8)	0.025*
Hypertension [n (%)]	175 (59.1)	331 (66.2)	0.045*
Hypercholesterolemia [n (%)]	145 (49.0)	233 (49.6)	0.870*
Family history of CHD [n (%)]	31 (10.5)	55 (11.1)	0.810*
BMI categories (kg/m^2) [n (%)]			0.320*
Underweight/Normal (< 24.9)	16 (5.4)	23 (4.6)	
Overweight (25-29.9)	261 (88.2)	456 (91.2)	
Obese > 30	19 (6.4)	21 (4.2)	
Comorbidity number [n (%)]			< 0.001*
0	75 (25.3)	31 (6.2)	
1	72 (24.3)	155 (31.0)	
2	70 (23.6)	155 (31.0)	
3	79 (26.7)	159 (31.8)	

* Chi-square test; # Independent t-test

SD: Standard deviation; CHD: Coronary heart disease; BMI: Body mass index

The percentage of HTN (66.2% vs. 59.1%, P = 0.045), DM (51.8% vs. 43.6%, P = 0.025), and smoking (35.6% vs. 28.0%, P = 0.028) were significantly higher in the second period of the study compared to the first period. Whereas, the prevalence of hypercholesterolemia and patients with family history of coronary heart disease (CHD) did not significantly changed over time (49.6% vs. 49.0%, P = 0.870; 11.1% vs. 10.5%, P = 0.810, respectively). Furthermore, there was no significant increase in the mean of BMI between two study periods (P = 0.310). As shown in table 1, the number of patients with multimorbidity increased in 2016 compared to 2010 (P = 0.001). The frequency of patients with two simultaneous diseases was 31% in second period, while approximately 23.6% of patients in first period had two chronic diseases. In addition, a dramatic decrease was observed in patients with only one chronic disease during study period.

In table 2, the serum level of laboratory data including FBS, LDL, TC, HDL, and TG significantly increased from 2009-2010 to 2015-2016. A one-way ANCOVA was conducted to compare the serum level of laboratory data between two periods of study whilst adjusting for age. Levene's test and normality checks were carried out and the assumptions met. As shown in table 2, result of ANCOVA analysis indicated that only FBS [F (1, 9.8), P = 0.002], LDL [F (1, 21.2), P = 0.001], and HDL [F (1, 92.3), P < 0.001] significantly increased. After adjusting for age, there was no significant increase in TC in second period of the study [F (1, 2.09), P = 0.089].

Table 2. Comparison of mean fasting blood sugar (FBS) and lipids profile in two periods of study

Variables	2009-2010 Mean ± SD	2015-2016 Mean ± SD	P*	Df	F	P#
FBS (mg/dl)	115.30 ± 31.90	124.40 ± 41.90	0.002	1	9.8	0.002
Cholesterol (mg/dl)	152.30 ± 42.30	159.90 ± 46.70	0.027	1	2.9	0.089
LDL (mg/dl)	86.80 ± 15.20	93.99 ± 22.10	< 0.001	1	21.2	< 0.001
HDL (mg/dl)	33.60 ± 6.70	39.40 ± 8.70	< 0.001	1	92.3	< 0.001
TG (mg/dl)	153.88 ± 17.69	156.93 ± 17.68	0.024	1	3.3	0.060

* Independent t-test; # Adjusted for age using analysis of covariance (ANCOVA)

SD: Standard deviation; FBS: Fasting blood sugar; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; TG: Triglyceride; Df: Degree of freedom

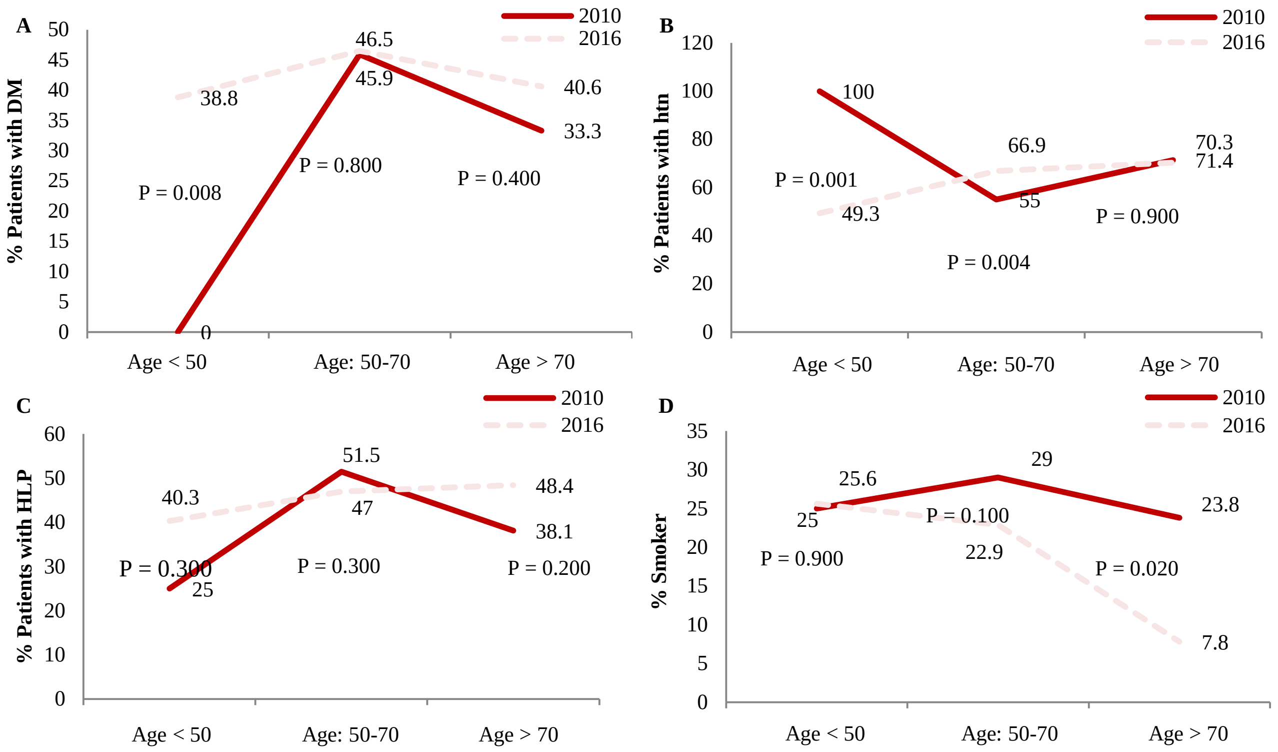

Figure 1. Differences in frequency of cardiovascular risk factors in two periods of study by age groups
A: Diabetes mellitus (DM), B: Hypertension (HTN), C: Hypercholesterolemia (HL), D: Smoking; P-value related chi-square test to compare the frequency of DM, HTN, hyperlipoproteinemia (HLP), and smoking between two periods of study by three age groups

The frequency of cardiovascular risk factors was illustrated in various age groups based on two periods of study in figure 1. Study population in both periods of study was divided into three age groups: age < 50 years, 50-70 years, and > 70 years. As shown in figure 1, the number of diabetic patients younger than 50 in second period were significantly higher compared to the first period (38.8% vs. 0, P = 0.008). However, there was no significant difference in the frequency of diabetic patients in those aged 50-70 years (45.9% in 2010 vs. 46.5% in 2016, P = 0.800). Although the rate of diabetic patients in second period in patients aged 70 and older were higher than first period of study, we could not detect a statistically significant difference (33.3% vs. 40.6%, P = 0.400). According to figure 1, the frequency of HTN in patients younger than 50 as well as those aged 50-70 in second period of study significantly increased compared to the first period (P = 0.001, P = 0.004, respectively). However, there was no significant increase in the frequency of HTN in patients older than 70 years (P = 0.900).

About hypercholesterolemia, no significant changes were observed in various age groups during the study periods (25.0% in 2010 vs. 40.3% in 2016, P = 0.300 for age < 50; 51.5% vs. 47.0%, P = 0.200 for age 50-70; 38.1% vs. 48.4%, P = 0.200 for age > 70). The frequency of cigarette smoking in patients younger than 50 years old increased a little in 2016 compared to 2010, but there was no significant difference (25.0% in 2010 vs. 25.6% in 2016, P = 0.900). On the other hand, the frequency of smoking decreased among patients aged 50-70 years as well as those aged 70 and older (29.0% in 2010 vs. 22.9% in 2016, P = 0.100; 23.8% in 2010 vs. 7.8% in 2016, P = 0.020, respectively).

Discussion

This study showed a decrease in the age of CABG patients in the second period of study, so that 13% of patients in 2016 were younger than 50 years old compared to 4.2% in 2010. Moreover, prevalence of lifestyle-related risk factors such as DM and HTN increased in 2016 in comparison to 2010. Further, we showed that both DM and HTN in younger patients had tragic increment in 2016; as we had no diabetic patients in first period of study among patients younger than 50 years old. Consistent with our study, Poddar et al. showed an increase in the prevalence of HTN and DM in younger patients undergoing revascularization during two periods of the study.[15] Two recent studies reported an increase in BMI level, prevalence of DM, HTN, and hypercholesterolemia in patients undergoing CABG over time.[16,17] According to the study on prospective data gathered in Tehran heart center, Tehran, Iran, in 2005, prevalence of DM and HTN in CABG patients was 27% and 34%, respectively,[18] which were lower than our data in 2010 and also in 2016. Interestingly, the number of female patients in both periods of present study was greater than Mandegar et al.[18] study in 2005. Similarly, Lopez-de-Andres et al.[19] based on Spanish national hospital discharge data showed that CABG incidence rate increased from 2001 to 2011. And also, female proportion in non-diabetic patients who underwent CABG increased during the 11-year study period in Spain.[19]

National Health and Nutrition Examination Survey (NHANES) in the United States (US) reported no significant decreasing trend in cardiovascular risk factors in women younger than 60 years of age and men younger than 40 during 12-year period.[20] Another similar finding in an Iranian study was related to increase in metabolic syndrome trend over the 12 years.[21] Hence, we can expect the higher prevalence of cardiometabolic risk factors in patients with coronary disease.

In addition to increasing in DM and HTN prevalence, cigarette smoking was more common in second point of the present study, especially in younger patients. Aligned with our finding, Poddar et al.[15] in a clinic-based data registry on 1914 patients with CAD aged ≤ 45 years showed that there was no decrease in smoking prevalence. Our study showed that cigarette smoking in the second period was more common in younger patients, while in the first phase of the study older patients were more smokers. Nowadays, a new health problem known as waterpipe has become prevalent among young population in the middle east countries[22] and even western countries.[23] A recent report by Sibai et al.[24] showed that long-term use of waterpipe increased the risk of coronary stenosis.

Furthermore, parallel to previous studies, we observed an overall increase in the frequency of comorbidities among CABG patients.[25,26] Thorsteinsson et al. indicated that CABG was increasingly performed on patients with a higher number of comorbidities between 1996 and 2012 in Denmark.[25] Also, the increasing trend of comorbidities prevalence was reported in a population-based study on 94328 patients undergoing CABG from 1987 to 2006.[26] Rising number of multimorbidity in cardiac patients leads to more difficult medical care and more cost of care. Furthermore, cardiologists and other physicians as well as health care workers need new protocol to help better multimorbidity care.

An important finding of the present study was a remarkable increase in the total number of coronary artery bypass over time. However, some medical records in the first period were excluded for incomplete history and weak archives. Another probable explanation could be related to new reform in health care system in Iran to reduce patients' payments for medical costs. Many patients suffered from chest pain and dyspnea for several years, but heavy cost of health care services was an important barrier for referring to physician and following up. A cross-sectional study in a large province of Iran showed that patients' payments for cost of medical equipment in hospitalized patients decreased after implementation of health reform in 2015.[27] In addition, one more probable explanation can be related to increase in the number of general cardiologists and surgeons in the hospital. More cardiologists provide more facility for quick diagnostic assessments and then greater number of medical interventions like percutaneous coronary intervention (PCI) and CABG. However, previous studies mentioned the greater growth of PCI compared to CABG.[28,29] But no information on PCI in our hospital was collected in this study.

Present study involved some limitations: due to the retrospective design of the study, the accuracy of data depended on recorded history. To decrease this error, we assessed all history recorded by cardiology residents. However, all medical histories were self-report for lacking electronic data registry system which was related to family physicians system. Furthermore, we could not collect information about other important chronic diseases like chronic kidney disease and respiratory disease. In addition, during this period of time, indications for CABG and PCI were changed. However, in the present study, we just reviewed the information about CABG. On the other hand, a number of patients delayed treatment due to the high cost of surgery. Recent health system reform in Iran reduced the health care cost for people.[30] Hence, we observed a considerable increase in the number of cardiac surgery.

In spite of having several limitations, our findings have some strength points as well. Since majority of Guilan citizens receive cardiovascular services from one and only university hospital, our finding can be extended to a large part of northern area of Iran.

However, it is worth mentioning that as a result of low cost of health care services in university hospital, our results might be more related to rural and lower socioeconomic status individuals.

Conclusion

CABG rate had increasing frequency in second period compared to the first period, and also age of people undergoing CABG was declined in second period compared to the first period of the study. In addition, the frequency of the cardiovascular risk factors like DM, HTN, and cigarette smoking increased during study period. Moreover, this superiority was observed in younger patients. Further, the prevalence of patients with multimorbidity increased in 2016 compared to 2010. More number of patients with multimorbidity undergoing CABG leads to more difficult medical care and more costs of care.

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Conflict of Interests

Authors have no conflict of interests.

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QT interval and P wave dispersion in slow coronary flow phenomenon

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Original Article

Abstract

BACKGROUND: Slow coronary flow (SCF) phenomenon is an angiographic finding which is defined as slow contrast passage through coronary arteries which may predispose patients to serious cardiac complications such as fatal arrhythmias. P-wave and QT-interval dispersion are electrocardiographic findings which are related to atrial fibrillation and ventricular tachyarrhythmias. In the present study, the relation between SCF and presence of P-wave and QT-interval dispersion in electrocardiography has been evaluated.

METHODS: 47 patients with normal coronary arteries and SCF and 40 patients with normal coronary artery flow without SCF were enrolled in this case control study. Standard electrocardiogram (ECG) was analyzed for P-wave and QT-interval dispersion. SCF was identified in normal coronary vessels by use of Thrombolysis in Myocardial Infarction (TIMI) frame count (TFC) method (TFC > 27). Corrected TIMI frame count (CTFC) of coronary vessels as well as mean CTFC along with QT-interval and P-wave dispersion were compared between 2 groups. The study data were analyzed by SPSS software and P value less than 0.050 was considered to be significant.

RESULTS: QT-interval [76.17 (35.23) ms versus 39.25 (19.26) ms] and P-wave [39.74 (17.48) ms versus 19.50 (8.54) ms] dispersion were significantly higher among patients with SCF phenomenon (P < 0.050). In addition, there was a positive significant linear correlation between TFC and P-wave and QT-dispersion (r = 0.857, r = 0.861, respectively, P < 0.050).

CONCLUSION: According to the results, increasing TFC among patients with SCF will result in P wave and QT interval dispersion and therefore this finding can be considered as an indicative marker for cardiac events.

Keywords: Coronary Angiography, Electrocardiography, Cardiac Arrhythmias

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Introduction

Slow coronary flow (SCF) phenomenon was first described by Tambe et al. and was defined as slow velocity of dye in coronary arteries.[1] A recent study in Iran showed that approximately 2% of patients who are scheduled for coronary angiography have the characteristics of SCF phenomenon.[2] While exact pathophysiology of this phenomenon is not clearly understood, thrombogenesis and enhancement of inflammation status are two possible mechanisms.[3] This phenomenon is seen in some cardiac effects such as ST elevation myocardial infarction (MI) and arrhythmias.[4,5] While patients with vulnerable myocardium such as those with ischemic heart disease are more susceptible to developing arrhythmias, patients with patent arteries are even at risk.[6,7] Dispersion in QT interval and P wave are 2 electrocardiographic findings which can predict predisposing of individuals for developing fatal arrhythmia.[6,8,9] P wave dispersion (PWD) is considered as an electrocardiographic marker for prediction of idiopathic paroxysmal atrial fibrillation and even its recurrence.[10,11] In addition to PWD, QT interval dispersion is also related to increased ventricular arrhythmias, cardiac death, and total mortality.[9,12] The P wave and QT interval dispersion

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is an interesting area of research and there is not enough evidence available for evaluation of these electrocardiographic findings among patients undergoing SCF phenomenon. According to prevalence of arrhythmias in SCF and predicting role of electrocardiographic findings such as P wave and QT interval dispersion for arrhythmias, possible relation between SCF and P wave and QT interval dispersion will be evaluated in this case control study.

Materials and Methods

The present case control study received approval from the research and ethics committee of Mashhad University of Medical sciences, Mashhad, Iran, in July 2012 and registered as a thesis (Code:7171) in the degree of Doctor of Medicine. Two groups of patients who were referred to Imam Reza Hospital angiography unit of Mashhad City enrolled in this study and the study was performed from August 2012 to August 2013. 47 patients who had documented SCF and 40 patients who had normal coronary artery flow filled an informed contest. The SCF phenomenon was documented angiographically as normal or near normal coronary arteries with less than 40% stenosis and Thrombolysis in Myocardial Infarction (TIMI)-2 flow in at least one major coronary arteries despite specific provocative maneuvere.[13] According to individual matching protocol, some confounding factors were matched between both groups. Confounding factors were defined as age, sex, diabetes mellitus (DM), hypertension, smoking, and systolic and diastolic function of left and right ventricles. Patients with significant valvular heart disease were excluded from the study. The patients who were presented with stable angina and did not respond to therapy had undergone angiography by femoral method (with non-ionized contrast agent and without using nitroglycerine) under the impression of typical angina and had normal coronary arteries. Stable angina was defined as chest discomfort occurring predictably and reproducibly at a certain level of exertion and was relieved with rest or nitroglycerin.

All the angiographies were performed by two expert interventional cardiologists who were blinded to the clinical details of the study. SCF was identified in normal coronary vessels by use of TIMI frame count (TFC) method in at least one of the main coronary vessels. TFC value greater than 27 was considered as SCF.[14] While normal frames for left anterior descending artery (LAD) were 1.7 times more than mean value of right coronary artery (RCA) and left circumflex artery (LCX), the mean corrected TFC (CTFC) values were calculated as follow:

$$\text{CTFC mean} = 1/3\ (\text{LAD}/1.7 + \text{RCA} + \text{LCX})$$

Every patient underwent a resting 12 lead ECG recorded at a paper speed of 50 ms and voltage of 1 mV. QT dispersion (based on the difference between maximum and minimum QT) and P dispersion (based on the difference between maximum and minimum P wave duration) were calculated based on patient’s ECG.[7] All standard 12-lead ECGs for every patient were obtained in a quiet room after 15 minutes of adjustment in supine position with the same recorder. Wave measurements were conducted blindly by a trained cardiologist. Patients who had evidence of obstructive coronary artery disease (more than 20% stenosis of luminal area), coronary ectasia, myocardial bridging, major coronary spasm, atrial fibrillation, branch blocks, connective tissue disease, uncontrolled hypertension and systemic disease, were not included in the study groups.

Study data including TFC of the three main coronary arteries, maximum and minimum of QT and P wave duration in both groups were analyzed by SPSS software (version 20, IBM Corporation, Armonk, NY, USA). The Kolmogorov-Simonov (K-S) test was used in order for examination of the normality of data distribution. Categorical variables such as smoking, blood glucose, blood pressure, and lipid profile in both groups were analyzed by chi-square test. Continuous variables were presented as mean and standard deviation (SD), while categorical variables were presented as frequency and percentage. Moreover, variables with normal and without normal distribution were analyzed by t-test and Mann Whitney test, respectively. The correlation between variables was evaluated by Spearman's correlation coefficient. P-value less than 0.050 was considered as “statistically significant”.

Results

A total of 87 patients (47 patients in case group and 40 patients in control group) were participated in this study. Mean ± SD of age in normal and SCF groups were 53.78 ± 9.72 and 51.62 ± 7.35, respectively (P = 0.252). The age distribution in both groups was normal and groups were homogenous for gender based on K-S and chi-square tests. Smoking, having DM, hypertension, or hyperlipidemia were not significantly different between both groups (P = 0.640, P = 0.777, P = 0.990, and P = 0.990, respectively). Left ventricular systolic function in both groups was within normal range (55 to 65%). CTFC of 3 main coronary vessels are shown in table 1.

Table 1. Comparison of baseline characteristics of study groups

Variable	Case group (n = 47) Rate (%)	Control group (n = 40) Rate (%)	P
Smoking	14 (29.8)	10 (25.0)	0.640
DM	9 (19.1)	6 (15.0)	0.777
Hypertension	17 (36.2)	15 (37.5)	0.990
Hyperlipidemia	15 (31.9)	13 (32.5)	0.990

DM: Diabetes mellitus

Mann-Whitney test showed that QT interval and PWD, mean CTFC, and TFC in 3 coronary vessels were significantly different in both groups ($P < 0.001$) (Table 2). These variables were not normally distributed in groups based on the K-S test.

The mean CTFC and QT disturbance were significantly correlated in SCF group ($P < 0.001$, correlation coefficient: 0.857), which was absent in normal flow group ($P = 0.536$, correlation coefficient: -0.101) (Figure 1).

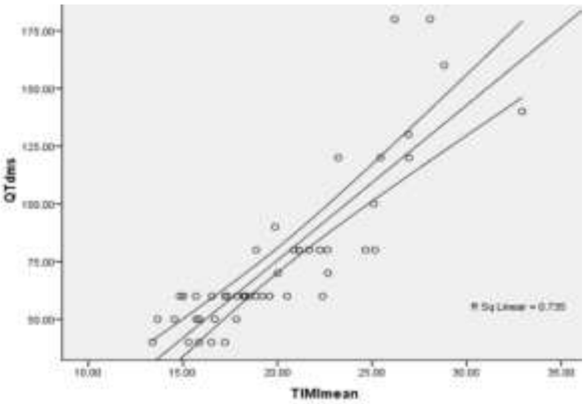

Figure 1. Corrected Thrombolysis in Myocardial Infarction (TIMI) frame count (TFC) mean and QT disturbance with a linear relation in slow coronary flow (SCF) group which was absent in normal flow group

The CTFC and PWD were significantly correlated in SCF group ($P < 0.001$, correlation coefficient: 0.861), which was absent in normal flow group ($P = 0.522$, correlation coefficient: -0.104) (Figure 2). The correlation between P wave and QT dispersion with CTFC in study groups are shown in table 3. These results indicated that QT interval and PWD significantly increased with increasing the CTFC among patients with SCF ($P < 0.001$).

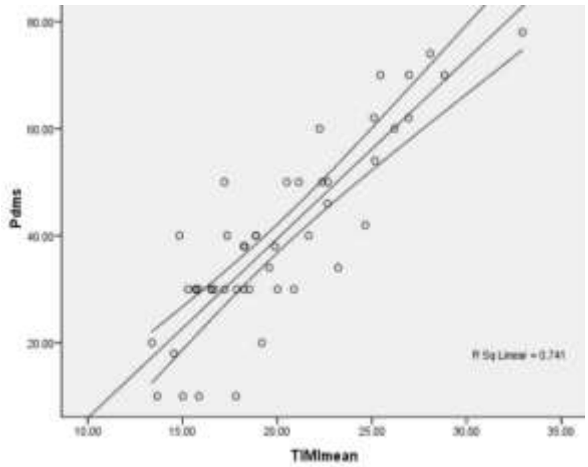

Figure 2. Corrected Thrombolysis in Myocardial Infarction (TIMI) frame count (TFC) mean and P wave disturbance with a linear relation in slow coronary flow (SCF) group which was absent in normal flow group

Discussion

The results of the present study showed that P wave and QT interval dispersion were electrocardiographic findings indicating good correlation with SCF phenomenon. Exact prevalence of SCF varied from 1 to approximately 6% in literature because of using different populations and study design.[2,13,15] While SCF is related to various clinical conditions such as ventricular dysfunction and acute coronary syndrome, serious arrhythmias are also considered to be a common finding in this phenomenon.[16,17]

Table 2. Mean of corrected TIMI frame count (CTFC) values in coronary vessels and dispersion of QT interval and P waves in study groups

	Case group (n = 47) (mean ± SD)	Control group (n = 470) (mean ± SD)	P*
CTFC (LAD)(30f/s)	29.48 ± 8.25	17.50 ± 2.48	< 0.001
CTFC (LCX) (30f/s)	21.89 ± 6.56	12.67 ± 2.50	< 0.001
CTFC (RCA) (30f/s)	21.04 ± 9.46	12.05 ± 2.57	< 0.001
CTFC mean (30f/s)	20.09 ± 4.49	11.68 ± 1.16	< 0.001
QT interval dispersion (ms)	76.17 ± 35.23	39.25 ± 19.26	< 0.001
PWD (ms)	39.74 ± 17.48	19.50 ± 8.54	< 0.001

SD: Standard deviation; CTFC: Corrected TIMI frame count; PWD: P wave dispersion; LAD: Left anterior descending artery; CTFC: Corrected TIMI frame count; LCX: Left circumflex artery; RCA: Right coronary artery
* The Mann-Whitney test was used for the comparison.

Table 3. Correlation of P wave and QT segment dispersion in case and control groups

ECG parameter	Involved vessel	Case group (n = 47)		Control group (n = 40)	
		P	Correlation coefficient *	P	Correlation coefficient*
QT dispersion	LAD	< 0.001	0.489	0.319	0.162
	LCX	< 0.001	0.668	0.846	-0.032
	RCA	< 0.001	0.508	0.220	-0.198
P dispersion	LAD	< 0.001	0.444	0.935	-0.013
	LCX	< 0.001	0.556	0.869	-0.027
	RCA	< 0.001	0.613	0.277	-0.176

ECG: electrocardiogram; LAD: Left Anterior Descending artery; LCX: Left circumflex artery; RCA: Right coronary artery
* Spearman's correlation coefficient

P wave and QT interval dispersion are 2 major electrocardiographic findings which are associated with serious arrhythmias. QT interval dispersion indicates ventricular electrical instability and variable ventricular repolarization.[6] PWD is also a marker for atrial remodeling and is considered to be related to paroxysmal atrial fibrillation.[18] Among arrhythmias, ventricular arrhythmias are reported to be associated with SCF.[19] P wave and QT interval dispersion can be seen with SCF. Similar to the results of the present study, Mahmoud with smaller study population had found that SCF phenomenon was associated with dispersion of P wave and QT interval.[20] Unlike the current study, Mahmoud had evaluated urea and creatinine levels and had found that SCF was related to increase of these values.[20] Mahfouz et al. with larger sample size has also approved that QT interval and PWD were associated with SCF.[21] According to these similar studies from different countries, a significant relation between SCF and certain electrocardiographic findings can be concluded. However, there are some clinical conditions with significant impact on electrocardiographic findings, especially QT interval dispersion. As an example, there are some environmental causes for QT dispersion such as smoking. Akbarzadeh et al. reported that even smoking a single cigarette among nonsmokers will increase QT dispersion.[22] Moreover, a meta-analysis study had shown that anxiety in clinically healthy patients would affect QT interval dispersion and predispose patients to develop arrhythmias.[23] According to these wide range of cofounding results on measuring QT interval dispersion, conducting a study to cover healthy individuals with SCF and without confounders for P wave or QT interval dispersion seems difficult but necessary.

The other concern was the factors influencing developing SCF phenomenon and the unknown underlying etiology. Given the present results, smoking, hypertension, and DM were not related to SCF phenomenon. Unlike this study, Ramakrishnan et al. reported that dyslipidemia, smoking, and hypertension were significantly associated with SCF and recommended endothelial dysfunction as a significant contributor in SCF phenomenon.[24] Similarly, in a study by Sanati et al., it was concluded that low level of high hyperalphalipoproteinemia (HDL-c) and hypertension were independent predictors of SCF phenomenon.[2] Some authors have evaluated the relation of more parameters and SCF phenomenon. Naing et al. reported uric acid level as an independent predictor of SCF phenomenon.[25] Hawkins et al. in a study reported obesity as an independent predictor of this phenomenon.[15]

Heterogeneous nature of this phenomenon might be the explanation of its association with different comorbidities.[15] As Sanati et al. suggested, a possible reason for different predictors in different studies could be an unknown confounder which is not addressed in any specific study.[2] Sezgin et al. reported that low coronary flow will increase QT dispersion and prolong QT interval duration and suggested that ventricular heterogeneity, autonomic neural tone changes or micro vascular ischemia may be responsible for QT dispersion.[6]

Limitations: Confounding factors such as autonomous disorders, electrolyte disturbances such as potassium, magnesium and calcium disturbances, congenital heart disease, anemia or chronic infections are believed to impact patient's electrocardiography. Although the cases in this study were matched and a study protocol was developed which included many of other confounding factors; however, due to various effective factors on electrocardiogram (ECG), considering an exact conclusion about the effect of SCF on P wave and QT interval is difficult.

Conclusion

The results of this study showed that QT interval and PWD were significantly related with SCF. Conducting further studies on healthy individuals with SCF phenomenon and without these mentioned confounders for electrocardiographic findings seems necessary.

Acknowledgments

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Conflict of Interests

Authors have no conflict of interests.

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Dill-normalized liver lipid accumulation, oxidative stress, and low-density lipoprotein receptor levels in high cholesterol fed hamsters

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Original Article

Abstract

BACKGROUND: High lipid accumulation in hepatocyte and blood vessels can lead to non-alcoholic fatty liver disease (NAFLD) and heart diseases, respectively. These disorders are the main reasons of mortality in various countries. In this experiment, we evaluated the effect of leaf extracts of Anethum graveolens (AG), also known as Dill, and AG tablet on expression of low-density lipoprotein receptor (LDLR) and liver lipid in hypercholesterolemic hamsters.

METHODS: In this experimental study, 36 male golden hamsters were divided into 6 groups: 1) standard diet + 0.5% cholic acid + 2% cholesterol [high cholesterol diet (HCD)], 2) HCD + 100 mg/kg hydroalcoholic extract of Dill, 3) HCD + 200 mg/kg hydroalcoholic extract of Dill, 4) HCD + 100 mg/kg Dill tablet, 5) HCD + 200 mg/kg Dill tablet, 6) chow. At the end of study (30^{th} day), hamsters were anesthetized and blood sample and liver tissue were collected. Biochemical factors and antioxidant parameters were determined. LDLR messenger ribonucleic acid (mRNA) level was measured using real time polymerase chain reaction (RT-PCR). Histopathological change of liver was determined using light microscope.

RESULTS: Compared to HCD group, blood lipids ($P < 0.0010$) and liver enzymes ($P < 0.0010$) markedly reduced in AG-treated groups. The expression of LDLR did not change significantly in animals which received low dose of hydroalcoholic extract or AG tablet, but it increased in animals receiving high dose of extract or tablet ($P < 0.0100$). Liver antioxidant significantly increased by AG ($P < 0.0010$). Liver histopathological changes were normalized by AG.

CONCLUSION: AG can significantly increase LDLR gene expression in HCD animals. This study showed that both AG extract and AG tablet had potential antioxidant and hypolipidemic effects in hamsters.

Keywords: Anethum Graveolens, Cholesterol, Hamsters, Herbal Medicine

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Introduction

In the recent years, heart diseases and alcoholic and non-alcoholic fatty liver disease (NAFLD) are known as the main causes of death in the world. In the recent decade, the prevalence of NAFLD strongly increased in various countries.[1] In these diseases, low antioxidant capacity and dyslipidemia criteria such as reduced amount of high-density lipoprotein cholesterol (HDL-C) and changes in low-density lipoprotein (LDL) particles can be observed. Many clinical trial studies have established a log-linear correlation between LDL-C levels and coronary artery disease (CAD) events. The recent evidence approves a plan of primary and potential lowering of blood lipid levels as the primary target for prevention and treatment of CAD.[2] On the other hand, accumulation of lipids in the liver leads to NAFLD. This disorder is directly accompanied by obesity, dyslipidemia, and hypertension, proposing the significant role of liver in metabolic disorders.[1]

It has been well documented that elevated deposition of LDL-C into blood vessel walls initiate and develop atherosclerotic plaque. Clearance of blood LDL-C particles is chiefly mediated by liver LDL receptor (LDLR), a main regulator of cholesterol metabolism. LDLR has a vital role in hepatic uptake and clearance of plasma cholesterol,

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and liver expresses about 80% of all LDLRs in the body.[2] With abnormal LDLR function or structure, plasma LDL-C level rises that can increase atherosclerosis risk.[1] Mutations in this gene, causing declined LDLR activity, are the chief reason for familial hypercholesterolemia (FH).[2] Hence, normalizing blood LDL-C levels via increase of LDLR expression by chemical drugs or herbal medicine may offer therapeutic advantages.[1]

Statins are used as the useful medications that inhibit cholesterol biosynthesis by suppression of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. However, statins have some adverse effects such as myopathy, myalgia, rhabdomyolysis, and myotoxicity.[3] In this respect, herbal medicine is suggested for management and treatment of many disorders, especially diabetes and dyslipidemia.[4-6]

Anethum graveolens L. (AG) is an annual plant which has been known to show hypolipidemic effects, and grows in Mediterranean region, Europe, and Asia.[7] In traditional medicine, AG has been applied for the handling of gastrointestinal disorder and used as an antifungal, antibacterial, antisecretory, and antispasmodic agent.[7] In the recent decade, the hypoglycemic properties of AG are approved by different studies.[8-10] Since AG has shown potential cholesterol lowering effects, it is prescribed for dyslipidemia in Iran as Anethum tablet. It contains AG (68%), Citrus aurantifolia (4%), Cichorium intybus (5%), and Fumaria parviflora (5%).[11] Although the hypolipidemic effect of AG has been revealed in different experiments, its mechanism remained unknown. On the other hand, the hepatoprotective effects of Dill during high-fat/high-cholesterol fed is not understood. Hence, the main purpose of this experiment was to evaluate the influence of Dill on the liver lipid accumulation and LDLR levels in hypercholesterolemic animals.

Materials and Methods

Fresh Dill was collected and identified by our colleague in the Department of Biology (School of Sciences, Bu-Ali Sina University, Hamadan, Iran), then dried at shadow, and coarsely powdered. A 100 g of dried powder was defatted with 500 ml water and ethanol (1:1) and incubated at room temperature for 72 hours. The obtained solution was filtered 3 times through Whatman (No.2) filter paper and evaporated under the vacuum at 40 °C (yield: 23%). Sample was stored in dark vials at -20 °C until use.[12] Anethum tablet was prepared from Iran Darouk Company, Tehran, Iran.

Male Syrian hamsters (130 ± 10 g) were obtained from Hamadan University of Medical Sciences, Hamadan City. They were maintained at standard situations with temperature at 24 ± 1 ºC, and 12-hour dark/light cycles were used throughout the study. After one week of adaptation, animals were divided into 6 groups of 6 hamsters and treated as follows: 1) standard diet + 2% cholesterol + 0.5% cholic acid [high-cholesterol diet (HCD)], 2) HCD + 100 mg/kg hydroalcoholic extract of Dill, 3) HCD + 200 mg/kg hydroalcoholic extract of Dill, 4) HCD + 100 mg/kg Dill tablet, 5) HCD + 200 mg/kg Dill tablet, 6) chow. Dill doses were selected based on previous reports.[13] Various studies selected these doses of various experiments.[14,15] The Desai and Patel conducted an experiment to determine the acute oral toxicity in animal model, and the results revealed that prescription of Dill at the dose of 1, 2, 3 and 5 g/kg did not show any mortality and behavior changes after 24 hours. They also showed that acute administration of these doses for about 1 month did not show any mortality and behavior changes.[16]

After one month, hamsters were anesthetized with diethyl ether after overnight fasting and then sacrificed. Blood was prepared from the heart of animals and liver tissue was removed and rapidly frozen with liquid nitrogen. All samples (n = 6) were blind for laboratory and pathologist. All the procedures of this experiment were permitted by Ethics Committee of Hamadan University of Medical Sciences. Exclusion criteria included old hamsters, unhealthy animals, and weighting more or less than 130 ± 10 g.

Total cholesterol (TC) and triglycerides (TG) of liver were determined according to a modified method of a previous published paper.[10] The liver tissue was homogenized and supernatant was used for determination of biochemical factors. For total antioxidant assay, 10 µl of butylated hydroxytoluene (BHT) (0.5 M in acetonitrile) was added to all samples to prevent oxidative reaction, and then total antioxidant capacity (TAC), superoxide dismutase (SOD), and malondialdehyde (MDA) were determined according to the formerly published paper.[17,18] Serum TAC, MDA, and SOD were also determined.

Quantitative real time-polymerase chain reaction (QRT-PCR) assay: Ribonucleic acid (RNA) was isolated from liver of each hamster (n = 6) using TrIzol (Invitrogen) according to manufacturer's instruction. The concentration and purity of RNA was evaluated by NanoDrop spectrophotometer and its integrity was determined by agarose gel electrophoresis. 1 μg of template was used for complementary deoxyribonucleic acid (cDNA) synthesis using QuantiTect Reverse Transcription Kit (Fermentas Life Sciences).[19] Determination of LDLR gene expression was done by RT-PCR. Primer was designed as follows: LDLR (F: 5'-CTC CAC TCT ATC TCC AGC ATT-3' and LDLR R: 5'-GAC AAG AGG TTT TCA GCCACC AAA -3') and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) (F: 5'-TGGCCTTCCTTCCTACG-3' and R: 5'-TAGCCCAGGATGCCCTTCAG-3') as internal control.

For histological examination, a small portion of each animal's liver (n = 6) was removed and fixed with 10% formalin. Sections were cut and stained with hematoxylin-eosin (H&E) and were photographed by light microscopy. Analysis was done by a pathologist who did not know the former information about the different groups.

All results were presented as mean ± standard error of the mean (SEM). Comparisons between the groups were performed by one-way analysis of variance (ANOVA) followed by Tukey test using SPSS software (version 20, IBM Corporation, Armonk, NY, USA). The P-values < 0.05 were regarded statistically significant.

Results

Liver's levels of TC and TG in HCD animals were higher compared with normal hamsters (P = 0.0005). Liver's TC amount markedly decreased in the animals treated by both doses of Anethum tablet (P = 0.0200 and P = 0.0080, respectively) and also in Anethum extract (200 mg/kg) receiving group (P = 0.0150) (Table 1).

Liver's levels of TG markedly decreased by Anethum tablet at both doses (P = 0.0340 and P = 0.0006, respectively) and Anethum extract at the dose of 200 mg/kg (P = 0.0060) (Table 1). The reduction of liver lipid was much more in 200 mg/kg Anethum tablet-treated animals in comparison to that of Anethum extract-receiving group (Table 1). Anethum extract and Anethum tablet markedly alleviated lipid profile and blood glucose in all treated groups compared with HCD animals (previously published data).

Serum total antioxidant levels of HCD animals were lower compared with normal hamsters (P = 0.0002). Hamsters treated by both doses of Anethum tablet and the 200 mg/kg Anethum extract receiving group (P = 0.0066) revealed potential rise in TAC levels compared to HCD group (Table 1). Liver total antioxidant levels of HCD animals were also lower compared with normal hamsters (P = 0.0001). Anethum-treated animals at the doses of 100 and 200 mg/kg (P = 0.0029 and P < 0.0001, respectively) and Anethum extract receiving group at the dose of 100 and 200 mg/kg (P = 0.0160 and P = 0.0081, respectively) exhibited significant rise in total antioxidant levels compared to those of HCD animals (Table 1).

The serum level of MDA significantly increased in HCD group compared to that of normal animals (P < 0.0001). Furthermore, treatment of animals with Anethum tablet at doses of 100 and 200 mg/kg (P = 0.0023 and P < 0.0001, respectively) and Anethum extract at the dose of 200 mg/kg (P = 0.0015) led to a significant reduction in MDA level. In the liver, the change in MDA level had almost the same pattern. However, the reduction in MDA when treated with 200 mg/kg Anethum tablet was more significant (P = 0.0047) compared with other groups (Table 1).

The serum SOD activity was markedly reduced in HCD animals (P = 0.0017). SOD is well recognized as the primary defense against free radicals. Treatment with Anethum tablet at doses of 100 and 200 mg/kg (P = 0.0300 and P < 0.0001, respectively) and Anethum extract at the dose of 200 mg/kg (P = 0.0032) caused notable rise in SOD levels in comparison with untreated animals (Table 1).

The activity of SOD in the liver also decreased in HCD animals compared with healthy hamsters (P = 0.0350). Treatment with Anethum extract and tablet caused significant increase in SOD levels in comparison with control animals (P = 0.0380 and P = 0.0410, respectively) (Table 1).

Figure 1 shows the fold change of LDLR in the hepatocyte of animals. Anethum extract or Anethum tablet-treated animals (200 mg/kg) showed rise in LDLR gene markedly, as compared with HCD or normal animals (P < 0.0001 and P < 0.0001, respectively), whereas the change by 100 mg/kg was not significant.

The liver sections of normal groups showed usual histological form. The liver destructive changes were revealed in HCD hamsters. In these animals, normal concentric organization of hepatocytes was changed and sinusoids and portal vessels of liver were congested.

Table 1. Comparison of the oxidative stress markers in different-treated rats

Groups	Serum TAC (nmol/ml)	Liver TAC (nmol/mg pro)	Serum MDA (nmol/ml)	Liver MDA (nmol/mg pro)	Serum SOD (U/ml)	Liver SOD (U/ml)	Liver TG (mg/g)	Liver TC (mg/g)
Control	109.5 ± 4.5	85.5 ± 4.3	10.0 ± 2.0	3.0 ± 0.5	150.7 ± 6.5	157.5 ± 7.3	7.5 ± 1.2	6.8 ± 0.8
HCD	80.5 ± 4.0$^{£}$	58.0 ± 4.2$^{£}$	16.5 ± 1.5$^{£}$	7.0 ± 0.8$^{£}$	118.2 ± 6.3$^{£}$	131.3 ± 3.4$^{£}$	13.5 ± 0.8$^{£}$	12.0 ± 0.7$^{£}$
HCD + AE (100 mg/kg)	79.0 ± 2.0	67.0 ± 2.0*	14.6 ± 2.8	6.8 ± 0.5	130.5 ± 4.5	155.4 ± 3.8*	12.0 ± 2.0	12.2 ± 0.7
HCD + AT (100 mg/kg)	101.9 ± 4.5**	81.8 ± 5.0**	12.5 ± 1.4**	5.0 ± 0.4*	136.2 ± 3.7*	152.3 ± 12.6	10.0 ± 1.3*	9.5 ± 1.3*
HCD + AE (100 mg/kg)	106.6 ± 3.5**	82.2 ± 3.5**	12.2 ± 1.0**	5.5 ± 0.5*	143.0 ± 4.2**	153.0 ± 5.7*	9.7 ± 0.7**	9.0 ± 1.0*
HCD + AT (100 mg/kg)	112.5 ± 4.4***	91.0 ± 5.7***	10.3 ± 1.4***	5.0 ± 0.6**	144.4 ± 5.8***	155.4 ± 6.2*	7.3 ± 0.6***	7.0 ± 1.4**

Data were expressed as mean ± standard error of the mean (SEM)

$^{£}$ P < 0.0010 compared with the normal control animals; * P < 0.0500; ** P < 0.0100; *** P < 0.0010 compared with high cholesterol diet (HCD) group

AT: Anethum tablet; AE: Anethum extract; HCD: High cholesterol diet; TC: Total cholesterol; TG: Triglyceride, MDA: Malondialdehyde; TAC: Total antioxidant capacity; SOD: Superoxide dismutase

In HCD animals leukocyte infiltration, foam cell formation, and fat accumulation were observed. Treatment with Anethum tablet or its extract at the dose of 200 mg/kg markedly alleviated histological change of liver in high fat diet animals (Figure 2).

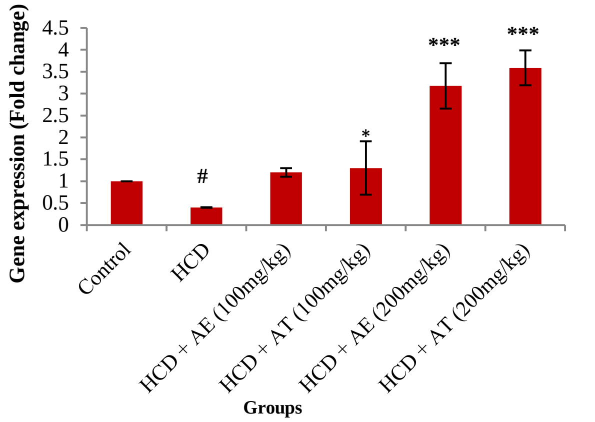

Figure 1. The fold change of low-density lipoprotein receptor (LDLR) in liver of different-treated rats

* $P < 0.0500$; *** $P < 0.0010$ compared with high cholesterol diet (HCD) group; # $P < 0.0010$ compared with the normal control animals.

HCD: High cholesterol diet; AT: Anethum tablet; AE: Anethum extract

Discussion

Pervious experiments have reported that HCD leads to reactive oxygen species (ROS) generation in the liver, causing liver injury in human and animal models. Impairment of membrane by OH^- and peroxynitrite ($ONOO^-$) rises lipid peroxides which is able to react with redox metals to generate MDA, a main biomarker for oxidative stress assessment.[20]

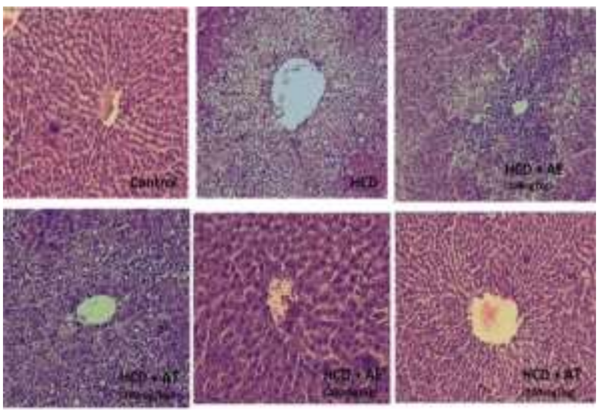

Figure 2. Histological changes of liver of different groups. The liver of Anethum graveolens (AG) extract- and AG tablet- treated animals showed restoration (at the dose of 200 mg/kg was more significant, ×400).

HCD: High cholesterol diet; AT: Anethum tablet; AE: Anethum extract

Final product of lipid peroxidation such as MDA has been recognized as an atherogenic and toxic agent. Clinical experiments established that patients with high levels of MDA and low levels of total antioxidant have increased susceptibility to atherosclerosis, diabetes, and other metabolic disorders. Different studies showed that declining of MDA and increasing of antioxidant levels with different medicine therapy is probably an advantage in management of metabolic disorders.[21] In this study, total antioxidant in the liver significantly declined and MDA increased in hypercholesterolemic hamsters compared to normal group. Treatment of animals with AG tablet and AG extract normalized total antioxidant and MDA levels in hypercholesterolemic hamsters. We recently demonstrated the valuable properties of AG administration in improving dyslipidemia in animal models, proposing that it can be used as an alternative option for management of cardiovascular disease (CVD).[22-24] For instance, 8-week use of AG tablet revealed markedly a decline in circulating levels of TC and LDL-C in diabetic rats.[11] In addition, we showed that 4-week supplementation of AG tablet and AG extract reduced LDL-C levels and raised HDL-C levels in hypercholesterolemic hamsters.[22]

We reported that TC, TG, very-low-density lipoprotein cholesterol (VLDL-C) and LDL-C were markedly reduced by AG tablet and AG extract, whereas HDL-C level was elevated in the treated groups. Our findings are similar to the previous results reported by Yazdanpanah.[25]

Setorki et al.[26] and Souri et al.[27] established the lipid lowering properties of AG. Mobasseri et al.[28] also showed that supplementation of Anethum in diabetic patients restored insulin sensitivity and normalized blood lipid levels.

In the current experiments, AG increased the LDLR gene expression, lower value of delta cycle threshold (ΔCt) means higher gene expression, and consequently modulated circulating cholesterol and LDL-C levels. High levels of LDLR are well established to decline serum LDL-C by increasing removal of circulating LDL-C. LDL-C clearance may suppress accumulation of cholesterol in the blood and result in a decline in the atherosclerosis risk. We showed that high cholesterol regimen decreased LDLR expression, which is probable because of the feedback mechanism motivated by high levels of cellular cholesterol in the hepatocyte. It has been reported that dietary cholesterol inhibits hepatic LDLR expression.[29] Our results indicated that LDLR expression significantly increased by AG extract and AG tablet. The hamsters in HCD group treated by AG extract or AG tablet at the dose of 200 mg/kg exhibited increase in LDLR gene expression. However, supplementation of AG tablet showed more increase in the LDLR expression compared with other groups. The exact lipid lowering mechanism of AG is not completely understood; but previously, Souri et al.[27] reported that AG was able to change HMG-CoA/mevalonate ratio. We previously reported that AG could decrease HMG-CoA reductase in the animal models.[22] Also, the HMG-CoA reductase activity was reduced by AG extract and AG tablet at the dose of 200 mg/kg. The HMG-CoA reductase suppression causes reduction of liver cholesterol production and leads to low levels of VLDL-C secretion by the liver. Some studies showed that rutin and quercetin (main components of AG) reduced serum LDL-C, TC, and liver lipid accumulation.[30] It has been shown that quercetin inhibits HMG-CoA reductase activity.[31]

In this study, AG administration significantly reduced the liver TC and TG. Previously, we showed that AG contained flavonoid, phenolic, and tannin.[11] According to our previous report, the total phenolic and flavonoid compounds in AG extract were 160 and 120 mg/g and in AG tablet were 190 and 151 mg/g, respectively.[22] Many studies reported that these compounds had hypocholesterolemic, hypoglycemic, antioxidant as well as anti-atherogenesis and anti-thrombosis effects.[32,33] Reduction of TC and TG levels in hepatocyte by AG may result in inhibition of cholesterol biosynthesis and stimulation of cholesterol conversion to bile acids.

The histopathological findings revealed that AG regenerated liver structure in HCD hamsters. Regeneration effects by Anethum may enlighten the positive effects of this medicine on liver antioxidants and fat accumulation. This useful effect of AG only was observed at high doses.

Conclusion

The findings of this experiment indicated that AG could be used in liver disease. Hypocholesterolemic activity of AG probably is through increasing LDLR gene expression in liver.

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Conflict of Interests

Authors have no conflict of interests.

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The estimate of average age at the onset of acute myocardial infarction in Iran: A systematic review and meta-analysis study

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Meta-analysis

Abstract

BACKGROUND: Research indicates that the age of onset of first acute myocardial infarction (AMI) is an essential element in the life expectancy that has been decreasing in developing countries. There are various studies performed in Iran reporting a range of ages at time of AMI. Thus, this meta-analysis study is designed to determine the mean age at first AMI in the Iranian population.

METHODS: All studies that met the inclusion and exclusion criteria were reviewed using standard keywords in the databases from 2000 to 2016. Two raters verified a total of 658 articles. Sixteen studies met the inclusion criteria of this study for meta-analysis. Cochran test and I-squared (I^2) were used for samples' homogeneity. Pooled estimates of mean were calculated using the random effects inverse-variance model.

RESULTS: The mean age of AMI varied between 55.9 to 62.9 years among the primary studies. The pooled mean age of first AMI with a 95% confidence interval (CI) for the total sample, men, and women were 59 (58.9, 60.4), 58.7 (58.3, 59.2), and 64.2 (63.5, 64.8), respectively.

CONCLUSION: Our meta-analysis shows that the mean age of first onset of AMI in Iranian people is slightly lower than that reported elsewhere; and it is lower for men than for women.

Keywords: Myocardial Infarction, Meta-Analysis, Iran

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Introduction

Coronary artery disease (CAD) is responsible for nearly 46 percent of the mortality in Iran.[1] This disease accounts for 80 percent of deaths in the low and middle-income countries.[2] A study conducted in Iran indicated that 40 percent of deaths are related to the CAD.[3] It is considered the leading cause of death in men and women.[4] It should be noted that the age of onset differs by gender.[5,6] Based on world statistics in United Kingdom (UK), the prevalence of cardiovascular disease (CVD) in men and women aged 35-44 years is 50% and 18%, respectively. These percentages are 20.5% and 17.1% for men and women over 60 years, respectively.[7] A systematic review of the 62 relevant studies among published articles between 1990-2014 reported that the annual incidence of CAD ranged from 27.6% to 57.0% per 100000 people.[8] Moreover, some studies conducted in the Gulf States have reported a high incidence of CAD at a younger age. Of those patients, 9.8%-25% were less than 45 years old.[9,10] Annually, CAD leads to approximately 6.3 million admissions to the hospitals affiliated to the Iranian Ministry of Health and Medical Education.[11] Moreover, death following CAD is estimated to be 205 per 100000 in all age groups and 4156 per 100000 per year in individuals older than 70. Although increasing age is a recognized risk factor for acute myocardial infarction (AMI), a study indicates that an early age

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of AMI is a serious problem, as it is associated with major morbidity, psychological effects, and financial limitations for the person and the family.[12] Awareness of age of AMI is important and useful in the evidence-based decisions, research, prioritization, monitoring and planning in the health system as well as identifying the AMI etiology and risk factors related to that.[3] Annually, approximately one percent of men aged 30 to 62 experience at least one symptom of CAD. Of those, about 42 percent evolve into an AMI.[13] It should be noted that AMI occurs in men at younger ages than women. For women who are hospitalized for AMI under the age of 50 years, risk of mortality is double that for men.[14]

The incidence of AMI is increasing and occurring earlier in life in developing countries due to sedentary lifestyle, weight gain, tobacco use as well as the lack of attention to job stress and mental health advice.[15,16] However, Okrainec et al. reported that AMI occurred in 38% of patients who were younger than 75 years old.[17] It seems that the age of first incidence of AMI is decreasing in Iran.[2] Also, the Global Registry of Acute Coronary Events (GRACE) defined age as an independent prognostic factor for AMI. Thus, the mortality risk will increase about 7.1 percent within a decade in all age ranges.[18] In other words, aging causes changes in the structure and function of vessels, increasing left ventricular wall thickness, reducing ventricular diastolic compliance, and weakening the sensitivity to changes in the neurohormonal beta receptors in the heart. These factors are just a few that have been postulated.[19]

The age of onset of AMI and its risk factors among different age and racial groups are influenced by variations in lifestyle and other circumstances.[20] Although an increased incidence of AMI is linked with a wide range of individual risk factors, these factors can explain only about 50-60 percent of demographical changes. Thus, there is a need to look beyond of individual factors. Logical and epidemiological context theories suggest that development of disease is influenced by different climates influences. Therefore, describing the demographic, clinical, geographical, and regional factors affecting the incidence of CAD can produce new hypothesis.[21]

As one of the risk factors of a disease epidemic is younger age,[22] a survey of the age at first incidence of AMI can lead to the determination of the epidemiology of AMI[22] in the prevention, diagnosis, treatment, and prognosis.[23] In Iran, one study reported the mean ± standard deviation (SD) age of AMI as 64.2 ± 10.1 and 57.5 ± 11.4 among men and women, respectively.[24] Another study reported the mean age of AMI as 57.2 ± 13.6 for men and 61.6 ± 9.5 for women.[23] Neamatipoor et al. also showed that the mean age of AMI has changed over time in the Iranian population. So that, the mean age of women with AMI decreased from 65 years in 1992 to 61 years in 2002. Also, the mean age of first AMI in Iranian men decreased from 59 years in 1992 to 57 years in 2002.[20]

Considering the opposite findings of previous studies in different countries and time periods, estimation of the mean age of AMI incidence is important to estimate the prevalence of it. This study has the potential to give valuable information to health system policymakers in Iran to use this information for the development of preventive programs. In addition, results of the present survey can provide valuable information for resource allocation. Thus, this study was performed to estimate the average age of AMI onset in Iranian men and women.

Materials and Methods

The present meta-analysis study was based on the sample articles available about the age of AMI in Iran. The databases including PubMed, Web of Knowledge, ScienceDirect, Google Scholar, SID, MedLib, Magiran, and Iranmedex were reviewed. The following key terms were searched: age, onset, incidence, and acute myocardial infarction, with the use of OR and AND operators. Moreover, sources that were not online were searched manually. These sources included MSc or PhD published theses and related books in library, and consultation with researchers. Two independent reviewers screened titles and abstracts for relevance. Articles were obtained and assessed in detail for inclusion. Studies had to meet all three of the following criteria for inclusion: 1) keywords should be mentioned in the title or the abstract section; 2) both mean and SD of the onset age in AMI is needed to be mentioned, and 3) cross-sectional studies. Each of the papers was reviewed for the presence of the selected inclusion and exclusion criteria. Studies were conducted at different times of the year and by different researchers. Studies were excluded if they were or had: 1) incomplete data (mean and SD of the onset age in MI), 2) subjects with diagnosis of acute coronary syndrome (ACS), 3) abstracts only. Some of the authors provided publications of a finding; in this case, only the study with the largest sample size was included in the meta-analysis.

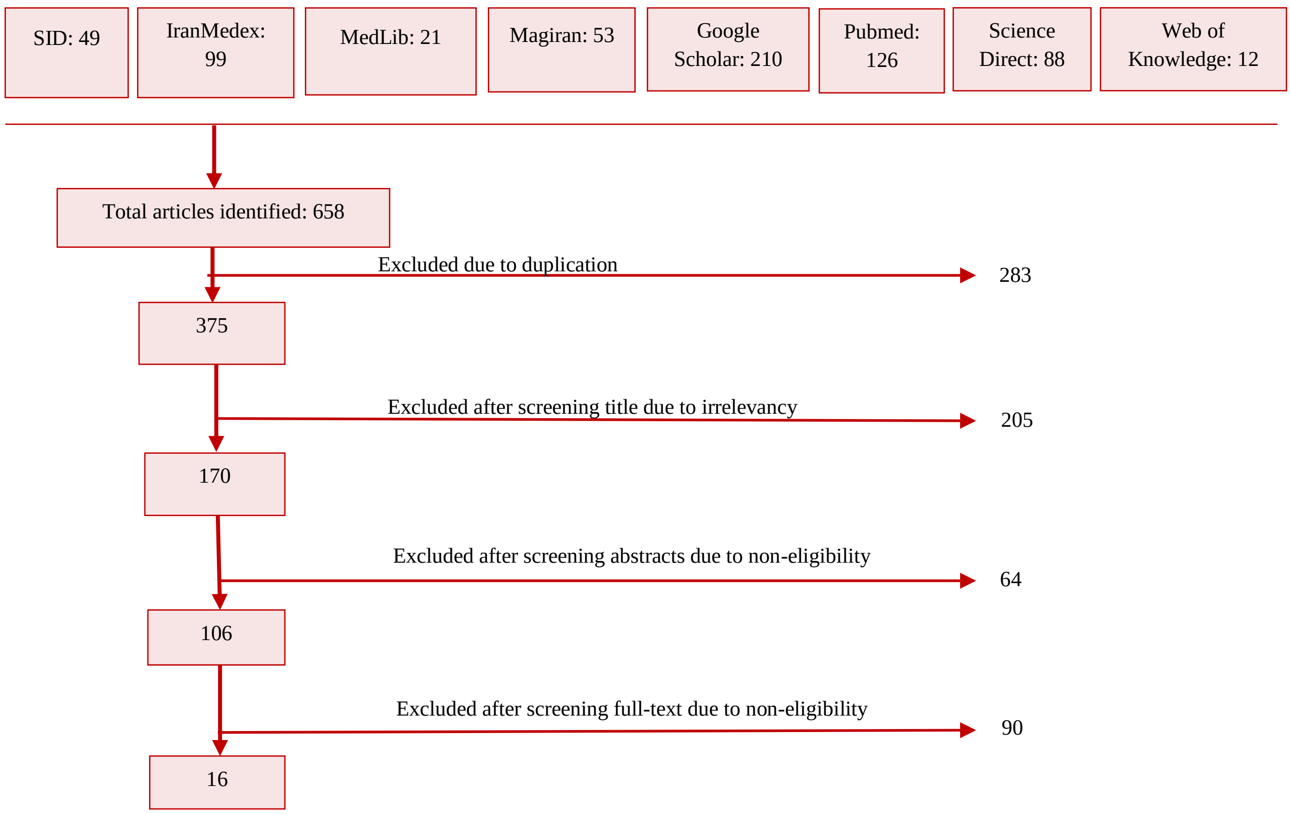

Figure 1. Flow chart of the process and rationale used in selecting studies for inclusion

Sixteen papers were found after the thorough search from January1st, 2000 to December 31st, 2016 in Iranian population. Search strategies and the number of articles in each level of study are separately given in figure 1 and table 1, respectively.

The following information was extracted for each study: author(s), year of publication, age of AMI, geographical area, sampling methods, mean age of participants, and sample size.

The quality of the extracted studies from the databases was assessed by two raters using checklist of the cross-sectional studies (STROBE), and the disagreements between the two raters were referred to a third rater.

Table 1. Characteristics of the studies selected for the meta-analysis

Authors	Geographic regions	Sample size	Sampling methods	AMI age (year) (mean ± SD)		
				Total	Men	Women
Ahmadi et al.[25]	Tehran	20750	Census	61.20 ± 13.40	59.60 ± 11.80	65.40 ± 12.60
Farshidi et al.[26]	Bandar Abbas	227	Census	57.93 ± 13.10	Unknown	Unknown
Gholi et al.[27]	Karaj	140	Convenient	58.80 ± 11.50	Unknown	Unknown
Hadjian and Jalali[28]	Babol	1233	Census	60.60 ± 11.20	60.10 ± 11.80	61.50 ± 11.00
Hasan pour et al.[29]	Shahr-e Kord	150	Convenient	57.70 ± 10.50	Unknown	Unknown
Hojat[30]	Jahrom	150	Convenient	55.92 ± 11.00	Unknown	Unknown
Sezavar et al.[16]	Tehran	1829	Census	60.63 ± 13.50	56.90 ± 12.90	66.10 ± 11.60
Kazemy and Sharifzadeh[31]	Birjand	918	Census	60.70 ± 12.10	58.90 ± 12.20	65.30 ± 10.70
Kiani et al.[32]	Zahedan	213	Convenient	58.30 ± 12.60	Unknown	Unknown
Taghipour et al.[23]	Amol	366	Convenient	58.70 ± 12.20	57.44 ± 13.30	65.40 ± 12.60
Mohammadian et al.[33]	Isfahan	12815	Census	61.85 ± 12.60	60.00 ± 12.50	66.72 ± 11.30
Beyranvand et al.[34]	Tehran	300	Convenient	56.60 ± 9.50	55.50 ± 9.50	58.20 ± 9.40
Momeni et al.[35]	Rasht	162	Convenient	60.29 ± 12.40	59.71 ± 12.90	60.87 ± 11.90
Sharif Nia et al.[1]	Amol	169	Convenient	59.49 ± 11.68	57.34 ± 13.60	61.64 ± 9.50
Rajaei Behbahani et al.[36]	Tehran	33831	Census	62.91 ± 0.50	59.70 ± 0.80	66.13 ± 0.10
Rostamzadeh et al.[37]	Urmia	81	Census	60.00 ± 7.80	57.40 ± 13.50	67.10 ± 9.00

AMI: Acute myocardial infarction; SD: Standard deviation

Data were analyzed using Stata software (version 11). Samples' heterogeneity was determined using Cochran's Q test and I-squared (I^2). The heterogeneity criterion was $P < 0.001$. Considering the heterogeneity existence, random effects inverse-variance model was used for calculating the mean age of AMI. Egger's test was used to examine publication bias on study outcome. Sensitivity analysis was run for assessing the effect of each study on overall estimate. Also, meta-regression was used in order to estimate the effect of suspicious factors on heterogeneity.

This study was approved by Ethics Committee of Mazandaran University of Medical Sciences, Sari, Iran (Code IR.MAZUMS.REC.95-2179).

Results

Of 16 eligible studies, 73334 AMI cases were included. The level of heterogeneity among the average age of AMI was highly significant (I^2: 98.8%, Q = 948.54, $P < 0.001$). Hence, we applied the random effects inverse-variance model to aggregate their findings. As shown in figure 2, the mean age of AMI was 59.7 [95% confidence interval (CI): 58.9-60.4).

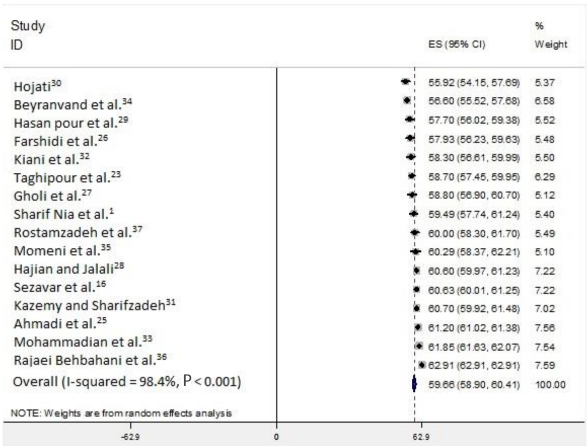

Figure 2. The mean age of total patients with acute myocardial infarction (AMI) in each of the first studies entered into meta-analysis and its overall estimate
ES: Effect size; CI: Confidence interval

The mean age of AMI (95% CI) for men and women were 58.7 (58.3, 59.2), I^2: 94.4%, Q: 176.99, $P < 0.001$, and 64.2 (63.5, 64.8), I^2: 98.4%, Q: 615.30, $P < 0.001$, respectively. According to figures 3 and 4, the observed difference between the age of AMI among men and women was statistically significant.

A meta-regression model was used and the role of publication year as a potential source of heterogeneity was assessed.

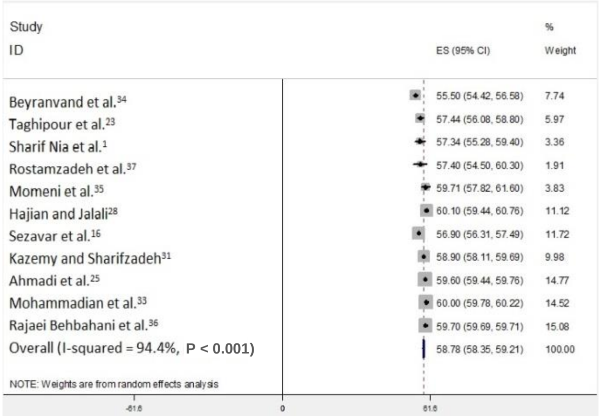

Figure 3. The mean age of acute myocardial infarction (AMI) in men in each of the first studies entered into meta-analysis and its overall estimate
ES: Effect size; CI: Confidence interval

The coefficient of year was -0.07 in this model with a $P = 0.370$; it should be noted that the incidence of AMI decreased by 0.07 units per year according to the results of meta-regression. However, the publication year did not explain a considerable part of the overall heterogeneity. In addition, the Egger's test showed that publication bias was evident ($\beta = -7.02$, $P < 0.001$).

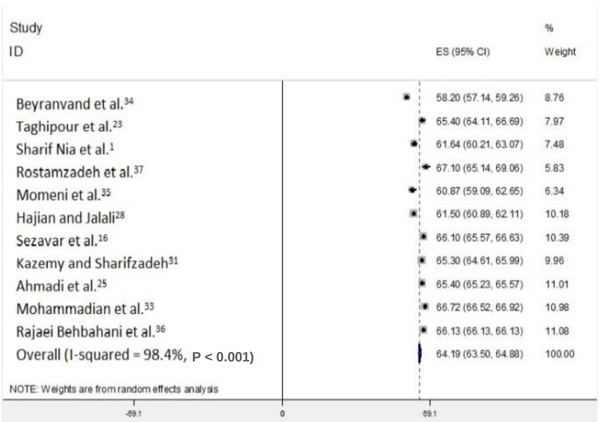

Figure 4. The mean age of acute myocardial infarction (AMI) in women in each of the first studies entered into meta-analysis and its overall estimate
ES: Effect size; CI: Confidence interval

Discussion

The present study estimated that the age of onset of first AMI was 59.66 years among 112837 men and women in Iran. The results showed that the mean age of onset of AMI in Iran for men and women were 58.78 and 64.19 years, respectively. A study conducted in Italy reported the mean age of AMI onset 63.1 and 73.1 for men and women, respectively.[38] Also, in Netherlands the average age of patients with the first AMI was 66.7 ± 13.2. The mean age of first AMI reported to be 64.2 ± 12.7 for men and 71.6 ± 12.8 for women.[39] The average age of 71.8 years in women in comparison with the 65.0 years in men was reported in the USA.[40] While in the developed countries, CAD occurs in the mid-sixties and early seventies among men and women, respectively, this happening has been reported to occur a decade earlier in developing countries like Qatar[41] and Lebanon.[42] Another study showed that the incidence of first AMI in the South Asian countries such as India, Pakistan, Bangladesh, Sri Lanka, and Nepal was occurred at a lower age compared to the rest of the world (i.e., women: 58.6 ± 11.6, and men: 53.0 ± 11.2 years old). The same study examined the risk factors in this population and stated that the lower prevalence of protective risk factors such as leisure time, physical movement, regular alcohol drinking, and everyday intake of fruits and vegetables as well as the higher prevalence of harmful risk factors including elevated apolipoprotein B-100/apolipoprotein A-I (apoB-100/apoA-I) ratio in South Asian countries can be considered as the reason for age difference.[43] It should be pointed that the cost of hospitalization, treatment, rehabilitation, and other health care costs are higher in developing countries such as Iran.[41] This can lead to late patients' referral and delay in receiving different levels of prevention.

The results of these studies reveal two aspects. First, it reflects the lower mean age of first AMI among Iranian people compared to developed countries. This difference can be explained by higher level of social welfare in developed countries in comparison with Iran and also cultural, lifestyles, and preventive health care differences between developed and developing countries. Possibly the socioeconomic levels are also associated with CAD development;[44] areas with lower socioeconomic status have shown a higher risk of AMI.[21] It may be due to the fact that in the low-income societies, there are more challenges including less access to health care services, poor quality of health services, limited resources for the policies implementation, and insufficient programs to prevent and manage CAD.[45] Moreover, fewer tendencies to engage in the health care behaviors, greater proneness to the stress, and the presence of higher rates of cardiovascular risk factors are other reasons that predispose individuals to be susceptible to AMI.[33] Therefore, it is accepted that living in less developed regions places the population at higher risk of cardiovascular events.[46]

The second important finding is the consistency of the lower age of men compared with women for the onset of the AMI. Higher age of onset in women is due to the protective effect of estrogen on the vascular endothelium. This assumption is greatly formed with the increased rate of AMI approximately 10 years after menopause.[47,48] However, it is difficult to separate the effects of aging and menopause. Complex mechanisms that affect the risk of CAD by estrogen is not fully understood. The direct effects of estrogen on the cardiovascular system include increased secretion of nitric oxide that causes vessels dilatations, regulates the production of prostaglandins, and inhibits the smooth muscle proliferation.[49] Also, at the time of menopause, estrogen reduction causes endothelial dysfunction and increasing in deposition of fat in the arteries. Therefore, this can accelerate the progression of atherosclerosis.[40] However, studies about gender differences in the incidence of CAD have addressed these variations in terms of biological factors.[50] Less frequent attention has been given to the social, environmental, and societal factors that have potential effects on the occurrence age of MI.[51,52] Although CAD is a major cause of AMI in both men and women, plaque features are varied among different women. Recent data suggest the important role of the microscopic vascular disease in the pathophysiology of coronary events. Naturally, the increased rate of AMI in women is multifactorial, and is influenced by age, race, and ethnicity.[40] The study conducted in USA showed that in the age range of 75-84 years, AMI in black men reported to be 12.9 persons per 1000 people, yearly. While black women, white men, and white women were ranked for incidence rate of 10.2, 9.1, and 7.8 persons per 1000 people, respectively.[53]

Limitations: The meta-analysis was done using studies of hospitalized patients; thus, persons who died of AMI before admission to the hospital were not included. Therefore, there is likely an underestimation. The other limitation of the present study was that Iran is a vast territory with diverse geographical regions. So, failure to include each climatic zone may limit the generalizability of the results.

Conclusion

The results of the current study indicate that the mean age of onset of AMI is 59.3 years and it is lower in men than in women. These findings can be used for planning CAD prevention.

Acknowledgments

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Conflict of Interests

Authors have no conflict of interests.

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Pulsating mass following plain old balloon angioplasty on left anterior descending artery (LAD) via radial access

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Case Report

Abstract

BACKGROUND: Trans-radial coronary intervention is a popular technique due to patient comfort and lower complication rate. The main complications of this method are artery spasm, vessel perforation, and formation of pseudo-aneurysm.

CASE REPORT: In this report, an unusual complication of radial access angiography was encountered. Shortly after the procedure, the patient's right arm began to swell and a pulsating mass grew over the medial aspect of the arm. Right brachial artery angiography was performed immediately for rolling out brachial artery perforation. There was no evidence of extravasation in brachial angiography. Surprisingly, the mass began to disappear after some active flexion and extension at elbow joint. The same problem occurred again after percutaneous coronary intervention (PCI) on left anterior descending artery (LAD) in this case 2 days later and was resolved by the same maneuver.

CONCLUSION: It can be conculded that the brachial artery path was shifted and became entrapped after the procedure due to low soft tissue support.

Keywords: Balloon Angioplasty, Percutaneous Coronary Intervention, Brachial Artery

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Introduction

Radial and femoral arteries are two common access sites for coronary angioplasty procedures. Easy hemostasis and immediate ambulation after the procedure have made radial access a preferable choice for the intervention of cardiologists among patients. While successful trans-radial technique requires expertise, failure usually occurs due to anatomical variations in the arm.[1] There is notable tendency toward using radial access around the world. While south and Central American countries have lower rates, Malaysia and Norway have the highest rate of radial use. In the Middle East and Africa, the radial access use is infrequent.[2] Artery spasm, bleeding, hematoma, and perforation are among the main complications of trans-radial catheterization, which may occur shortly after or even during the procedure.[2] However, rare presentations may occur during trans-radial catheterization which mimic acute and life threatening complications including hematoma. In this report, a case of brachial artery displacement following plain old balloon angioplasty (POBA) in left anterior descending artery (LAD) via right radial approach is discussed.

Case Report

A 70 years old man referred to emergency department of Qaem Hospital, Mashhad, Iran, for rescue percutaneous coronary intervention (PCI) with ongoing severe retrosternal chest pain after thrombolytic therapy after anterior myocardial infarction (MI). He had a history of prolonged smoking and consumption of anti-hypertensive drugs. 12-lead electrocardiogram (ECG) showed anterior MI. The patient underwent echocardiography and initial management of acute MI was immediately initiated. Left ventricle ejection fraction was 30% accompanied with severe aortic insufficiency and hypokinetic anterior myocardium as well as mild mitral valve and tricuspid valve regurgitation (pulmonary artery pressure: 39 mmHg). Coronary artery angiography revealed insignificant plaque in left main artery and cut off in LAD, despite normal left circumflex (LCX) and right coronary arteries. Due to severe aortic valve insufficiency, he was candidate for coronary artery bypass graft (CABG) and aortic valve replacement (AVR).

Because of ongoing chest pain, POBA on LAD was performed to reduce pain. POBA was

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performed on LAD by a 2*15 balloon followed by prolonged dilation with a 3*20 balloon. Post POBA thrombolysis in myocardial infarction (TIMI) 3 was established in the last view.

After POBA on LAD and withdrawing of guiding catheter, a pulsating mass began to grow on patient's right arm at right brachial artery area. Distal pulses on both upper extremities were symmetrical and there was no sign of distal pallor or cyanosis. Compression along brachial artery began immediately according to possible diagnosis of brachial artery hematoma. The initial diagnosis was brachial artery perforation, so Immediate brachial angiography was performed and no extravasation was seen (Figure 1).

Figure 1. Pulsatile mass observed in the right arm (red arrow) after plain old balloon angioplasty (POBA) procedure

The pulsating mass was not resolved after compression for several times. Therefore, vascular surgeon consultation was performed and the patient was transferred to the coronary care unit. Surprisingly, after a few minutes, the mass disappeared when the patient started to use his hand by performing active flexion of the elbow. As the patient refused CABG and aortic valve replacement, PCI on LAD was performed. The follow up for brachial angiography revealed no pathologic finding in right brachial artery (Figures 2 and 3). After a successful PCI, the arm began to swell again and the mass disappeared by flexion and extension of elbow. The patient had an uneventful recovery period and was discharged in healthy condition.

Figure 2. Immediate brachial angiography findings: (1) proximal brachial artery angiography, (2) angiography at elbow joint, and (3) angiography below elbow (Bifurcation site)

Discussion

The radial artery is a good access site for coronary catheterization while its advantages outweighs its complications.[3] This procedure requires expertise and experience in order to avoid possible life threatening complications.[4]

Figure 3. Control brachial artery angiography after 24 hours

Hematoma, artery dissection, and artery spasms are among the complications that happen early after the procedure. Among these complications, hematoma and hemorrhage due to artery perforation may manifest as a palpable mass. Hematoma is among the most important complications of catheterizations which require immediate management. They are generally small and may grow in size if left untreated. Most hematomas can be managed by manual pressure. Due to the lack of bleeding at the access site and the observed expanding pulsating swelling in the patient under examination, the most probable diagnosis was an expanding hematoma arising from brachial artery, thus immediate compression along the artery was performed to prevent compartment syndrome.[3] Due to the unsuccessful artery compression and lack of signs of distal ischemia or discoloration, it was decided to observe the patient and plan a vascular surgeon consultation. During preparation of the patient, the pulsating mass disappeared after performing active flexion and extension maneuvers in the elbow and possible diagnosis of hematoma or hemorrhage was ruled out. It was then hypothesized that the patient had an anatomical variation in arm muscles and wire and catheter passing manipulated the brachial artery root around cubital fossa.

Biceps muscle is the most common muscle of the arm and shoulder which has accessory heads.[5] The insertion site of biceps tendons are mostly separated and in a quarter of cases are bifurcated. Neurovascular structures may be entrapped in accessory muscles attached to the elbow.[6] In some cases, the humeral head of the pronator teres has an abnormally high attachment to a bony spore raised from distal portion of humorous. In such cases, the distal portion of brachial artery may be entrapped behind the humeral head of pronator teres.[7] Meda et al. reported a case of brachial artery entrapment syndrome due to supracondylar spore.[7] Regarding the patient in this study, no bony lesion was observed on the humorous neither in palpation nor in X-ray. Moreover, no signs of ischemia or abnormal neurological examinations were observed in this patient. Another differential diagnosis of palpable mass in arm is brachial artery aneurysm. Tetik et al.[8] reported a case of brachial artery aneurysm in a 50 year old woman who was presented with a swollen and pulsatile mass in right arm with symmetrical pulses in both hands. Although the patient in this study did not have any history of trauma or other iatrogenic causes of pseudo aneurysm, they decided to operatively repair the true aneurysm. The hypothesis in the current study is the shift of brachial artery from its location due to severe low soft tissue support.

Catheterization via radial access is usually an uncomplicated procedure. However some anatomical variations may complicate this technique. In the present case, an anatomical variation in adjacent tissues caused acute dislocation of brachial artery.

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Conflict of Interests

Authors have no conflict of interests.

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Increased levels of high-sensitivity C-reactive protein in coronary artery diseases

Yousef Rasmi[(1)]

Letter to Editor

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Dear Editor-in-Chief

We read the article "Relationship between high-sensitivity C-reactive protein (hs-CRP) serum levels and the severity of coronary artery stenosis in patients with coronary artery disease (CAD)" written by Seyedian et al., with a great interest.[1] Their results showed that the mean levels of hs-CRP in patients with unstable angina was significantly higher compared to patients with stable angina and patients with normal coronary angiography. It also appeared that the level of hs-CRP in patients with unstable angina is associated with the severity of coronary stenosis. Previously, patients with cardiac syndrome X were detected to have significantly higher plasma hs-CRP level in comparison with the controls.[2]

This is an interesting study. We believe that these findings will enlighten further studies about the relation between hs-CRP and coronary artery stenosis. But, we would like to make a minor criticism on methodological aspect as follows:

1- The activity of glucose oxidase and cholesterol oxidase-peroxidase, and the levels of white blood cells, blood sugar, triglycerides, cholesterol, blood creatinine, and degree of stenosis on a scale of 0 to 4 were measured. But, the authors did not mentioned applications of these data in the study.

2- Patients were classified into three groups of participants who were enrolled consecutively: patients with stable angina who have angiographic lesions (Group I), patients with unstable angina who had angiographic lesions (Group II), and patients with stable or unstable angina who had normal coronary angiographies (Group III). They reported that mean levels of hs-CRP in patients with unstable angina was significantly higher compared to patients with stable angina and normal coronary angiography. But we would like to remember this point that the group III, mixture of stable and unstable angina, were missed in final conclusion. According to these results, they should change the name of groups I and II as stable angina with CAD and unstable angina with CAD, respectively; in all of the text and conclusions.

3- Moreover, the number of patients in table 2 is not match with the body of text.

It would be better if the authors explain these issues.

Conflict of Interests

Authors have no conflict of interests.

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