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2. Bonow RO, Mann DL, Zipes DP, Libby P. Braunwald's Heart Disease E-Book: A Textbook of Cardiovascular Medicine. 7th ed. Philadelphia, PA: Elsevier Health Sciences; 2007. p. 1976, 1981, 1982.

3. Gaston M. The psychological care of patients following a myocardial infarction [Online]. 2003; Available from: URL: http://www.nursingtimes.net/the-psychologicalcare-of-patients-following-a-myocardialinfarction/199464.article/

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

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The effect of evidence-based care guidelines on outcomes after removal of arterial sheath in patients undergoing angioplasty

Alireza Parach[(1)] , **Mohsen Sadeghi-Ghahroudi**[(2)], **Yaser Saeid**[(1)], **Abbas Ebadi**[(3)]

Original Article

Abstract

BACKGROUND: Evidence-based clinical care guidelines effectively assists medical teams to increase the quality of clinical practice, and improve outcomes in patients. This study aimed to design and implement evidence-based care guidelines for removing arterial sheath in patients undergoing angioplasty of coronary artery.

METHODS: This clinical trial study was performed on 200 patients (two groups of 100 patients) with mean age of 62.5 ± 10.8 years, from July 2014 to February 2014 in Baqiyatallah University of Medical Sciences (BUMS), Tehran, Iran. First, we designed a five-step guideline for removing arterial sheath. Then, the designed guideline (based on five-step Stetler model, i.e. preparation, validation, comparative study, implementation, and execution) in the current study, and the routine guideline were used for removing arterial sheath in patients in the intervention and the control groups, respectively. In both groups, the relevant outcomes including bleeding, vasovagal reactions, urinary retention, and pain were evaluated.

RESULTS: There were significant differences between the two groups in terms of bleeding, hematoma, vasovagal reactions (n = 11 versus n = 24), urinary retention (n = 8 versus n = 31), and back pain after removing arterial sheath (P < 0.050 for all).

CONCLUSION: Based on the results of this study, the use of evidence-based care guidelines after removal of atrial sheath in patients undergoing angioplasty is recommended.

Keywords: Evidence-Based Practice, Guideline, Peripheral Catheterization, Transluminal Coronary Balloon Dilation, Outcomes Assessment

Introduction

Currently, cardiovascular diseases are considered as the most common serious diseases in developed and developing countries. The coronary heart disease ranks first among all cardiovascular diseasesin terms of prevalence. The coronary heart disease is the most important cause of death in the developed countries, and also in the developing countries, such as Iran.[1,2]

In Addition to coronary artery bypass graft surgery (CABG), percutaneous trans luminal coronary angioplasty (PTCA) is also one of the preferred treatments for coronary artery disease.[3,4] Performing PTCA in eligible patients reduces the cost and recovery time, significantly as compared to the coronary artery bypass graft surgery. The rate of death caused by the PTCA, approximately 1%-4%, is similar to that caused by the coronary artery bypass surgery.[3,5,6] After angioplasty procedure, arterial sheath is remove,d and patients are monitored for 24-48 hours for clinical outcomes in stay in the cardiac care unit (CCU).

In recent years, the use of evidence-based guidelines has been highlighted in improving the outcomes of the disease, and improving the quality of care. Evidence-based practice is an attempt to use data from scientific methods in various clinical aspects, especially in the assessment of advantages and disadvantages of a treatment.[7,8] Therefore, the process of evidence-based is an effort to enhance the quality of information based on which an efficient decision can be achieved. In fact, an evidence-based practice can improve the clinical outcomes in terms of patient's safety, recovery time, and cost;[9,10] evidence-based guideline reduces the gap between scientific evidence and clinical practice,

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and guides the clinical care.[11]

There is no established and standard clinical guideline for removing arterial sheath in health centers and hospitals in Iran. In addition, the use of different methods results to adverse events in patients undergoing angioplasty. Therefore, an efficient guideline can result in high quality care, prevent improper clinical procedures, assist in correct clinical decision, improve patients' safety and outcomes of clinical care, and reduce significantly the cost and time of removing arterial sheath. This study aimed to design and implement an evidence-based care guideline for removing arterial sheath in patients undergoing angioplasty of coronary artery.

Materials and Methods

This study was conducted in two phases. First, we designed a guideline according to the Stetler model for removing arterial sheath.[12] Then, in a clinical trial study on patients undergoing PTCA, outcomes of removing arterial sheath were investigated in 100 patients in intervention group and also in 100 age- and sex-matched patients in control group. This study was carried out in Baqiyatallah University of Medical Sciences (BUMS), Tehran, Iran, from July 2014 to February 2015.

Patients under hemodialysis and patients with emergency PTCA were excluded. Additional exclusion criteria was as patients who, for any reason, had a sudden increase in serum creatine leading to hemodialysis, and patients who developed severe hemorrhage in the arterial sheath place, and returned to cath lab.

Data entry forms were initially designed based on a literature review, and then finalized on the basis of suggestions and comments from eleven cardiologists and nurses. In this form, the demographic information, and also the outcome measures such as bleeding, vasovagal reactions, urinary retention, and back pain were recorded. To monitor blood pressure and heart rate, we used a cardiac monitoring device (LX110, SAIRAN Electronics Inc., Iran). We also used Hemochron-JR for measuring activated clotting time (ACT). Gauze (10 × 10 cm) was used to calculate blood volume as well. Each piece of gauze has a maximum absorption of 35 and a minimum absorption of 21.5 grams of blood. Mean absorption of gauze was assumed to be 30 grams in this study.

In routine care, the arterial sheath was removed 4 to 6 hours after angioplasty, and then the manual compression was used for hemostasis. Two 8-kg sandbags compressed the dressing position. The first and second sandbags were removed two hours and 4-6 hours after removing the arterial sheath, respectively. Patients were out of bed 6 hours after removing the arterial sheath.

To design an evidence-based guideline, we used a five-step Stetler model, i.e. preparation, validation, comparative study, implementation, and execution.[12]

- Preparation: We investigated problems of removing arterial sheath in patients undergoing angioplasty of coronary artery. An extensive review of the literature was performed in order to address these problems.

- Validation: We designed an initial guideline after reading and discussing the related articles thoroughly. This initial guideline was validated and completed by considering the comments and instructions from several cardiologists and cardiac nurses in CCU.

- Comparative study: A panel of nurses and residents were consulted to determine practicality of the designed guideline.

- Implementation and execution: After designing the guideline, nurses and residents were trained to execute procedures, and remove arterial sheath.

Patients were studied in intervention and control groups. In control patients, arterial sheath was removed routinely, as mentioned before. Finally, outcomes of removing arterial sheath, during this procedure and up to one day after that, were logged in data record form.

In the intervention group, removal of the arterial sheath and clinical care were based on the following protocol.

1. Control ACT in the third hour after angioplasty.

2. If ACT was less than or equal to 175 seconds, arterial sheath would be removed by manual compression.

3. Put direct pressure on the arterial sheath insertion site for two to three minutes; so that the dorsalis Pedi's pulse disappears. Then, lower the pressure to feel the dorsalis pedis pulse. Continue pressuring until hemostasis (10 to 20 minutes).

4. Put pressure dressing on arterial sheath area by a trained physician or nurse.

5. Put two sandbags (4 kg of weight per bag) on the dressing by nurse.

6. Remove the first and the second sandbags two and three hours after removing the arterial sheath, respectively.

7. Patients can be out of bed three hours after removal of arterial sheath in case of no complication.

8. Record outcomes of removal of arterial sheath in the data record form (all outcomes during the removal and up to one day after that were recorded).

Table 1. Disease history and other information of the control and intervention groups of patients (n = 100 for each one)

Variables		Group		P
		Intervention	Control	
Sex [n (%)]	Women	37 (37)	37 (37)	> 0.999
	Men	63 (63)	63(63)	
HTN (n)	Yes	59	66	0.307
PVD (n)	Yes	4	1	0.176
Arterial length (n)	11 cm	100	98	0.155
	23 cm	0	2	
Operator (n)	Nurse	36	29	0.293
	Physician	64	71	
Age (year) [Mean ± SD]		63.01 ± 11.03	61.90 ± 10.50	0.410
BMI [Mean ± SD]		26.50 ± 2.01	27.01 ± 2.55	0.160

Chi-square test was applied for arterial length and operator, independent-samples t test was applied for age and BMI, and Fisher's exact test was applied for others variables.
HTN: Hypertension; PVD: Previous vascular disease; SD: Standard deviation; BMI: Body mass index

This study was approved by the Ethics Committee of the BUMS (number 5904 approved at 07/02/2014). Objectives of the study were explained to the patients and informed consent was obtained from them.

We used SPSS software (version 20. IBM Corporation, Armonk, NY, USA) for the descriptive [mean and standard deviations (SD)] and inferential (e.g. chi-square, Fisher's exact, and independent-samples t tests) statistics in this study.

Primarily, the normality of the study variables was assessed by performing the Kolmogorov-Smirnov test. This test showed that the distribution of all study variables was normal. Consequently, we used the Fisher's exact test for examining the correlation between groups in terms of variables such as sex, blood pressure, previous vascular disease, tacking aspirin, vasovagal reactions, urinary retention, and used gauzes, chi-square test for back ache, operator, and arterial length, and independent-samples t test for between-groups comparisons of group in terms of variables such as age, body mass index (BMI), prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR), hemoglobin (HB), and hematocrit (HCT).

Results

Content of evidence-based care guidelines included 8 steps as described in methods.

Based on our findings, using our designed guideline for removing arterial sheath (based on the Settler model) prevented effectively misconduct in treating patients, and assisted in obtaining appropriate clinical decisions. If there were any complication, evidence-based measures for clinical management in our guideline would be considered.

The chi-square and Fisher's exact tests showed that control and intervention groups were homogeneous in terms of demographic and other variables. The results of the independent-samples t test revealed that age and BMI in two groups were also homogenous (P > 0.050 for both) (Table 1).

The results of independent-samples t test showed that there was no significant difference in mean ± SD of PT, PTT, HB, and HCT between control and intervention Group (Table 2).

Table 2. Compassion of results in two study groups (n = 100 for each one)

Consequence	Group		P
	Intervention	Control	
	Mean ± SD	Mean ± SD	
PTT (s)	28.9 ± 6.30	29.10 ± 7.79	0.870
INR	1.07 ± 1.11	1.07 ± 0.13	0.110
HB (g/dl)	13.80 ± 1.69	13.70 ± 1.85	0.820
HCT (g/dl)	40.80 ± 4.46	40.90 ± 5.16	0.880

The results are from using independent-samples t test.
SD: Standard deviation; PTT: Partial thrombin time; INR: International normalization ratio; HB: Hemoglobin; HCT: Hematocrit

However, the results of chi-square and fisher's exact tests revealed that the patients in intervention group had urinary retention, back pain, and vasovagal reactions lower than control group (P < 0.050 for all) (Table 3).

Discussion

Findings of this study show that the proposed evidence-based guideline for removing arterial sheath in patients undergoing angioplasty can reduce bleeding, vasovagal reactions, urinary retention, and back pain during and after removing the sheath.

Table 3. Comparison of the relative prevalence of bleeding, vasovagal, urinary retention, and back pain in two study groups (n= 100 for each one)

Consequence		Group		P
		Intervention (%)	Control (%)	
Vasovagal		11	24	0.010
Urinary retention		8	31	0.001
Back pain	Severe	0	16	0.001
	Moderate	3	19	
	Light	11	33	
	Does not have	86	32	
Used gauzes	10-15	0	1	0.020
	5-10	0	6	

Chi-square test was applied for back pain and Fisher's exact test was applied for others variables.

Study conducted by the American Association of Critical Care Nurses (AACN) showed that bleeding was an important side effect of the coronary angioplasty, and appropriate protocol for removing arterial sheath could reduce bleeding from location of the sheath.[13] In agreement with findings of the AACN study, our results demonstrated importance of an effective guideline for removing arterial sheath. Although guideline plays an important role in outcome of removing arterial sheath and also in patients' comfort, it is interesting that this guideline is not standardized across different hospitals.[13-15]

In another clinical trial study, arterial sheath was removed immediately after angioplasty, and vascular complications, including hematoma greater than 10 cm, pseudoaneurysm, and arterial bleeding, were reported.[16] We had less bleeding compared to this study, since we removed arterial sheath three hours after angioplasty by checking ACT (ACT ≤ 175 s).

Juergens et al. reported that vasovagal reactions during removal of arterial sheath caused stent thrombosis and adverse cardiac events (myocardial infarction).[17] To address this issue, the arterial sheath removed according to care instructions in our study, and we found a significant reduction in vasovagal reaction in intervention group that decreased the risk of stent thrombosis. Capasso et al. reported that the most effective method for hemostasis after removal of arterial sheath was to use manual compression.[18] Consistent with their study in terms of bleeding, we also used the manual compression for hemostasis in the current study.

In a clinical trial study, Augustin et al. investigated the effects and outcomes of early removal of arterial sheath in two groups of patients.[16] Arterial sheath in the first group (172 patients) was removed immediately after angioplasty, and the patients were allowed to come down from the bed three hours later. Complications such as hematoma greater than 10 cm, pseudoaneurysm, and arterial bleeding during or after walking in these patients were reported. Arterial sheath was removed 4-6 hours after angioplasty in the second group (175 patients), and then the patients were allowed to come down from the bed 4-6 hours after removal of the sheath. Although hematoma was less than 10 cm in patients in the second group, they had more back pain and urinary retention compared to the patients in the first group.[16] We removed arterial sheath three hours after angioplasty if ACT was less than 175 s, and then patients were allowed to come down of bed three hours after removal of the sheath. Using our guideline, we found that urinary retention and back pain significantly reduced in these patients.

Conclusion

Implementation of an evidence-based guideline for removing arterial sheath in patients undergoing angioplasty can have an effective role in reducing bleeding, hematoma, vasovagal reactions, urinary retention, and back pain. Using a guideline in clinical practice prevents misconduct, assists appropriate clinical decision, improves patient's safety and outcomes, and saves treatment time and cost.

Acknowledgments

Conflict of Interests

Authors have no conflict of interests.

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Syncope risk factors among military training soldiers; A case-control study

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Original Article

Abstract

BACKGROUND: Syncope is a transient brief loss of consciousness accompanied with loss of postural tone. Of common places in which people experience syncope, military barracks can be named where training soldiers spend their military courses. The current study aimed to assess etiology and risk factors of syncope among military training soldiers.

METHODS: This was a retrospective case-control study conducted on training soldiers of Army-501 hospital in Tehran, Iran, during the years 2017-2018. Cases were consisted of 50 soldiers who experienced syncope during military training, and controls were 150 soldiers who had not experienced syncope during their military training. Demographic data were recorded for cases and controls.

RESULTS: Members of case and control groups were not statistically different regarding age (P = 0.46) and height (P = 0.70). Logistic regression test was performed and considering crude model, weight [odds ratio (OR): 0.94; 95% of confidence interval (95%CI): 0.90-0.98], body mass index (BMI) (OR: 0.72; 95%CI: 0.61-0.85), standing duration (OR: 1.007; 95%CI: 1.00-1.01), history of syncope (OR: 15.47; 95%CI: 4.15-57.60), positive family history of syncope (OR: 5.94; 95%CI: 1.66-21.25), smoking (OR: 3.5; 95%CI: 1.54-7.91), medical problems (OR: 7.97; 95%CI: 1.98-32.17), anxiety (OR: 2.02; 95%CI: 1.13-4.26), stress (OR: 6.68; 95%CI: 3.28-13.57), and depression (OR: 4.25; 95%CI: 2.15-8.39) were detected as significant predictors of syncope occurrence.

CONCLUSION: Based on the findings of this study, lower BMI, positive history of syncope, smoking, depression, and stress were significant risk factors of syncope occurrence among training soldiers. Higher BMI has protective role in syncope occurrence.

Keywords: Syncope, Risk Factors, Case-Control Studies, Military Personnel

Introduction

Syncope is a transient brief loss of consciousness presentation with concurrent loss of postural tone. This condition occurs due to general interruption in brain blood flow. Cases with syncope may experience prodromal symptoms including mild vertigo, lightheadedness, perspiration, pallor, visual changes, nausea, vomiting, and flushing prior to loss of consciousness.[1-3]

Syncope has been estimated to occur among 20-35 percent of general population with variety of etiologies from negligible reasons to potentially severe life-threatening ones including cardiovascular and neurological disorders, and/or orthostatic hypotension.[4,5]

Cardiovascular etiology is responsible for approximate 10% of syncope cases, although least prevalence, most significant ones. Syncope related to cardiovascular etiologies may occur due to dysrhythmia, cardiac valvular or muscular problems, aortic dissection, and/or vascular occlusion due to thromboembolism.[6] On the other hand, neurological disorders are the most common underlying reason of syncope. This type may occur following exposure to a sensatory situation such as emotional state, exposure to blood, notable pain, or following particular activities such as urination, defecation, and even cough.[7] Stimulation of carotid sinus, specially bilaterally, can induce syncope occurrence.[8] Another etiology of syncope is hypotension that induces syncope following a sudden alteration in postural status. This type, that

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is known as orthostatic hypotension, can occur due to medicines taken by the person or etiologies that poses significant reduction in effective circulatory volume (e.g., severe dehydration, hemorrhage, and sepsis).[9]

Of common places in which people experience syncope, military barracks can be named where training soldiers spend their military courses. This fact that may usually occur during soldiers' long time stance in ranks or line for routine military ceremonies and marches, can potentially cause harm for their health.[10] Studies assessing etiological reasons and prognosis about syncope incidence in military services soldiers are limited; while it seems somewhat necessary to evaluate this potential life-threatening event among this population, who should tolerate long-time military ceremonies.[10,11]

According to limited studies about the etiologies of syncope occurrence among military soldiers and lack of any study in this regard is Iranian military community, the current study aimed to assess syncope etiologies among military training soldiers.

Materials and Methods

After obtaining institutional approval from Ethics Committee of AJA University of Medical Sciences, Tehran, Iran, this retrospective case-control study conducted on training soldiers from June 2017 to April 2018.

Cases were consisted of 50 soldiers who experienced syncope and referred to Army 501 hospital during study duration from. Controls were 150 age-matched training soldiers. Both groups were included through convenience sampling.

Soldiers with documented presentation of syncope, and those who declared their willingness to study participation were included, and those with incomplete medical records (more than 20% defect in their records) and with any history of neurological disorders and cardiac syncope were excluded. Participants were informed about all of the process of the study, and were reassured about confidentiality of their information. Then, they signed consent form of participation in the study. This study was approved based on IR.AJAUMS.REC.1396.51 code from Research Council and Ethics Committee of AJA University of Medical Sciences.

Demographic data including age, educational level, body mass index (BMI), previous history of syncope experience, family history of syncope, smoking, alcohol consumption, drug history, duration of standing prior to syncope occurrence, and presence of dehydration/emotional stress before syncope were recorded in a checklist. Then, all cases underwent electrocardiography (ECG), head-up tilt test (in cases with suspicion of syncope occurrence), and measurement of blood pressure and pulse rate. In addition, prodromal symptoms were asked from cases.

Control group was provided with similar checklist, blood pressure and pulse rate were measured for them as well. Mental health problems including stress, depression, and anxiety in both case and control group were measured by the validated Chinese version of Depression Anxiety Stress Scales (DASS21).[12] The 21-item instrument (including three subscales, 7 questions each) asked respondents to rate the presence of these items of symptoms over the past week from 0 to 3 (0: not at all; 1: some of the times; 2: a good part of the time: and 3: most of the time). According to DASS21 guidelines, the score of each subscale was summed up, and then was multiplied by two. Scores were ranged from 0 to 42. Cut-off scored for each subscale used according to previous studies, depression: normal 0-9 and abnormal 10-42, anxiety: normal 0-7 and abnormal 8-42, and stress: normal 0-14 and abnormal 14-42.[13,14]

Thereafter, obtained data were gathered in checklist and entered SPSS software (version 22, IBM Corporation, Armonk, NY, USA) for analysis. For presentation of continues and categorical variables mean ± standard deviation (SD) and absolute number (percentages) were utilized respectively. Independent t test was used for analysis of continuous variables. Categorical variables were analyzed using chi-square and Fisher's exact tests if necessary. Logistic regression test (Forward LR method) was used to evaluate association between risk factors and syncope occurrence. Variables including weight, BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), duration of standing, stress, anxiety and depression scores, positive history and family history of syncope, and history of smoking and medical problems were inserted in the model. Thereafter, statistically non-significant ones were eliminated during 1st to 3rd stages. P-value of less than 0.050 was considered as level of significance.

Results

This study was conducted on 50 cases and 150 controls with mean age of 22.94 ± 2.69 and 22.61 ± 2.75 years, respectively. 90% of cases presented history of long-time standing prior to syncope occurrence.

Table 1. Comparison of quantitative demographics information among study groups

Variable	Group		P
	Case (n = 50)	Control (n = 150)	
	(Mean ± SD)	(Mean ± SD)	
Age (year)	22.94 ± 2.69	22.61 ± 2.75	0.460
Height (cm)	177.56 ± 4.80	175.98 ± 5.54	0.070
Weight (kg)	69.32 ± 4.95	73.74 ± 10.35	0.004
BMI (kg/m^2)	21.97 ± 1.16	23.79 ± 3.02	< 0.001
SBP (mmHg)	117.42 ± 5.58	119.35 ± 12.32	0.040
DBP (mmHg)	75.64 ± 5.91	76.60 ± 7.79	0.420
Standing duration (minutes)	457.40 ± 71.28	416.46 ± 78.03	0.001
Sleeping duration (minutes)	457.40 ± 49.14	449.86 ± 48.17	0.270

SD: Standard deviation; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure

In addition, 64% of syncope occurred in summer (18% in spring, 14% in fall, and 4% in winter). Vertigo (70%), light headedness (54%), and nausea (54%) were among the most common symptoms of patients. Other symptoms included sweating (40%), vomiting (36%), and head pressure (34%).

Quantitative demographics information of participants are shown in table 1. Cases and controls were significantly different regarding weight, BMI, SBP, and duration of standing prior to syncope occurrence, while other variables including age, height, DBP, and sleeping duration were not statistically different between the two groups.

Table 2 is demonstrating the prevalence of variables among cases and controls. There were significant differences between cases and controls regarding positive history of syncope, family history of syncope, smoking, medical problems, anxiety, depression, and stress that all were statistically more common among those presented syncope.

Table 3 is demonstrating syncope risk factors. Logistic regression test was performed and considering crude model, weight, BMI, standing duration, history of syncope, positive family history of syncope, smoking, medical problems, anxiety, stress, and depression were detected as significant predictors of syncope occurrence. Based on model 1, by adjusting BMI, SBP, and smoking, BMI, standing duration, positive history of syncope, positive family history of syncope, smoking, medical problems, anxiety, stress, and depression were statistically significant. Model- 2 was performed by adjusting family history, anxiety, stress, and depression. This model showed significant outcomes of BMI, positive history of syncope, smoking, stress, and depression.

Table 2. Comparison of qualitative demographics between cases and controls

Variable		Group		P
		Case (n = 50) [n (%)]	Control (n = 150) [n (%)]	
Positive history of syncope		12 (24.0)	3 (2.0)	< 0.001
Positive family history of syncope		7 (14.0)	4 (2.7)	0.002
Positive history of smoking		14 (28.0)	15 (10.0)	0.002
Positive history of alcohol use		4 (8.0)	4 (2.7)	0.180
Marital status	Single	13 (26.0)	42 (28.0)	0.770
	Married	37 (74.0)	108 (72.0)	
Educational status	Less than high school	11 (22.0)	29 (19.3)	0.800
	High-school graduation	27 (54.0)	89 (59.3)	
	College education	12 (24.0)	39 (26.0)	
Occupational status	Student	28 (56.0)	91 (60.7)	0.940
	Farmer	6 (12.0)	13 (8.7)	
	Worker	7 (14.0)	19 (12.7)	
	Jobless	3 (6.0)	11 (7.3)	
	Self-employed	6 (12.0)	16 (10.7)	
Medical problems	Yes	7 (14.0)	3 (2.0)	0.003
	No	43 (86.0)	147 (98.0)	
Anxiety	Abnormal	32 (64.0)	67 (44.7)	0.018
	Normal	18 (36.0)	83 (55.3)	
Stress	Abnormal	28 (56.0)	24 (16.0)	< 0.001
	Normal	22 (44.0)	126 (84.0)	
Depression	Abnormal	33 (66.0)	47 (31.3)	< 0.001
	Normal	17 (34.0)	103 (68.7)	

Table 3. Crude and adjusted odds ratio for predicting syncope occurrence

Risk factor	OR (95%CI)		
	Crude model	Model 1	Model 2
Height (cm)	1.057 (0.99-1.24)	1.04 (0.98-1.11)	1.02 (0.94-1.09)
Weight (kg)	0.94 (0.90-0.98)[*]	1.05 (0.97-1.14)	1.01 (0.92-1.11)
BMI (kg/m^2)	0.72 (0.61-0.85)[*]	0.72 (0.60-0.86)[*]	0.75 (0.61-0.90)[*]
SBP (mmHg)	0.98 (0.95-1.01)	1.01 (0.97-1.04)	0.99 (0.95-1.04)
Standing duration (minutes)	1.01 (1.00-1.01)[*]	1.01 (1.00-1.01)[*]	1.01 (1.00-6.88)
Positive history of syncope	15.47 (4.15-57.60)[*]	14.85 (3.82-57.70)[*]	11.98 (2.42-59.29)[*]
Positive family history of syncope	5.94 (1.66-21.25)[*]	4.85 (1.28-18.38)[*]	2.45 (0.55-10.91)
Positive history of smoking	3.50 (1.54-7.91)[*]	3.13(1.33-7.36)[*]	4.09 (1.53-10.93)[*]
Medical problems	7.97 (1.98-32.17)[*]	8.12 (1.39-47.33)[*]	3.99 (0.66-23.89)
Anxiety	2.02 (1.13-4.26)[*]	2.24 (1.10-4.55)[*]	0.44 (0.15-1.27)
Stress	6.68 (3.28-13.57)[*]	7.08 (3.24-15.47)[*]	7.00 (2.43-20.17)[*]
Depression	4.25 (2.15-8.39)[*]	4.29 (2.06-8.93)[*]	2.86 (1.21-6.77)[*]

OR: Odds ratio; 95%CI: 95% of confidence interval; BMI: Body mass index; SBP: Systolic blood pressure
Model 1: Adjusted for BMI, SBP, and Smoking; Model 2: Further adjusted for family history, anxiety, stress, and depression
[*] Significant at level of 0.050

Discussion

Syncope is a relevant reason of referring to emergency rooms worldwide accounting for 1-3 percent of patients' referrals.[1] This condition occurs routinely among training soldiers standing for long duration in ranks and lines. Syncope is a usual etiology of cardiologist referral of military services officials, and has the third rank following palpitation and cardiac attack respectively.[10,15]

This condition occurs mostly among younger military populations (10-30 years old). The range of age is consistent with the most common age that participants of military training services have.[16]

Based on our searches, this case-control study is the first one in community of Iran that compared demographic etiologies of syncope among military training soldiers. In addition, it tried to assess risk factors of syncope occurrence among training soldiers.

According to findings of the current study, cases presenting syncope had significant less BMI and also SBP, while significantly experienced more duration of standing and presented higher scores of depression, anxiety, stress, and total score of DASS21. Other findings with significant higher prevalence among those with syncope presentation were history of syncope in family members and themselves, history of other medical problems, in addition to history of smoking. Marital, educational, and occupational statuses were among factors that were not associated with syncope incidence.

Gender distribution of syncope has been assessed previously, and no difference has been found.[10,17] Because of rules in Iran, all studied population of current study was men. Other factors that have been evaluated previously and found to be in association with re-experience of syncope included previous history of syncope occurrence in the self and their family members.[16,18]

The ratter factor that has been found to be significantly higher among those with presentation of syncope in comparison to control group was emotionally-related factors. Variety of studies has presented association of stress, anxiety, and depression with syncope, vasovagal type in special.[1,19,20]

Prodromal symptoms of syncope commonly known as presyncope was evaluated in the current study as well; while of limitations of our study was lack of assessing occurrence of syncope after presyncope/near syncope among our cases. Most common prodromal symptom was vertigo, followed by nausea, and lightheadedness. These symptoms were presented in other studies conducted by Peeters et al.,[1] Rubenstein and Josephson,[21] Gracie et al.,[22] and others, as well.

The ratter variables evaluated in our study were risk factor in association with syncope occurrence among training soldiers. Our study showed that higher BMI was in association with less probability of syncope. This factor was presented in the study of Basavarajegowda that presented this effect in vasovagal (neurocardiogenic) type of syncope,[23] and Christou and Kiortsis that declared this association with orthostatic type of syncope, also can be considered in association with neurocardiogenic type.[24] Of most considerable limitations of our study was lack of assessment of syncope type and its relations with risk factors.

Standing duration was another factor associated with syncope occurrence among soldiers. Wieling et al. reported this association as a risk factor of orthostatic, autonomic dysfunction, and vasovagal syncope.[25]

History of syncope in soldier and his family were other risk factors of syncope among troops which have been well-documented previously as well.[16,20,26] Colman et al. declared that 42% of patients with history of syncope may re-experience it within a year after first time, and 36% within the second year.[18]

Among emotional statuses, depression was the only statistically significant predicting risk factor of syncope occurrence in the current study. There are several studies that have stated this association with vasovagal type.[22,27-29] Bhangu et al. emphasized that treatment of depression can potentially prevent syncope occurrence.[30]

Of limitations of the current study was small number of cases and assessment of neurally-mediated syncope. Thus, further studies with larger sample size and assessment of all types of syncope are recommended.

Conclusion

This is a case-control study conducted on training soldiers experiencing syncope.

Based on findings of this study, higher BMI has protective role in syncope occurrence while depression and smoking are risk factors that make a person prone to syncope occurrence.

Thus controlling risk factors of syncope occurrence among training soldiers prior to their dispatch is strongly recommended. On the other hand, as some of them are modifiable, potential treatments are suggested, in addition, changing training course emotional state to a milder condition can help these cases.

Acknowledgments

Conflict of Interests

Authors have no conflict of interests.

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Comparison of the effect of fibrinogen concentrate with fresh frozen plasma (FFP) in management of hypofibrinogenemic bleeding after congenital cardiac surgeries: A clinical trial study[*]

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Original Article

Abstract

BACKGROUND: Hypofibrinogenemia is an independent factor of excessive bleeding after congenital cardiac surgeries. Fresh frozen plasma (FFP) and fibrinogen concentrate are examples of recommended products for management of hypofibrinogenemic bleedings. Unfortunately, there is no study to compare these treatments in pediatric cardiac surgeries. Therefore, this study aimed to compare the effect of fibrinogen concentrate with FFP on postoperative bleeding and clinical outcome after congenital cardiac surgeries in pediatric population.

METHODS: Phis prospective clinical trial study was carried out on 90 consecutive pediatric patients who underwent congenital cardiac surgeries. The eligible pediatrics who met our study criteria, randomly received FFP (10 ml/kg) or fibrinogen concentrate (70 mg/kg) to assess postoperative bleeding and blood-products requirements.

RESULTS: Each of FFP and fibrinogen concentrate significantly reduced total chest tube drainage (CTD) at 3, 6, 12, and 24 postoperative hours (P = 0.04). The analysis of time*intervention revealed that our intervention (fibrinogen group) significantly reduced CTD more (P = 0.01). Moreover, fibrinogen group had a significantly higher plasma fibrinogen level in first 24 hours (P = 0.02).

CONCLUSION: Nowadays, both of fibrinogen concentrate and FFP product are widely used for management of hypofibrinogenic bleedings after cardiac surgeries. According to our results, we concluded that although the both product had a comparable effect on management of hypofibrinogenemic bleeding in pediatrics undergoing congenital cardiac surgeries, choosing better product depended on general condition of patients such as their body fluid status.

Keywords: Congenital Defects, Fibrinogen, Cardiac Surgery, Pediatric Intensive Care Units, Blood Coagulation, Blood Transfusion

Introduction

Hypofibrinogenemia (plasma fibrinogen level of lower than 200 mg/dl) is associated with increasing risk of perioperative bleeding after cardiac surgeries.[1,2] Utilization of cardiopulmonary bypass (CPB) during congenital cardiac surgeries cause a significant drop (by approximately 34-42 percent) in plasma fibrinogen level, which would then result in excessive postoperative bleeding.[2,3] Pediatric patients are more susceptible to CPB-induced coagulopathies and excessive bleeding after congenital cardiac surgeries.[4]

The traditional treatment of hypofibrinogenemic bleeding is transfusion of allogeneic blood products such as fresh frozen plasma (FFP).[1,5] Unfortunately, transfusion of allogeneic blood products are strongly associated with increased mortality, infection, allergic reaction, neurologic complications, renal failure, and poor outcome.[1,6] Hence, hypofibrinogenemic bleeding is a life-threatening condition after congenital cardiac surgeries in pediatric patients, not only because of excessive blood loss, but also because of the additional risks of transfusion-related

complications.[4,7] Therefore, fibrinogen concentrate is currently preferred by many clinical practitioners, because of the lack of risks of transfusion-related complications.[1,5]

Despite the importance of hypofibrinogenemic bleeding in pediatrics, there is no study on comparing the efficacy of fibrinogen concentrate with FFP in hypofibrinogenemic bleeding in pediatric population after congenital cardiac surgeries.[8,9] Therefore, this study was carried out to compare this efficacy. In addition, this study compared the efficacy of fibrinogen concentrate with FFP on correction of plasma fibrinogen level, and blood requirement in pediatric cardiac intensive care unit (PCICU).

Materials and Methods

The study protocol was approved by ethical committee of Isfahan University of Medical Sciences, Isfahan, Iran (with number of 394081). Informed written consent was obtained from patients' parents or legal guardian. This clinical trial study was carried out between March 2014 and February 2015 in a single center. The inclusion criteria was fibrinogen levels of lower than 200 mg/dl in presence of bleeding exceeded 3 ml/kg in first postoperative hour. Exclusion criteria were age older than 2 years, history of cardiothoracic surgery (redo operation), emergency surgery, anemia [preoperative hemoglobin (Hb) level < 10 g/dl], thrombocytopenia [platelet count (Plt) < $100 \times 10^3/\mu l$], coagulopathy [prothrombin time (PT) > 14.8 s], liver disease (alanine aminotransferase or aspartate aminotransferase > 150 IU/l), active infection, using anticoagulant agents during last month, requirement for additional dose of FFP or fibrinogen concentrate, and known hypersensitivity to fibrinogen concentrate. Our study population primarily consisted of 162 patients who were candidate for congenital cardiac surgery in our center (between March 2014 and February 2015). The patients who did not meet our criteria (n = 54) or their parents (or guardians) did not sign informed consent (n = 18) were excluded from study. Finally, we totally recruited 90 eligible pediatric patients in our study.

We assigned eligible patients (n = 90) into two equal groups of fibrinogen concentrate and FFP product. The first eligible patient allocated to fibrinogen group by lottery, then, the next recruitments were performed in a 1:1 ratio (one patient in FFP group and one patient in fibrinogen group). The fibrinogen group received 70 mg/kg fibrinogen concentrate (Haemocomplettan® P, CSL Behring GmbH, Marburg, Germany), and the FFP group received 10 ml/kg FFP. Blood loss and plasma fibrinogen level of each group was measured and recorded every hour. Coagulation and hematology tests including Hb, Plt, PT, activated partial thromboplastin time (aPTT), and activated clotting time (ACT) was obtained at the 1st, 12th, and 24th postoperative hours.

Routine cardiorespiratory care was performed for all of the patients. Operations performed under standard general anesthesia. After median sternotomy, cardiopulmonary bypass with aortobicaval cannulation was initiated under mild hypothermia (35 °C). Myocardial protection achieved with single injection of cold-crystalloid cardioplegia. Before initiation of CPB, anticoagulation therapy was established via heparinization of patients. In order to achieve ACT of 480 seconds as a target value, 400 IU/kg heparin was administrated through central venous line. According to our perfusionist's protocol, the priming solution was consisted of 10-20 ml/kg human albumin 20%, 10-20 mEq/l bicarbonate sodium, and 0.5 g/kg mannitol 20%. CPB circuit filled up with 300-1000 ml lactated Ringer's solution as needed. In order to maintain hematocrit (HCT) between 20%-25%, packed red blood cells (RBCs) added to solution during bypass. A centrifugal blood pump (Medtronic, Minneapolis, MN, USA), and a hollow-fiber oxygenator (Dideco, Sorin Group Italia, Mirandola, Italy) was used for CPB. Following completion of surgeries and correction of cardiac anomalies, protamine sulfate was administrated in ratio of 1 mg per 100 IU of the total heparin dose to neutralize anticoagulant effect of heparin. The value of ACT less than 150 second was accepted as target value for adequate reversal of heparin. After medical normalization of coagulation and weaning from CPB, surgical hemostasis was performed by placement of suture and using diathermy. Surgical hemostasis was continued until surgeon ensured that there was no source of active bleeding or obvious blood loss. Hypofibrinogenemic bleeding was managed using fibrinogen concentrate (in fibrinogen group) or FFP (in FFP group). Then, patients were rewarmed to 37°C, and transferred to PCICU.

Following PCICU arrival, any blood products were transfused, if necessary, according to our institutional protocol. The protocol consisted of transfusion of 10 ml/kg RBCs if hemoglobin was below 12 g/dl (to maintain Hb > 12 g/dl), and 20 ml/kg of platelets if Plt count was below $100 \times 10^3/\mu l$ (to maintain Plt count > $100 \times 10^3/\mu l$).

Table 1. The demographic characteristics of the participants (n = 90)

Characteristic		Group		P
		Fibrinogen concentrate (n = 45)	Fresh frozen plasma (n = 45)	
		Mean ± SD	Mean ± SD	
Age (month)		21.93 ± 12.20	21.15 ± 28.80	0.88[*]
Height (cm)		76.91 ± 16.30	73.95 ± 19.94	0.44[*]
Weight (kg)		8.95 ± 4.17	8.42 ± 4.82	0.57[*]
Body mass index (kg/m^2)		14.31 ± 1.56	14.91 ± 2.66	0.18[*]
CPB time (minute)		125.15 ± 20.14	128.33 ± 28.80	0.82[*]
		n (%)	n (%)	
Gender	Male as boy	27 (60.00)	23 (51.11)	0.52[**]
	Female as girl	18 (40.00)	22 (48.89)	
Diagnosis	PS	2 (4.44)	4 (8.88)	N/A
	AS	0 (0)	3 (6.66)	
	ASD	14 (31.11)	8 (17.77)	
	TR	4 (8.88)	4 (8.88)	
	ASD + PDA	4 (8.88)	0 (0)	
	ASD + PS	2 (4.44)	0 (0)	
	PDA	4 (8.88)	10 (24.40)	
	VSD + ASD	6 (13.33)	2 (4.44)	
	VSD	9 (20.00)	14 (31.11)	
Open Sternum		2 (4.44)	2 (4.44)	> 0.99[**]

SD: Standard deviation; CPB: Cardiopulmonary bypass; PS: Pulmonary stenosis; AS: Aortic stenosis; ASD: Atrial septal defect; TR: Tricuspid regurgitation; PDA: Patent ductus arteriosus; VSD: Ventricular septal defect; N/A: Not available
[*] Continues variables were analyzed using paired-sample t test; [**] Categorical variables were analyzed using chi-square or Fisher's exact tests (as appropriate).

None of antifibrinolytic agents were routinely administrate in our institute. As mentioned before, requirement for additional doses of FFP/fibrinogen considered as an exclusion criterion in our study.

Statistical analysis was performed using SPSS software (version 20, IBM Corporation, Armonk, NY, USA). Continuous variables of the study were presented as mean ± standard deviation (SD). Normal distribution of sample data was determined by normality tests. Therefore, parametric tests including paired-sample independent t test and repeated measures ANOVA (as appropriate) were used to find statistically significant differences between continuous variables of patient's characteristics and outcome. Homogeneity of variance (assumption of sphericity) determined by Mauchly test. Categorical variables were shown as frequency (percent), and were analyzed using chi-square or Fisher's exact tests (as appropriate).

P-value of less than 0.05 was considered as significant level for all of the tests.

Results

Demographic Data: There was no significant difference in demographic and baseline characteristics of patients in fibrinogen and FFP groups. The mean age of participants was 21.93 ± 12.20 and 21.15 ± 28.80 month in fibrinogen and FFP groups, respectively. The mean CPB time was 125.15 ± 20.14 minute and 128.33 ± 28.80 in fibrinogen and FFP groups, respectively (Table 1).

Postoperative Bleeding: Postoperative chest tube drainage (CTD) in the groups are summarized in table 2. As the table shows, CTD was significantly reduced in the two group over the time (P = 0.04), but our intervention significantly decreases the amount of bleeding more in fibrinogen group (P=0.01).

Table 2. Postoperative chest tube drainage (CTD) in studied groups (n = 90)

Time duration	Chest tube drainage (ml/kg/hour)		P			
	Fibrinogen concentrate group (n = 45)	Fresh frozen plasma group (n = 45)				
First 3 hours	4.77 ± 2.05	6.94 ± 6.05	0.02[*]	0.02[**]	0.04[£]	0.01[§]
First 6 hours	4.13 ± 1.84	6.31 ± 6.22	0.02[*]			
First 12 hours	3.40 ±1.29	4.52 ± 4.37	0.04[*]			
First 24 hours	1.93 ± 6.63	2.64 ± 2.18	0.04[*]			

[*] Analysis was performed using paired-sample t-test; [**] Analysis of the effect of intervention, performed using repeated measures ANOVA; [£] Analysis of the effect of time, performed using repeated measures ANOVA; [§] Analysis of the effect of time*intervention, performed using repeated measures ANOVA.

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Table 3. Postoperative outcomes in studied groups (n = 90)

Characteristic	Group		P
	Fibrinogen concentrate (n = 45)	Fresh frozen plasma (n = 45)	
	Mean ± SD	Mean ± SD	
Length of, (hour)			
Mechanical ventilation support	14.00 ± 4.00	12.53 ± 4.24	0.08*
ICU stay	3.04 ± 1.79	3.66±1.80	0.89*
Inotrope requirement	29.71 ± 18.77	26.40 ± 17.16	0.38*
	n (%)	n (%)	
Total allogeneic blood transfusion			
Platelet (Plt)	0 (0)	2 (4.44)	0.38*
Red blood cells (RBCs)	5 (11.11)	9 (20.00)	0.49*
Complication			
Renal failure	0 (0)	1 (2.22)	> 0.99**
Respiratory failure	0 (0)	1 (2.22)	> 0.99**
Neurologic (Stroke, CVA)	0 (0)	0 (0)	-
Hemodynamic instability	4 (8.88)	1 (2.22)	0.36**
Reoperation due to surgical bleeding	0 (0)	1 (2.22)	> 0.99**

SD: Standard deviation; ICU: Intensive care unit; CVA: Cerebrovascular accident
* Continues variables were analyzed using paired-sample t test; ** Categorical variables were analyzed using chi-square or Fisher's exact tests (as appropriate).

Allogeneic Blood Transfusions: As is shown in table 3, there were no requirement for Plt transfusion in fibrinogen group whereas 2 patients received Plt in FFP group. Moreover, 5 patients in fibrinogen group and 9 patients in FFP group received RBCs; however, but the difference was not significant. None of the patients received antifibrinolytic agents.

Postoperative Outcome: In contrast with the FFP group, the fibrinogen group non-significantly had a longer time of mechanical ventilation (14.00 ± 4.00 vs. 12.53 ± 4.24 hours) and inotrope support (29.71 ± 18.77 vs. 26.40 ± 17.16 hours). In contrary, the FFP group non-significantly had a higher intensive care unit (ICU) stay than the fibrinogen group (3.66 ± 1.80 vs. 3.04 ± 1.79 days). No differences were observed between the two groups in incidence of postoperative complications (Table 3).

Discussion

Hypofibrinogenemic bleeding is a common complication of on-pump congenital cardiac surgeries, as a result of hemodilution and consumption of coagulation factors during CPB.[10,11] Currently, allogeneic blood products (i.e., FFP) and fibrinogen concentrate are highly used for management of hypofibrinogenemic bleeding after congenital cardiac surgeries.[12] Unfortunately, there is only a few studies comparing the efficacy and safety of fibrinogen concentrate with FFP in management of postoperative bleeding in pediatric patients undergoing cardiac surgeries.[3,13-15]

Clinical efficacy of fibrinogen concentrate comparing with traditional management of postoperative bleeding in pediatrics with severe cardiac disease was assessed by Cui et al.[4] To their results, fibrinogen concentrate (in combination with Plt) reduced postoperative blood loss of the first postoperative hour (3.5 ± 1.6 vs. 2.9 ± 2.0 ml/kg/h, P = 0.43). The magnitude of the effect of fibrinogen therapy in next 6 hours was not as high as the first hour (1.5 ± 0.6 vs. 1.3 ± 0.1 ml/kg/h, P = 0.41). Moreover, Galas et al. study[5] indicated that 48-hour blood loss of patients reduced after administration of fibrinogen concentrate compared with cryoprecipitate (320 vs. 410 ml, P = 0.67). However, these findings were not statistically significant. Our results are supported by other studies that compared the efficacy of fibrinogen concentrate with traditional management of postoperative bleeding in adult populations.[12,16-18] A retrospective cohort study of patients with ruptured abdominal aortic aneurysm demonstrated that preoperative hypofibrinogenemia was significantly associated with increased risk of perioperative bleeding.[19] The authors noted that plasma fibrinogen level of less than 150 mg/dl resulted in a 10-fold increase in perioperative blood loss as much as 2000 ml. Two prospective randomized trials that studied high-risk aortic surgeries, reported that early fibrinogen concentrate management after removal of CPB significantly reduced postoperative blood loss and transfusion of allogeneic blood products.[3,17] Similarly, three cohort and one review studies endorsed the use of fibrinogen concentrate

as an effective management for hypofibrinogenemic bleeding after adult cardiac surgeries.[12,18,20,21] However, generalization of this results to complex congenital cardiac surgeries in pediatric patients is limited.

Transfusion of RBCs occurs in more than 50% pediatric patients in PCIUCs. Transfusion of RBCs in the pediatrics is independently associated with increased mortality, infection, allergic reaction, prolonged mechanical ventilation, inotrope requirement, neurologic complications, renal failure, and poor outcome.[1,6] Our study showed that our patients who received fibrinogen concentrate, although non-significantly but, received lesser RBCs products. The current evidences from adult cardiac surgeries proposed a beneficial effect for fibrinogen concentrate compared with FFP in reduction of postoperative blood loss and requirement for transfusions.[14] However, the effect of fibrinogen concentrate on reduction of postoperative blood loss is unclear and debated.[5,14,22] Several reasons such as multifactorial nature of blood loss after congenital surgeries, dose and timing of management, and design of studies can explain these controversies.

Conclusion

There is a large body of evidences which proposing that the FFP product has not adequate quantity of fibrinogen concentrate to manage severe hypofibrinogenemia.[12] Transfusion of large volumes of FFP increase the risk of hypercoagulability, hemodilution, volume overload, pulmonary edema, and congestive heart failure.[13,22] In contrast, the fibrinogen concentrate is a small-volume fluid (after dissolution) that does not require a long time for thawing and preparing.[1,8] Moreover, hypercoagulability and thromboembolism do not increase by administration of even high doses of fibrinogen concentrate (up to 600 mg/kg).[21] Considering the differences in volumes of FFP and fibrinogen concentrate, administration of fibrinogen concentrate may be valuable in pediatric patients that need volume restriction such as cases of congestive heart failure, renal disease, volume overload, or any other restricted fluid intake conditions. In contrast, FFP is a high-volume allogeneic product which contains lower fibrinogen concentration, and may be a better choice in management of patients with hypofibrinogenemia requiring volume replacement or with multiple coagulation factor deficiencies. However, cryoprecipitate is an alternative product for FFP which is preferred by many clinicians to avoid issues with volume loading.[5]

Conflict of Interests

Authors have no conflict of interests.

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The association between the serum 25-hydroxyvitamin D level and cardiovascular events in individuals with and without metabolic syndrome

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Original Article

Abstract

BACKGROUND: Previous studies revealed that the level of 25-hydroxyvitamin D [25(OH)D] could be consider as one the risk factors for the occurrence of cardiovascular diseases (CVDs). This study aimed to evaluate the relationship between serum 25(OH)D level and CVD events in individuals with and without metabolic syndrome (MetS) in an Iranian population.

METHODS: In this nested case-control study conducted as a part of the Isfahan Cohort Study (ISC), 55 patients with CVD events were selected as case group, and 55 sex- and age-matched individuals without CVD events as control group. These participants were divided into the two main groups based on the presence of MetS at baseline.

RESULTS: The level of 25(OH)D in individuals with and without MetS was significantly lower among patients with CVD compared to those without CVD events at the baseline of study and after the follow-up (P = 0.036 and P = 0.039, respectively). The level of 25(OH)D significantly decreased risk of incidence of CVD events in individuals without MetS after adjusting for age, sex, nutrition, and exposure to sunlight [0.19 (0.05-0.73); P = 0.016]. There was not any significant relationship between the amount of 25(OH)D at the baseline and CVD events in individuals with MetS.

CONCLUSION: In individuals with MetS, the level of 25(OH)D is not related to CVD events; as MetS directly influence the pathophysiology of mechanisms which are responsible for CVD events, and maybe this effect obscure the effect of 25(OH)D.

Keywords: Cardiovascular Diseases, Metabolic Syndrome, 25-Hydroxyvitamin D

Introduction

Cardiovascular disease (CVD) is considered as the main cause of mortality and morbidity around the world,[1] and diabetes mellitus, hypercholesterolemia, smoking, hypertension, obesity, metabolic syndrome (MetS), and physical inactivity are primary risk factors for CVD.[2] The prevalence of CVD and its primary risk factors is increasing more rapidly in Asia than in Western countries.[3] Although, pharmacological therapy and lifestyle modification are critical steps in the management of patients with MetS, but several meta-analyses show several factors are involved in the pathogenesis of MetS.[4]

Epidemiological studies confirm a high prevalence of CVD and metabolic syndrome (MetS) among the Iranian population.[5] Results of previous studies show that the level of vitamin D [25-hydroxyvitamin D or 25(OH)D] can be consider as one of the risk factors for CVD occurrence.[6-8] Previous studies show that

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the level of 25(OH)D is lower than recommended amount among Iranian population.[9] But, still it is unclear that how the level of 25(OH)D can affect the incidence of CVD among Iranian subjects with MetS.

This study aimed to evaluate the relationship between serum level and CVD in individuals with and without metabolic syndrome in an Iranian population. The selected population was free of CVD at baseline, so could be consider as one of the most reliable databases for prediction of CVD and related risk factors.

Materials and Methods

This research was based on a large longitudinal cohort study, begun in 2001. Isfahan Cohort Study (ICS), as one of the biggest longitudinal studies in the Middle East, followed a large population. ICS is a population-based, ongoing longitudinal study on adults aged 35 years or more, living in urban and rural areas of three counties in central Iran namely Isfahan, Najafabad, and Arak.[10] The participants were recruited from January 2 to September 28, 2001 to date.[11] A total of 6323 participants were studied in 2001, 925 were lost to the follow-ups, and the remaining 5398 were followed during 12 years. A large sample was selected from urban and rural population of 35-year-old people and more from Isfahan, Najafabad, and Arak with the use of a random multistage cluster sampling method, and was followed for 12 years. The exhaustive methods, sampling and quantities, and population characteristics of the ICS were previously published.[10,11] Patients with metabolic and inflammatory diseases, and those advised by any agents such as lipid and carbohydrate lowering agents, and consumed 25(OH)D or calcium supplements were excluded from this sub-study.

At first, each participant offered his/her written informed consent. The research committee at Isfahan Cardiovascular Research Institute, as a collaborating center of World Health Organization (WHO), approved the protocol. By the use of a validated questionnaire such as demographic data, socioeconomic information, history of drugs, and risk factors for CVDs, the skilled medical personnel collected the baseline statistics. Besides, dimensions of body weight and height were done on a calibrated beam scale and stadiometer barefoot to the nearest 0.1 kg and 0.1 cm, one-to-one. Then, body weight (kg) was divided by height (m²) to get body mass index (BMI). Moreover, questions concerning nutrition, physical activity and smoking habits, stress, and exposing in the sunlight were gathered by validated questionnaire which filed out by trained nurses.

Clinical and para clinical tests: Fasting (12 hours) blood samples (10 ml) were collected from all contributors, and were tested at the Isfahan central laboratory of Cardiovascular Research Center. Serum total cholesterol (TC), triglycerides, and fasting blood sugar (FBS) were calculated enzymatically, using an autoanalyzer (Eppendorf, Hamburg, Germany), and serum high-density lipoprotein-cholesterol (HDL-C) was measured after precipitation of low-density lipoproteins with dextran sulfate-magnesium. By using the Friedewald equation, we calculated serum low-density lipoprotein-cholesterol (LDL-C) in subjects who had triglycerides less than 400 mg/dl, otherwise we used standard kits to measure. Blood samples were centrifuged immediately in each county, total samples were transported to the central laboratory in 1 hour, and FBS and 2-hour post-prandial [0] (2hpp) glucose tests were measured immediately in the reference area. Serum frozen at -20 °C transported to the central laboratory by a 3-hour transportation with cold chain (-20 °C), and kept frozen there until measured within 72 hours.[11]

25(OH)D was measured using the enzyme-linked immunosorbent assay (ELISA) kit (Cal biotech, USA). A serum level of less than 25 ng/ml was considered as vitamin D deficiency.[6]

Subjects selected based on the Adult Treatment Panel (ATP III) criteria. When a subject had three of the five listed criteria, a diagnosis of the MetS could be made. The primary clinical outcome of MetS was identified as CVD. ATPIII defined the MetS essentially as a clustering of metabolic complications of obesity. The listed criteria included abdominal obesity, determined by increased waist circumference (WC), raised triglycerides, reduced HDL, elevated blood pressure, and raised plasma glucose.[12]

CVD events defined as acute myocardial infarction (AMI), unstable angina pectoris (UAP), sudden cardiac death (SCD), and stroke.[13]

The methodology used to obtain measurements of clinical and biochemical variables have been previously published.[14] All the cohorts participants followed through telephone call, and all the events were recorded. The cohort follow-up procedure is explained in detail elsewhere.[11]

Discrete variables were presented as frequency (percentage). Continuous variables were expressed as mean ± standard deviation (SD). Comparison of categorical variables between two groups was done

using chi-square test, and across quantitative variables by one-way ANOVA test. Cox proportional hazards model was chosen as the best approach for analyzing survival time data to investigate the association of 25(OH)D level and occurrence of CVD events in MetS and non-MetS groups separately. We fitted three adjusted models further than crude model to remove the effects of covariates including, adjusted for age and sex, adjusted for age, sex, and dietary score, and adjusted for age, sex, dietary score, and exposure to sunlight for the last one, which quantity was reported as hazards ratio (HR) [95% of confidence interval (95% CI)]. For all analyses, statistical significance was considered at a level of 0.050. All data were analyzed by using Statistical Package for the Social Sciences (SPSS) software (version 19.0, SPSS Inc., Chicago, IL, USA).

Results

In this sub-study, 52 patients with MetS and 58 age- and sex-adjusted individuals without MetS participated, all of them free of CVD events at baseline.

Comparisons of baseline characteristics between the groups are presented in table 1. The mean of age was higher among subjects with CVD events without considering MetS. There were no significant differences between education, marital status, residency in rural or urban area, physical activity, smoking, nutritional habits, and level of

stress in subjects with and without MetS, No significant differences existed in the time spent on exposure to the sunlight in the study groups as well.

Table 2 shows clinical and biochemical characteristics of the study groups. The level of 25(OH)D in subjects with and without MetS was significantly lower among patients with CVD compared with those without CVD events at the baseline of study and after follow-up (P = 0.036 and P = 0.039, respectively).

No significant difference existed between the study groups in terms of triglycerides, HDL-C, FBS, TC, LDL-C, WC, BMI, and diastolic blood pressure. In subjects without MetS, significant changes was seen in systolic blood pressure between those with or without CVD events [129.39 ± 22.65 and 117.58 ± 19.31 mmHg, respectively, P = 0.030].

Table 3 shows the HR of the level of 25(OH)D and risk of incidence of CVD among the participants with and without MetS at the baseline. The level of 25(OH)D non-significantly decreased the risk of incidence of CVD events in the subjects without MetS at the baseline [0.39 (0.14-1.03), P = 0.060]. But after adjusting for age, sex, nutrition, and exposure to sunlight, we found that the level of 25(OH)D decreased the risk of CVD events [0.19 (0.05-0.73), P = 0.016]. These findings did not show any significant relationship between amount of 25(OH)D at the baseline and CVD events in participants with MetS.

Table 1. The demographic characteristics of study groups

Variable	Group					
	With metabolic syndrome			Without metabolic syndrome		
	With CVD event (n = 26)	Without CVD event (n = 26)	P	With CVD event (n = 29)	Without CVD event (n = 29)	P
	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
Age (year)	56.50 ± 8.90	51.30 ± 7.20	0.024	58.50 ± 8.40	51.30 ± 7.90	0.001
Physical activity (Mets/week)	786.51 ± 365.69	957.20 ± 658.53	0.250	661.28 ± 401.06	1165.51 ± 1102.69	0.026
Global dietary index	0.92 ± 0.32	0.95 ± 0.22	0.770	0.98 ± 0.24	1.11 ± 0.17	0.020
	n (%)	n (%)		n (%)	n (%)	
Men	5 (19.2)	5 (19.2)	> 0.999	25 (86.2)	14 (48.3)	0.004
Women	21 (80.8)	21 (80.8)		4 (13.8)	15 (51.7)	
Illiterate	11 (42.3)	8 (30.8)	0.660	5 (17.2)	8 (27.6)	0.640
Primary school	11 (42.3)	14 (53.8)		17 (58.6)	15 (51.7)	
More than primary school	4 (15.4)	4 (15.4)		7 (24.1)	6 (20.7)	
Urban	18 (69.2)	12 (46.2)	0.160	27 (93.1)	19 (65.5)	0.021
Rural	8 (53.8)	14 (53.8)		2 (6.9)	10 (34.5)	
Married	21 (80.8)	22 (88.0)	0.370	28 (96.6)	27 (93.1)	0.500
Low stress	9 (34.6)	8 (30.8)	> 0.999	13 (44.8)	9 (31.0)	0.410
High stress	17 (65.4)	18 (69.2)		16 (55.2)	20 (69.0)	
Smoking	1 (3.8)	1 (3.8)	> 0.999	9 (31.0)	3 (10.3)	0.100
	Median (IQR)	Median (IQR)		Median (IQR)	Median (IQR)	
Exposure to sunlight (minute)	120 (60-240)	60 (30-120)	0.110	120 (45-240)	60 (30-150)	0.730[*]

CVD: Cardiovascular disease; SD: Standard deviation; IQR: Interquartile range
[*] Mann-Whitney test

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Table 2. The clinical characteristics of study groups

Variable	Group					
	With metabolic syndrome			Without metabolic syndrome		
	With CVD event (n = 26)	Without CVD event (n = 26)	P	With CVD event (n = 29)	Without CVD event (n = 29)	P
	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
Serum vitamin D (ng/ml)	22.14 ± 14.49	32.99 ± 21.15	0.036	16.84 ± 12.61	24.24 ± 14.01	0.039
Fasting blood glucose (mg/dl)	122.96 ± 52.64	119.63 ± 42.34	0.800	90.00 ± 9.82	92.46 ± 23.36	0.600
Triglyceride (mg/dl)	239.80 ± 141.29	228.66 ± 143.86	0.770	152.44 ± 108.29	164.08 ± 110.73	0.680
Total cholesterol (mg/dl)	226.40 ± 46.83	219.16 ± 27.29	0.500	213.31 ± 41.81	209.55 ± 48.04	0.750
High-density lipoprotein (mg/dl)	43.82 ± 9.05	40.93 ± 8.28	0.230	46.65 ± 12.01	50.49 ± 9.84	0.180
Low-density lipoprotein (mg/dl)	135.23 ± 23.43	131.60 ± 21.46	0.490	127.65 ± 33.32	128.06 ± 29.36	0.960
Waist circumference (cm)	104.07 ± 7.78	103.23 ± 6.92	0.680	87.48 ± 9.57	88.72 ± 10.12	0.630
BMI (kg/m^2)	31.88 ± 4.32	30.91 ± 3.30	0.370	24.55 ± 3.04	25.47 ± 4.40	0.360
Systolic blood pressure (mmHg)	134.90 ± 21.61	132.50 ± 20.27	0.680	129.39 ± 22.65	117.58 ± 19.31	0.030
Diastolic blood pressure (mmHg)	82.11 ± 13.27	82.59 ± 10.68	0.880	77.84 ± 12.56	78.10 ± 11.15	0.940
	n (%)	n (%)		n (%)	n (%)	
Vitamin D ≥ 25 ng/ml	11 (42.3)	15 (57.7)	0.270	6 (20.7)	11 (37.9)	0.140

CVD: Cardiovascular disease; SD: Standard deviation; BMI: Body mass index

Discussion

This nested case-control study compared the impact of 25(OH)D status on CVD events among subjects with or without MetS at baseline prospectively; and demonstrated significant relationship between serum 25(OH)D level at baseline and incidence of CVD events in individuals without MetS in an Iranian population. Although, several studies focused on the relationship between 25(OH)D and CVD events, but this study, for the first time among Iranian population, showed the relationship between CVD events and 25(OH)D in subjects with MetS at the baseline and after follow up for 10 years (during ICS) with focusing on the occurrence of CVD events. In addition, very few researchers have been evaluated the effect of 25(OH)D on risk of CVD events in longitudinal studies.

Our previous results displayed having MetS increased the risk of CVD by 2 times,[14] so it seems that in subjects with MetS, the effect of MetS is obscure the effect of 25(OH)D; as MetS affects the pathophysiology of mechanisms which are responsible for CVD events. It is clear that

hypovitaminosis D has extra-skeletal effects that influence the progress of various pathologies including those that make up a large number of morbidity and mortality cases, such as CVD, diabetes mellitus, and MetS.[15] Mechanism for how 25(OH)D may improve CVD events is unclear; though, it has postulated that down regulation of the renin-angiotensin aldosterone system could have effect on the cardiovascular system.[16] A few studies have evaluated the role of 25(OH)D acting directly on cardiac tissue, particularly in response to injury.[17] Proposed mechanisms have effects on the renin-angiotensin system, on glycemic control, and inflammatory cytokines, and direct effects on the vasculature and regulation of parathormone (PTH) levels, and calcium deposition in vascular smooth muscle. Earlier studies support the proposal that low serum 25(OH)D concentrations are associated with increased risk of the development of the MetS.[18] For example, Gagnon et al.[19] studied 4164 adults (mean age of 50 years; 58% women; 92% Euripides) over the following 5 years, and identified 528 incident cases (12.7%) of the MetS.[19]

Table 3. The hazard ratio of vitamin D serum level and risk of cardiovascular disease (CVD) among the study groups

Models	Group			
	With metabolic syndrome		Non metabolic syndrome	
	HR (95% CI)	P	HR (95% CI)	P
Crude	0.70 (0.32-1.53)	0.370	0.39 (0.14-1.03)	0.060
Model 1	0.53 (0.24-1.18)	0.120	0.23 (0.07-0.73)	0.013
Model 2	0.53 (0.24-1.18)	0.120	0.24 (0.07-0.82)	0.023
Model 3	0.54 (0.23-1.24)	0.140	0.19 (0.05-0.73)	0.016

HR: Hazard ratio; CI: Confidence interval
Mode 1: Adjusted for age and sex; Model 2: Adjusted for age, sex, and dietary score ; Model 3: Adjusted for age, sex, dietary score, and exposure to sunlight

We found positive relationship between systolic blood pressure and CVD events among subjects without MetS; interestingly, it seems that exposure to the sunlight is related to the synthesized 25(OH)D and could be playing a vital role in the regulation of blood pressure. The effect of 25(OH)D level on blood pressure could decrease by increasing age.[20]

We used the cutoff point of 25 ng/ml for 25(OH)D; so our results showed subjects in the lowest quartile for 25(OH)D had increased hazard ratios for cardiovascular mortality compared with subjects in the highest quartile for 25(OH)D. Similar findings have been reported in incident hemodialysis patients.[21] Previous and smaller study from India did not find any benefit from having optimal levels of 25(OH)D in subjects with CVD. In contrast, they described that very high levels of 25(OH)D (> 89 ng/ml) were associated with increased risk of ischemic heart disease.[22]

This study was limited to the small sample size; but its strength is related to the long follow-up period. We do not have any information about the use of sunscreen by participants in this study.

Conclusion

Our findings showed significant relationship between serum 25(OH)D level and CVD events in individuals without MetS in an Iranian population which participated in the ICS. It seems that in subjects with MetS, the level of 25(OH)D is not related to the CVD events, as MetS affects the pathophysiology of mechanisms responsible for CVD events.

Acknowledgments

Conflict of Interests

Authors have no conflict of interests.

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The effects of low-volume high-intensity interval versus moderate intensity continuous training on heart rate variability, and hemodynamic and echocardiography indices in men after coronary artery bypass grafting: A randomized clinical trial study

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Original Article

Abstract

BACKGROUND: Heart rate variability (HRV) declines after coronary artery bypass grafting (CABG). The purpose of this study was to evaluate the effect of low-volume high-intensity interval training (LV-HIIT) and moderate-intensity continuous training (MICT) on HRV as well as, hemodynamic and echocardiography indices.

METHODS: Forty-two men after CABG (55.12 ± 3.97 years) were randomly assigned into LV-HIIT, MICT, and control (CTL) groups. The exercise training in LV-HIIT consisted of 2-minute interval at 85-95 percent of maximal heart rate (HR_{max}), 2-minute interval at 50% of HR_{max} and 40-minute interval at 70% of HR_{max} in MICT for three sessions in a week, for 6-weeks. HRV parameters were evaluated by 24-hour Holter electrocardiography (ECG) recording, and echocardiography parameters at baseline and end of intervention were measured in all 3 groups.

RESULTS: At the end of the intervention, left ventricular ejection fraction (LVEF) significantly increased in LV-HIIT group (58.53 ± 7.26 percent) compared with MICT (52.26 ± 7.91 percent) and CTL (49.68 ± 7.27 percent) groups (P < 0.001). Furthermore, mean R-R interval, root mean square successive difference (RMSSD) of R-R interval, and standard deviation of R-R interval (SDRR) in LV-HIIT group considerably increased compared with MICT group (P < 0.001). High-frequency power (HF) significantly increased in LV-HIIT and MICT groups compared with CTL group (P < 0.001). On the other hand, low frequency (LF) and LF/HF ratio significantly decreased in LV-HIIT group in comparison with MICT group (P < 0.010).

CONCLUSION: These results suggest that LV-HIIT has a greater effect on improvement of cardiac autonomic activities by increasing R-R interval, SDRR, RMSSD, and HF, and decreasing LF and LF/HF ratio in patients after CABG.

Keywords: High-Intensity Interval Training, Continuous Training, Cardiac Rehabilitation, Cardiac Autonomic Activity

Introduction

Cardiovascular disease (CVD) is one of the major causes of death in the world.[1] Patients with coronary artery disease (CAD) are at risk for life-threatening arrhythmias and sudden death. In patients with CAD, alterations in cardiac autonomic control, that are characterized by relative increase in sympathetic activity and decline of vagal modulation, play a major role in the occurrence of arrhythmic events.[2,3] The variation of the time intervals between consecutive heartbeats or the instantaneous heart rates is called heart rate variability (HRV). HRV is a non-invasive method for assessing autonomic activity and providing information about heart's ability to respond to the normal regulatory impulses, vagal modulation, and sympathovagal interactions.[4] Cardiac autonomic dysfunction, as evidenced by low HRV, has strong

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detrimental effects on subsequent clinical outcome in patients with CAD.[5] Low HRV is associated with all-cause mortality and increased risk of sudden cardiac death after myocardial infarction (MI).[3,5]

Some studies indicate that HRV significantly decreases in patients after coronary artery bypass grafting (CABG) surgery, a condition that is even riskier than that of patients with MI.[6] Cardiac autonomic nerves are permanently damaged after CABG surgery, leading to impairment of cardiac parasympathetic modulation.[7] In contrast, many studies have demonstrated that exercise training has numerous benefits, including improvements in cardiorespiratory fitness, exercise capacity, cardiovascular risk factors, and endothelial function.[8-10] Aerobic exercise training is a well-established means of improving autonomic function (through enhancing vagal, and reducing sympathetic cardiac modulation) in patients with MI, heart failure, and CABG.[11-13]

Murad et al. reported significantly greater increase in root mean square successive difference (RMSSD) of R-R interval and standard deviation of R-R interval (SDRR) in elderly patients with congestive heart failure (CHF) after 16-weeks of moderate intensity training, which represented improved HRV induced-exercise training.[14] Another study reported that low-intensity exercise has a minimal adaptive effect on cardiac parasympathetic modulation after CABG surgery.[15] These findings suggest that exercise rehabilitation program may be used to improve HRV in CVD. However, the optimal dose of exercise, defined as the volume and intensity of exercise for improvement in cardiac autonomic regulation, is a crucial issue that is not fully understood.[16,17]

Aerobic exercise training is the cornerstone of exercise training programs which beneficial effects of aerobic exercise training in cardiac autonomic regulation as well as, physiological and clinical parameters in patients with CVD is known.[18] Recent studies have indicated that high-intensity interval training (HIIT) has a superior effect on exercise capacity, endothelial function, and quality of life than moderate-intensity continuous training (MICT) in healthy subjects and patients with CHF/CAD.[19-21] HIIT consists of alternating periods of high-intensity exercise involving 30-300-second bouts of aerobic exercise at 85-100 percent of maximum rate of oxygen consumption (VO_{2max}) that are separated with periods of low-intensity exercise of equal or shorter duration, to allow patients to allocate greater time to high-intensity rather than continuous exercise.[22] It has been shown that a single session of HIIT improves cardiac autonomic function in healthy trained and non-trained people, as well as patients with CHF.[22,23] Various HIIT protocols (with difference in intensity, stage duration, nature of the recovery, and number of intervals) may have different impacts on patients with CAD. The parameters of HIIT, including work/recovery intensity and interval duration, are important factors in training effectiveness, because manipulating these parameters alters time of exercise at a high percentage of VO_{2peak}.[19] Existing studies have demonstrated that both long- and short-duration HIIT protocols are safe, and have beneficial effects on cardiopulmonary fitness in patients with CAD and CHF.[21,24,25] The mechanisms of the HIIT affecting HRV in patients with CABG are not completely clear so far. Nonetheless, there is little evidence about the effect of exercise intensity on HRV, and hemodynamic and echocardiography indices in the patients after CABG.

In the present study, we hypothesized that low-volume high-intensity interval training (LV-HIIT) may improve HRV in patients with CABG even more than MICT. To test our hypothesis, we assessed 24-hour HRV, as well as hemodynamic and echocardiography indices in patients after CABG.

Materials and Methods

Participants were recruited from cardiovascular rehabilitation center of Baqiyatallah hospital in Tehran, Iran, in January-March 2016. At the beginning of the study, 200 post-CABG men were enrolled by responsible supervisor and researchers in the rehabilitation center. Inclusion criteria were as aging 50-70 years, being male, in sinus rhythm, and having CABG surgery during past 6 weeks. Furthermore, they should have left ventricular ejection fraction (LVEF) $\geq$ 40% measured at least 6 weeks after the surgery. The subjects were excluded if they had peripheral vascular disease, ventricular premature beats or other arrhythmias, conduction defects, history of pacemaker insertion, significant valvular heart disease, arterial blood pressure (BP) > 180/100 mmHg, or functional limitations (such as osteoarthritis). The subjects were randomly assigned to one of the three groups of LV-HIIT (n = 14), MICT (n = 14) and control (CTL) (n = 14). Randomization was done by block randomization with the block size of 4 (Figure 1). Written informed consent was obtained from all subjects before participation in the study.
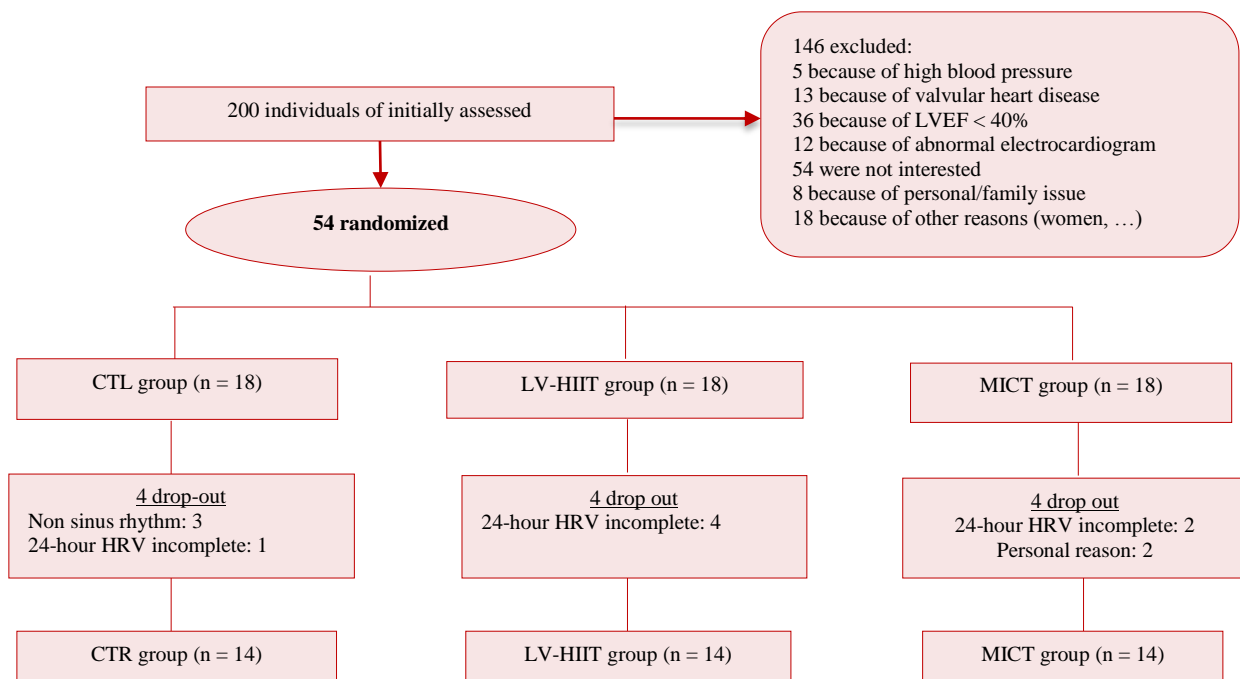
Figure 1. Flow chart of participant
LVEF: Left ventricular ejection fraction; CTL: Control; LV-HIIT: Low-volume high-intensity interval training; MICT: Moderate intensity continuous training; HRV: Heart rate variability.

The present study protocol was approved by the Ethic Committee of Baqiyatallah University of Medical Sciences, was conducted according to the Helsinki Declaration, and is registered at Iranian Registry of Clinical Trials (IRCT20150701223002N1).

This study investigated the effect of interval exercise training and continuous exercise training on HRV in post-CABG men. Maximal heart rate (HR_{max}), resting heart rate (HR_{rest}), resting diastolic BP (DBP), resting systolic BP (SBP), LVEF, end-systolic and diastolic volumes (ESV and EDV, respectively), and ambulatory HRV were measured at the beginning and end of the six-week exercise training. Resting BP and HR_{rest} were measured in supine position, at the beginning and at the end of study before starting exercise, using digital Sphygmomanometer (Beurer GmbH, Soflinger Str.218, D-89077 Ulm, BM 75; Germany). Participants' height and weight were measured using a stadiometer (GMP, Switzerland) and digital, medical scale (Radwage WPT 100/200, Poland), respectively, while subjects were wearing light clothes and had taken off their shoes. Body mass index (BMI) was calculated through dividing weight by square root of height (kg/m^2). Echocardiograms were checked for checking the existence of arrhythmias. After measurement of variables at the baseline, participants were informed about the exercise protocols in an orientations session. To minimize risks of exercise, protocols were performed under the supervision of a cardiologist. Moreover, patients were requested to report any problems and complications, such as chest pain and breathlessness, during exercise.

All subjects were asked to refrain from strenuous physical activities, and the consumption of caffeine and tobacco for 24 hours before exercise test. Subjects' last meal was ingested at least 2 hours before the beginning of the exercise. The exercise test was performed on ergometer (3G cardio Elite Runner, Phoenix, AZ, USA) with a 12-lead continuous electrocardiography (ECG) monitoring in a room with controlled temperature (24 to 26 °C) between 9:00-17:00. One week before the exercise test, all participants underwent a similar exercise test that consisted of short duration and low intensity in order to get them familiarized with the testing procedures. The workload of incremental cycle exercise test was initially set at 30 watts, for 2 minutes, and power output increased every 1 minute by 10 watts until the subjects could not continue and maintained on a fixed pedaling frequency of 40 rpm. HR_{rest} was measured as the mean of the 30 seconds of the resting period in the supine position. HR_{max} was also computed during the last 30 seconds of exercise test before exhaustion.

All subjects performed the exercise training program three times a week for 6 weeks (between

09:00-11:00). Exercise training was monitored by an exercise physiologist. A polar S810 HR monitor was connected to patients for measuring beat-to-beat HR during exercise. Each exercise training session consisted of 5 minutes of warm-up that included walking, running, and stretching movements up to 40% of HR_{max}. MICT session training consisted of 40 min running on a treadmill (Technogym, Italy) at 70% HR_{max}. Each LV-HIIT session followed by 10 intervals of 2 minutes at 85-95 percent of HR_{max}, and separated by 2 minutes at 50% of HR_{max}. The training session ended by a cool-down period that was 5 minutes at 40% of HR_{max}.

Exercise intensity was determined based on workload reaching during the exercise test. The cardiovascular workloads of the two programs were calculated to promote the same workload. MICT included 40 minutes at 70% of HR_{max} on the treadmill. LV-HIIT resulted in a mean workload of 70% HR_{max} $[(10 \times 2 \times 90\%) + (10 \times 2 \times 50\%)]/40$, (Repeated interval $\times$ time of exercise $\times$ percent of HR_{max} in high-intensity periods + repeated interval $\times$ time of exercise $\times$ percent of HR_{max} in low-intensity periods/total time of exercise).

The treadmill velocity was continually adjusted as along as training adaptions occurred, a move to ensure that every training session was carried out at the desired HR_{max} throughout the 6-weeks training period. The control group subjects were encouraged to maintain their daily activities without exercise training during the 6-weeks period. Additionally, subjects in three groups were advised to follow their normal food intake pattern during the intervention.

24-hour ECG monitoring was performed at the baseline and 48 hours after the end of last sessions. Ambulatory ECG recordings were obtained from a 3-channel Medilog Digital Holter recorder FD3, Oxford, with 1024 Hz sampling rate. HRV was analyzed by computer and a commercial system (Oxford Instruments, with Excel ECG Replay System-Rel 8.5). The MT-210 Analysis Software Version 1.0.0 (Schiller) was used to analyze SDRR, RMSSD, low-frequency power (LF), high-frequency power (HF), and the LV/HF ratio. Subjects were requested to maintain their normal daily activities, and to avoid caffeine, smoking, and walking/running during the recording. An experienced technician who was blinded to subjects' information analyzed the recordings. All HRV variables were measured. If the variables were recorded for less than 20 hour, the subject was excluded from the study.[4]

M-mode, Doppler, and two-dimension echocardiography were performed at baseline and end of the study using a GE Vivid 3 device, and a 3 MHz phased-array transducer, respectively, by a single experienced cardiologist who was blinded to patients groups. The measurements of the echocardiography included left ventricular end diastolic dimension (LVEDD), left ventricular end-systolic dimension (LVESD), EDV, ESV, EF, LVEF was calculated based on the following formula: $(LVEDD^2 - LVESD^2)/LVEDD^2$ measured in the left lateral decubitus according to the guidelines of the American Society of Echocardiography.[26]

Data were analyzed using the SPSS statistical software (version 16.0; SPSS Inc., Chicago, IL, USA), and the continues and categorical variables were reported by mean $\pm$ standard deviation (SD) and absolute number (percent) respectively. The Shapiro-Wilk test was used for evaluating normality of distribution. Moreover, chi-square was conducted for analyzing categorical variables. One-way ANOVA was further carried out in order to assess the difference between groups with regard to clinical characteristics of subjects at baseline and heart changes variables in three groups. To compare the changes in all research variables in three groups (CTL, LV-HIIT, and MICT), the differences between values before and after exercise in each groups were calculated and compared by using the one-way ANOVA. Moreover, Bonferroni and Games-Howell tests were used as a post-hoc to determine differences between groups, respectively. Paired t-test was used for evaluating the difference of variables between pre and post. The level of significance in all statistical analyses was set at $P < 0.050$.

Results

Subject characteristics: Out of the 200 patients who were assessed for eligibility, 54 met the inclusion criteria, so were randomly assigned into the three groups. Seven patients were excluded from the study, because the data of 24-hour Holter were incomplete. Three participants of the CTL group had non sinus rhythm, hence their data were excluded from analysis, too. Two patients withdrew consent for reasons unrelated to their clinical status (Figure 1). There was no drop out subjects during the exercise training period. During the study period, medication of subjects did not change. At the baseline, one way-ANOVA revealed that the three groups demonstrated no significant difference in age, weight, height, BMI, medical history, and medications (Table 1).

Table1. Demographic and baseline clinical characteristics and medication of studied groups

Variable	Group			P
	CTL (n = 14)	LV-HIIT (n = 14)	MICT (n = 14)	
	Mean ± SD	Mean ± SD	Mean ± SD	
Age (year)	58.80 ± 4.41	53.90 ± 3.44	54.10 ± 4.02	0.565
Weight (kg)	84.14 ± 6.66	82.73 ± 4.86	83.47 ± 6.14	0.235
Height (cm)	175.90 ± 4.95	176.8 ± 4.02	177.00 ± 4.89	0.882
BMI (kg/m^2)	27.18 ± 1.70	26.49 ± 1.88	26.61 ± 1.13	0.518
Time after surgery (week)	8.13 ± 1.60	9.40 ± 2.85	7.86 ± 1.23	0.267
	n (%)	n (%)	n (%)	
Hypertension	4 (28.5)	5 (35.7)	3 (21.4)	0.450
Diabetes mellitus	6 (42.8)	3 (21.4)	3 (21.4)	0.285
Medication				
β-blockers	3 (21.4)	4 (28.5)	5 (35.7)	0.340
ACE inhibitors	4 (28.5)	3 (21.4)	3 (21.4)	0.310
Diuretics	4 (28.5)	3 (21.4)	2 (14.3)	0.270
Statins	2 (14.3)	3 (21.4)	4 (28.5)	0.281

SD: Standard deviation; BMI: Body mass index; ACE: Angiotensin converting enzyme; CTL: Control; LV-HIIT: Low-volume high-intensity interval training; MICT: Moderate-intensity continuous training
Baseline levels of anthropometric and clinical variables examined using one-way ANOVA and chi-square, respectively.

Hemodynamic and echocardiography: The values of hemodynamic and echocardiography indices are displayed in table 2. No baseline difference was detected between the groups with regard to DBP, SBP, HR_{max}, HR_{rest}, LVEF, EDV, ESV, LVEDD, and LVESD (P < 0.050 for all). Results of the one-way ANOVA indicated that DBP and SBP significantly decreased in LV-HIIT and MICT groups compared with CTL group (P < 0.010). Post-hoc analysis indicated that DBP had greater decrease in the LV-HIIT group compared with MICT group (P < 0.050). Moreover, changes of the SBP in LV-HIIT group had a greater decrease compared with MICT group (P < 0.050). At the end of intervention, HR_{max} significantly increased in exercise groups (P < 0.001). Post-hoc analysis indicated that change of HR_{max} in the LV-HIIT group had a greater increase compared with MICT group (P < 0.050). HR_{rest} significantly decreased after 6-weeks exercise training (P < 0.010). Post-hoc analysis showed that change of HR_{rest} in LV-HIIT group had a greater decrease compared with MICT group (P < 0.050). The result showed that LVEF increased after 6-weeks exercise training in both groups (P < 0.005). However, the post-hoc analysis showed that LVEF more significantly increased in LV-HIIT group compared with MICT group (P < 0.050). EDV and ESV after 6-weeks exercise training significantly increased and decreased, respectively. The post-hoc analysis demonstrated that LV-HIIT had a greater effect in increase and decrease of EDV and ESV, respectively (P < 0.010, P < 0.050). There was no significant difference in LVEDD and LVESD at the end of study.

Heart rate variability: Baseline and follow-up HRV data are shown in table 3. The results of one-way ANOVA showed that mean R-R interval following the 6-weeks intervention increased in both exercise groups (P < 0.010). Post-hoc analysis showed that mean R-R interval increased considerably in LV-HIIT and MICT groups compared with CTL group (P < 0.010). Paired t-test analysis of mean R-R interval in LV-HIIT and MICT groups was more than post-hoc test (P < 0.010). Furthermore, percent changes of mean R-R interval had a greater increase in LV-HIIT group compared with MICT group (P < 0.001) (Figure 2-A). There was also a significant increase for SDRR after 6-weeks in both exercise groups (P < 0.010) (Table 3). The paired t-test showed that SDRR increased in posttest of LV-HIIT (P < 0.010) and MICT (P < 0.050) groups compared with pretest. Although, percent change in SDRR increased after exercise intervention, percent change in LV-HIIT group more increased than MICT group (P < 0.001) (Figure 2-B). RMSSD demonstrated a significant increase in both groups after 6-weeks intervention (P < 0.050). There was no significant difference for changes of RMSSD between LV-HIIT and MICT groups (Table 3). The percent change of RMSSD increased more profoundly in LV-HIIT group compared with CTL group (P = 0.050) (Figure 2-C). The paired t-test showed that RMSSD increased in posttest of LV-HIIT and MICT (P < 0.050) groups compared with pretest. Similarly, there was a significantly increase in terms of HF after 6 weeks in both exercise groups (P < 0.010).

Table 2. Baseline and follow-up of hemodynamic and echocardiography

Variable		CTL (n = 14)	LV-HIIT (n = 14)	MICT (n = 14)	P
		Group			**P**
DBP (mm Hg)	Baseline	81.70 ± 11.62	82.80 ± 11.37	83.80 ± 11.84	0.913
	After intervention	82.90 ± 10.81	80.10 ± 9.70*	80.60 ± 10.78*	0.041
	P (from paired t-test)	0.423	0.034	0.012	
	Change	1.20 ± 2.69	-3.20 ± 2.69*	-2.70 ± 2.21*	< 0.010
SBP (mm Hg)	Baseline	135.10 ± 18.94	138.50 ±18.05	136.30 ± 17.02	0.922
	After intervention	136.30 ± 16.36	122.80 ± 13.55**	125.90 ± 21.10*	0.019
	P (from paired t-test)	0.278	0.005	0.023	
	Change	1.20 ± 3.67	-15.70 ± 7.54**#	-6.10 ± 5.44*	0.013
HR$_{max}$ (beat/minute)	Baseline	128.80 ± 22.23	121.10 ± 20.12	125.90 ± 21.10	0.217
	After intervention	127.60 ± 23.24	128.60 ± 22.17	128.40 ± 19.65	0.823
	P (from paired t-test)	0.238	0.003	0.026	
	Change	-1.20 ± 3.90	7.50 ± 4.46**#	2.50 ± 4.26*	0.005
HR$_{rest}$ (beat/minute)	Baseline	80.50 ± 12.27	80.10 ± 13.73	83.10 ± 12.25	0.851
	After intervention	80.20 ± 11.15	72.10 ± 12.86	78.50 ± 12.28	0.194
	P (from paired t-test)	0.783	0.001	0.031	
	Change	-0.30 ± 2.71	-8.00 ± 2.62**#	-4.60 ± 1.50*	< 0.010
LVEF (%)	Baseline	48.14 ± 7.25	52.06 ± 7.04	48.67 ± 6.69	0.410
	After intervention	49.68 ± 7.27	58.53 ± 7.26**#	52.26 ± 7.91*	0.034
	P (from paired t-test)	0.198	0.007	0.042	
	Change	1.53 ± 0.74	6.46 ± 3.76*#	3.59 ± 3.73	0.005
EDV (ml)	Baseline	116.20 ± 27.54	128.20 ± 36.23	117.60 ± 32.51	0.660
	After intervention	117.10 ± 26.61	135.30 ± 35.90**#	123.30 ± 33.62*	0.013
	P (from paired t-test)	0.385	0.002	0.021	
	Change	0.90 ± 2.18	7.10 ± 3.75**	5.70 ± 2.71*	< 0.010
ESV (ml)	Baseline	59.10 ± 10.97	59.30 ± 10.12	58.80 ± 11.38	0.995
	After intervention	57.80 ± 10.39	54.10 ± 10.35*	57.20 ± 11.27	0.045
	P (from paired t-test)	0.128	0.001	0.041	
	Change	-1.30 ± 1.25	-5.20 ± 4.13*#	-1.60 ± 4.03	0.029
LVEDD (mm)	Baseline	49.60 ± 6.43	51.10 ± 8.58	50.00 ± 8.37	0.910
	After intervention	50.30 ± 6.43	53.00 ± 8.88	51.00 ± 8.96	0.338
	P (from paired t-test)	0.589	0.098	0.123	
	Change	0.70 ± 1.33	-1.90 ± 0.99	-1.00 ± 1.49	0.116
LVESD (mm)	Baseline	33.30 ± 9.44	34.80 ± 8.59	31.20 ± 8.30	0.657
	After intervention	34.20 ± 9.25	33.70 ± 8.40	30.90 ± 8.00	0.398
	P (from paired t-test)	0.612	0.510	0.467	
	Change	0.90 ± 2.51	-1.10 ± 2.28	-0.30 ± 1.70	0.141

Data are presented as mean ± standard deviation (SD).
CTL: Control; LV-HIIT: Low-volume high-intensity interval training; MICT: Moderate-intensity continuous training; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HR$_{max}$: Maximal heart rate; HR$_{rest}$: Resting heart rate; LVEF: Left ventricular ejection fraction; EF: Ejection fraction; EDV: End-diastolic volume; ESV: End-systolic volume; LVEDD: Left ventricular end diastolic dimension; LVESD: Left ventricular end systolic dimension
One-way ANOVA was used for evaluating difference between groups (post-hoc test).
* P < 0.050 compared to CTL group; ** P < 0.010 compared to CTL group; # P < 0.050 compared to MICT group

HF increased in the exercise groups compared with CTR group (P < 0.010). Post-hoc analysis showed a significant greater enhancement in the changes of HF in LV-HIIT group compared to MICT group (P < 0.010). In addition, the percent change of HF in LV-HIIT group increased more than MICT group (Figure 2-D). The paired t-test showed that HF increased in posttest of LV-HIIT (P<0.010) and MICT (P<0.050) groups compared with pretest. After the 6-weeks exercise intervention, LF decreased in the exercise groups (P < 0.050). Post-hoc analysis revealed a significant increase in the changes and percent changes of LF in the LV-HIIT group compared with MICT group (P < 0.050) (Table 3, Figure 2-E). The paired t-test showed that LF increased in posttest of LV-HIIT and MICT groups (P < 0.010) compared with pretest. The LF/HF ratio following exercise intervention significantly reduced in the exercise groups (P < 0.050). Post-hoc analysis showed that the percent change of LF/HF ratio significantly reduced in the LV-HIIT group compared to MICT group (P < 0.001) (Figure 2-F). The paired t-test showed that SDRR increased in posttest of LV-HIIT and MICT groups (P < 0.050) compared with pretest.
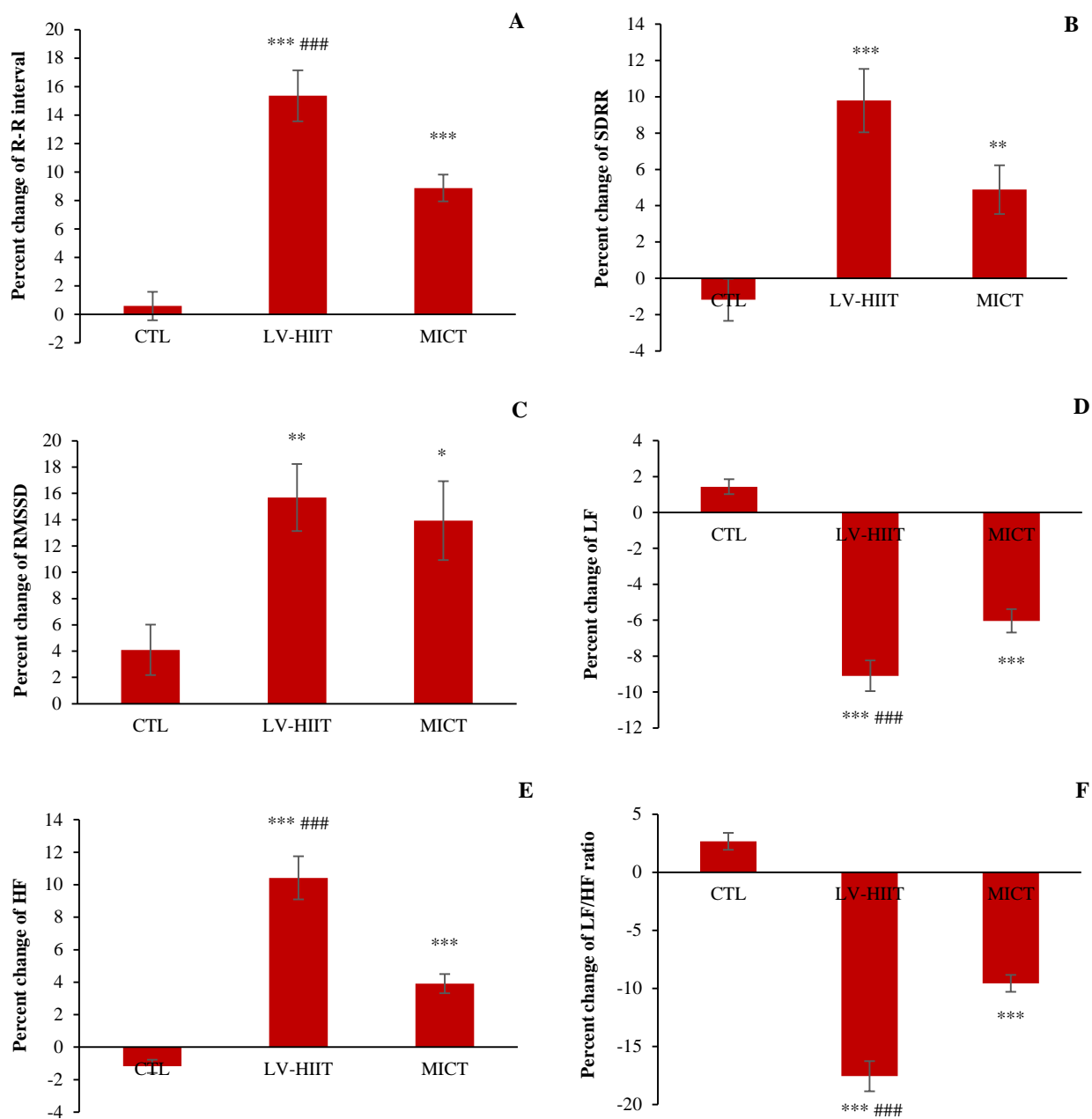
Figure 2. Heart rate variability (HRV) assay demonstrated that exercise intervention for 6 weeks improved HRV in post-CABG men. A) Percent change of mean R-R interval; B) Percent change of standard deviation of R-R interval (SDRR); C) Percent change of root mean square difference of successive (RMSSD); D) Percent change of high-frequency power (HF); E) Percent change of low-frequency power (LF); F) Percent change of LF/HF ratio.
CTL: Control; LV-HIIT: Low-volume high-intensity interval training; MICT: Moderate intensity continuous training; CABG: Coronary artery bypass grafting
One-way ANOVA was used for evaluating difference between groups in percent changes.
* $P < 0.050$ compared to CTL group; ** $P < 0.010$ compared to CTL group; *** $P < 0.001$ compared to CTL group; $^{###}$ $P < 0.001$ compared to LV-HIIT group

Discussion

The findings of the present study indicate that a 6-weeks HIIT improves HRV in post-CABG men. To our knowledge, this study is the first to assess the effects of LV-HIIT protocol on HRV-parameters in these patients. This study show that, compared with MICT and control, LV-HIIT induces a greater improvement in the time domain indices (i.e. SDRR and RMSSD) in patients with CABG.

Table 3. Baseline and follow-up parameters of heart rate variability (HRV)

Variable		Group			P
		CTL (n = 14)	LV-HIIT (n = 14)	MICT (n = 14)	
Mean R-R interval (ms)	Baseline	818.70 ± 104.24	864.00 ± 113.56	837.90 ± 111.90	0.657
	After intervention	824.00 ± 112.03	997.00 ± 142.43[**#]	912.50 ± 127.36[**]	0.010
	P (from paired t-test)	0.345	0.001	0.010	
	Change	5.30 ± 25.86	133 ± 55.14[**##]	74.60 ± 29.11[**]	< 0.010
SDRR (ms)	Baseline	83.70 ± 28.26	91.30 ± 29.43	91.60 ± 30.39	0.794
	After intervention	83.00 ± 28.97	99.30 ± 28.70[**]	95.30 ± 29.35[**]	0.028
	P (from paired t-test)	0.913	0.001	0.023	
	Change	-0.70 ± 2.54	8.00 ± 3.43[**#]	3.70 ± 2.40[*]	< 0.010
RMSSD (ms)	Baseline	38.30 ± 16.89	42.20 ± 17.37	43.70 ± 17.26	0.770
	After intervention	39.40 ± 16.99	47.70 ± 16.76[**]	48.50 ± 15.77[**]	0.019
	P (from paired t-test)	0.434	0.018	0.025	
	Change	1.10 ± 1.59	5.50 ± 1.43[*]	4.80 ± 2.14[*]	< 0.050
HF (ms)	Baseline	124.03 ± 38.16	131.52 ± 33.24	132.80 ± 41.71	0.943
	After intervention	122.50 ± 37.63	144.80 ± 34.60[**#]	137.50 ± 41.99[**]	0.011
	P (from paired t-test)	0.273	0.006	0.034	
	Change	-1.50 ± 1.50	13.30 ± 5.29[**##]	4.70 ± 1.33[*]	< 0.010
LF (ms)	Baseline	252.62 ± 69.83	244.42 ± 61.48	242.61 ± 75.61	0.855
	After intervention	255.80 ± 69.49	222.30 ± 57.64[**]	227.70 ± 70.57[**]	0.039
	P (from paired t-test)	0.561	0.008	0.003	
	Change	3.20 ± 2.57	-22.10 ± 7.72[**#]	-14.90 ± 6.83[**]	0.012
LF/HF ratio	Baseline	2.34 ± 1.18	2.08 ± 1.04	2.21 ± 1.40	0.900
	After intervention	2.39 ± 1.20	1.72 ± 0.89[**#]	1.98 ± 1.22[**]	0.041
	P (from paired t-test)	0.673	0.018	0.029	
	Change	0.53 ± 0.05	-0.36 ± 0.17[*]	-0.23 ± 0.18[*]	0.023

Data are presented as mean ± standard deviation (SD).
CTL: Control; LV-HIIT: Low-volume high-intensity interval training; MICT: Moderate-intensity continuous training; SDRR: Standard deviation of all R-R intervals; RMSSD: Root mean square of difference between successive R-R intervals; LF: Low-frequency power; HF: High-frequency power
One-way ANOVA was used for evaluating difference between groups (post-hoc test).
[*] P < 0.050 compared to CTL group; [**] P < 0.010 compared to CTL group; [#] P < 0.050 compared to MICT group; [##] P < 0.010 compared to MICT group

HIIT also results in HF enhancement and decline of LF and LF/HF ratio power. Additionally, LVEF and hemodynamic indices (SBP and DBP) improved significantly among subjects in LV-HIIT group compared with those of participants in MICT and CTL groups.

There was a significant increase in LVEF after 6 weeks of exercise training in the exercise groups compared with the CTL group. The post-hoc analysis revealed that this significant increase in LV-HIIT group was greater than MICT group. Exercise training improved LVEF in cardiovascular disease, though the mechanisms are unclear. Improved EF-induced HIIT may be attributed to attenuation in pathological remodeling and increase in ventricular compliance. In addition, it is demonstrated that structural changes in the heart led to increased LVEF.[21] This study demonstrated that exercise training results in significant decrease in LVEDD and LVESD. It also revealed that the decrease of LVESD in LV-HIIT could cause greater increase of LVEF compared with MICT.

After HIIT training, HR_{rest} significantly declined. These results are similar to those of other studies that have also reported aerobic exercise-induced bradycardia.[27] Although the mechanism of bradycardia induced by aerobic exercise is unclear, it seems that bradycardia-induced HIIT reflects a combination of reduced intrinsic heart rate, decreased sympathetic tone, and increased parasympathetic tone.[28] Katona et al. have demonstrated that endurance training in athletes and non-athletes leads to a reduction in intrinsic heart rate.[27] A previous study showed that 12 weeks of HIIT could decrease HR_{rest} in healthy men. This indicates that HIIT may increase cardiac performance by increasing cardiac dilation during exercise in young subjects. It seems that, increase of EDV contributes to the increase of SV and decline of HR_{rest}; however, the increase of SV induced-

increased myocardial contractility at rest appears to be a more likely.[28] A previous study has demonstrated that different types of exercise training may improve HRV in patients with CAD.[29] One of the candidate beneficial mechanisms of exercise is effects of autonomic nervous system, with numerous studies indicating that parasympathetic function improves after aerobic exercise training.[20,30,31] In CAD, low HRV is a predictor of morbidity and mortality. According to Bilchick et al., the increase of 10 ms in SDRR was associated with 20% decrease in the risk of mortality.[32] Exercise training could prevent CVD mortality by increasing SDRR. The result of this study indicate that HIIT is effective in improving cardiac autonomic modulation. LV-HIIT leads to enhancement of SDRR, RMSSD, and HF. Conversely, it decreases LF and LF/HF ratio in post-CABG. It seems that LV-HIIT has a greater effect in patients with CAD. Previous studies have demonstrated that short intervals of HIIT had a higher mean intensity and extracted higher perceived exertion (RPE) which was associated with lower exercise session compliance for CVD.[22,24]

A research showed that optimized HIIT protocols were associated with lower mean VO_2, lower ventilation, lower RPE, and higher exercise session compliance. Thus, HIIT with short intervals is well tolerated by patients with CAD, and leads to greater increase of VO_{2peak}.[33] The reduction of HR_{rest} in the patients after HIIT is directly correlated with vagal modulation, which was assessed through the increase in HF power. RMSSD increase in the exercise groups indicates a decline in sympathetic nervous activity, and a potential mechanistic shift toward increased vagal activity. The mechanisms by which exercise training improves cardiac autonomic modulation and HRV is not fully understood. Nevertheless, studies have shown that HIIT could lead to decrease in catecholamine levels, beta-adrenergic receptor density, and angiotensin II. On the contrary, it may increase nitric oxide (NO) bioavailability and potential mediators which improve cardiac autonomic modulation induced by exercise training.[34,35]

A reduction of angiotensin II levels after exercise training is an important mechanism that contributes to increasing parasympathetic activity. Angiotensin II is a peptide that increases sympathetic outflow, and inhibits cardiac vagal activity.[36] The results of one study demonstrated that angiotensin II levels declined significantly in animal models undergoing HIIT.[37] Additionally, another study has shown that, after HIIT, renin-angiotensin system (RAS) activity in mice is lowered by reduced expression of angiotensin-convertor-enzyme activity, angiotensin receptors, and renin.[38] Nevertheless, another study has recently shown that aerobic exercise training improves cardiac autonomic modulation in patients with hypertension, irrespective of angiotensin-converting enzyme inhibitor treatment.[39] Thus, it seems that exercise training contributes to cardiac autonomic modulation via other potential mechanisms such as NO bioavailability. NO may have indirect effect on inhibiting sympathetic influences, and play a role in increasing cardiac vagal tone.[40] NO bioavailability by induced exercise training, particularly HIIT, improves endothelial function in patients with CAD.[21,41] Moreover, animal and human studies have revealed that the increase of NO expression is associated with increases in vagal activity.[40,41] The effect of HIIT on NO bioavailability in patients with CAD may be due to the increase of apelin, expression, and phosphorylation of endothelial NO synthase, and the decrease of NO degradation.[42] However, Wisloff et al. have shown that HIIT causes fluctuation between high and low intensities, extracts a higher shear stress in patients, and triggers larger responses at the cellular and molecular level. Additionally, HIIT reduces the amount of reactive oxygen species, and increases the activity of superoxide dismutase and glutathione peroxidase.[21] However, we showed that HIIT enhanced HRV by increasing HF, SDRR, and RMSSD, as well as reducing LF and LF/HF ratio. The mechanism underlying these effects are not clear. Nonetheless, it was demonstrated that improvement of HRV in LV-HIIT subjects may maintain the subjects in greater time of exercise at a high percentage of VO_{2peak}.

Finally, several limitations of this study need to be emphasized. First, we worked on a relatively small sample size that only included men patients. Second, O_2 consumption of patients was not measured. The effect of HIIT on autonomic nervous system outcomes for sympathetic nerve activity could be characterized by using direct nerve recording. However, there are surrogate markers for neurohumoral modulation, such as renin-angiotensin system activity and NO bioavailability, which were not measured in this study. We used an ambulatory 24-hour Holter for HRV recording. This does not allow to control common factors (e.g. posture, breathing frequency, and tidal volume) known to affect HRV.

Conclusion

We investigated the effect of 6 weeks of LV-HIIT and MICT on HRV and some other

echocardiographic and hemodynamic indices in post-CABG men. Our results suggest that mean R-R intervals, SDRR, RMSSD, and HF power in LV-HIIT has a greater increase than MICT. Additionally, LF and LF/HF ratio decreases more in LV-HIIT than MICT.

Acknowledgments

Conflict of Interests

Authors have no conflict of interests.

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Cryoballoon ablation results and complications in mid-term follow-up of patients with atrial fibrillation

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Short Communication

Abstract

BACKGROUND: Atrial fibrillation (AF) is the most common cardiac arrhythmia, and its prevalence increases with advancing age. Pulmonary vein isolation is a standard approach in drug refractory paroxysmal AF which could be performed by cryoballoon ablation (CBA). We tried to evaluate its efficacy and safety in Iranian patients with AF.

METHODS: From 2015 to 2017, 97 patients with paroxysmal and persistent AF were enrolled in our observational historical cohort study. They were visited 1 and 6 months post-procedure in order to assess the efficacy (recurrence) and safety. Recurrence was defined as 30 seconds of arrhythmia on their 48-hours Holter monitoring.

RESULTS: Ninety-seven patients enrolled in the study, 64 (66.0%) of them were men, and their mean age was 55 ± 12 years. Hypertension was reported in 41 patients (42.3%), as the most common cardiac risk factor. 71 patients (73.2%) patients with paroxysmal AF and 15 patients (15.5%) with persistent AF underwent the procedure. After 6 months, recurrence was documented in only 17 patients (17.5%), and 82.5% of the patients were free from the recurrence. Post-procedural complication was detected only in 3 patients (3.1%).

CONCLUSION: In our study, the mid-term success and safety of CBA in patients with paroxysmal AF was showed. CBA is a safe and effective method in paroxysmal AF, and even in some cases with persistent AF.

Keywords: Catheter Ablation, Atrial Fibrillation, Follow-Up Studies

Introduction

Atrial fibrillation (AF) is the most prevalent cardiac dysrhythmia, and its prevalence increases with advancing age. About 1% of patients with AF are less than 60 years old, but it is more common in patients older than 75 years of age.[1] AF is evidently more problematic in patients with structural heart disease, hypertension, coronary artery disease (CAD), and any other chronic condition.[2] The role of catheter ablation in the management of AF continues to evolve rapidly, with improvements in the efficacy and safety of the procedure.

Cryoballoon ablation (CBA) is an alternative to point-by-point radiofrequency ablation (RFA) to achieve pulmonary veins isolation.[3]

Long-term success of RFA in AF has been constrained by the time consuming and unpredictable nature of point-by-point focal ablation and technical limitations.[4,5] CBA has been showed to nonbeing inferior to RFA with respect to efficacy for the treatment of paroxysmal AF, and there was no significant difference between the two methods with regards to overall safety.[6-9]

As there is lack of evaluation of efficacy and complication of CBA in an Iranian population, we decided to conduct this study to assess its effectiveness, safety, and recurrence rate.

Materials and Methods

This was an observational historical cohort study that analyzed the result of CBA performed in patients with symptomatic paroxysmal or persistent

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AF, who were candidates for ablation according to the latest AF guideline.[3,10] Patients with symptomatic paroxysmal or persistent AF that was refractory to antiarrhythmic drugs or beta-blockers were included. From all patients have been ablated by CBA from May 2015 to the March 2017, we could recruit 97 patients whom were reevaluated and revisited in 1 and 6 months after the procedure.

Patients were asked and assessed for their demographic measures, left ventricular ejection fraction (LVEF), and grade of mitral regurgitation (MR), if was present by echocardiography, the size of left atrium (LA), presence of cardiac risk factor as hypertension, CAD, or other structural heart diseases, past history of cerebrovascular accident (CVA) or transient ischemic attack (TIA), their medications before and after CBA including aspirin, rivaroxaban, dabigatran, warfarin, propafenone, sotalol, amiodarone, angiotensin-converting-enzyme (ACE) inhibitor, beta-blockers, angiotensin receptor blocker (ARB), and any other antiarrhythmic drug. Paroxysmal AF was defined as AF that terminated spontaneously or with intervention within 7 days.[3]

CHA$_2$DS$_2$-VASc score was calculated in office visits by the physician, but as some patients were just admitted for the procedure and due to the lack of fulfilled past history, we could not evaluate patients' CHA$_2$DS$_2$-VASc score; of course, all patients were anticoagulated based on the latest AF guideline, and it was withheld periprocedural time. After the procedure, patients all were visited 1 and 6 months later, after recruitment in the outpatient clinic. In 6-month follow up, to evaluate patients' recurrence, all patients underwent 48 hours of Holter monitoring to document any dysrhythmic abnormality or AF. Documented AF, atrial flutter, or atrial tachycardia, which lasted for more than 30 seconds, was defined as recurrence.

CBA procedure was performed according to the latest developed method; it induced necrosis by pumping N$_2$O through a balloon in a one-step mode, thereby freezing the tissue, and finally isolating blamed part of pulmonary vein (PV) to eradicate arrhythmia.[8,11,12]

All patients were informed about the study, and the consent form was signed by all enrolled patients.

Statistical analyses were performed using SPSS software (version 22, IBM Corporation, Armonk, NY, USA). To describe numerical variables, mean ± standard deviation (SD) was used, and categorical variables were presented as number and percentage. To explore the relationship between categorical variables, chi-square test was applied.

Results

From 97 patients in this study, 64 patients (66.0%) were men and 33 (34.0%) were women. Patients' demographic data and some echocardiographic measures were summarized in table 1.

Table1. Demographic and echocardiographic data

Variable	Minimum	Maximum	Mean ± SD
Age (year)	29.00	80.00	55.36 ± 11.00
BMI (kg/m^2)	17.30	47.26	29.27 ± 5.51
EF (%)	20.00	60.00	50.31 ± 7.10
LA diameter (cm)	1.40	5.00	3.63 ± 0.58
LA volume (ml)	17.00	67.20	37.23 ± 17.47
Serum creatinine (mg/dl)	0.60	1.60	0.97 ± 0.20

SD: Standard deviation; BMI: Body mass index; EF: Ejection fraction; LA: Left atrium

Hypertension was documented in 41 patients (42.3%), structural heart disease in 2 patients (2.1%), as the less number which means less inconvenience in our analysis, CAD in 10 patients (10.3%), and CVA or TIA in only 3 patients (3.1%). Echocardiography indicated 51 patients (52.6%) with mild MR, 29 (29.9%) with mild to moderate MR, 13 (13.4%) with moderate MR, and 4 patients (4.1%) with missing MR. Sixty-nine patients (71.1%) were categorized in paroxysmal AF, 15 patients in persistent type AF (15.5%), whose procedural success was considerable, and 1 patient (1.0%) was in the persistent group, but he intended to not take the antiarrhythmic drug because of its side effects.

Most patients (22 patients) who underwent CBA were taking sotalol, and 16 patients were on amiodarone, followed by flecainide and propafenone in the rest of patients. For rate control of the patients before ablation, most patients were prescribed metoprolol (in 53 patients), and bisoprolol, carvedilol, and propranolol were in the next places.

Based on the patients CHA$_2$DS$_2$-VASc score, 52 patients were taking anticoagulant drugs such as warfarin, rivaroxaban, or dabigatran.

Recurrent AF was detected in 17 patients, and 80 patients maintained their normal sinus rhythm (82.5%). In patients in whom recurrent dysrhythmia was documented, the most common type of recurrence was AF (11 patients), followed by atrial flutter (AFL) in 4 patients, and atrial tachycardia (AT) in 1 patient. Two patients underwent repeated ablation procedure due to recurrence.

CBA procedure was done by mean freeze time

of 184 seconds and mean balloon temperature of -45 °C. In this regard, patients with recurrent AF had the same procedural parameters as patients with successful CBA.

Postprocedural examination of patients revealed complication in 3 patients (3.1%), 1 pericardial effusion, 1 vascular complication, and phrenic nerve palsy in only 1 patient which resolved within 3 months. We also had no report of CVA, TIA, hemorrhagic complication, or death.

Discussion

In this cross sectional study, patients underwent CBA, and then were reevaluated 1 and 6 months postprocedure. Patients' enrollment was based on the latest guideline of AF, and no patient had the contraindication to the CBA.[3,13] Demographic measures of our patients were quietly similar to the studies have been conducted so far.[6,14] In 2 studies reported in China,[6,15] success rate was 76% with complication rate of 5% and 4% at 6- and 12-month follow-up, respectively; in our study, 82.5% of success rate and complication of 3% was achieved. In STOP AF trial study,[6] success rate at 1 year was reported as 69.9% compared to our 82.5% at 6 months. Moreover, we had 3% of complication rate, which was reported as 2% in that study.[6]

The success rate and complications in our study proved CBA as a novel procedure to eradicate paroxysmal AF. Many studies so far compared these two methods,[9,12,16-19] and FIRE and ICE randomized trial demonstrated their efficacy and safety.[9]

Nowadays, United States Food and Drug Administration (FDA) proves both methods for eradicating paroxysmal AF. Based on the results of the latest studies,[20-23] pulmonary vein isolation might be a sufficient ablation strategy in persistent AF. Therefore, cryoablation of the PVs may also suffice not only in paroxysmal but also in persistent AF. This hypothesis has been evaluated in several studies.[20-23] as we performed the procedure in 15 patients with persistent AF. In these studies success rate as freedom from AF was reported from 59% to 69%.[20-23]

Phrenic nerve palsy has been reported as the most common complication of the CBA with a prevalence of 2.7% in the FIRE and ICE trial,[9] and it was reported 1% in our population. Safety of the CBA was assessed by latest studies, and has been reported even safer than RF ablation.[12,24]

Procedural time and temperature of our study was comparable to other studies conducted so far.[16-19]

We need multicenter randomized studies to empower our results, as there was no control group in our study. We measured the recurrence by 48-hour Holter monitoring, but we might have missed some asymptomatic recurrences.

Conclusion

CBA is a safe and effective method in paroxysmal AF, and even in some patients with persistent AF.

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None.

Conflict of Interests

Authors have no conflict of interests.

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Case formulation and comprehensive cardiac rehabilitation programs tailored to the unique risk factors and consequences profile

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Letter to Editor

Dear Editor-in-Chief

Obviously, cardiac rehabilitation (CR) services are very important in controlling morbidity and mortality caused by cardiovascular diseases (CVDs), and the usefulness of these programs has already been approved.[1] However, it appears that the common formats of these programs do not cover the needs of all patients and some patients are unwittingly more benefiting from it.[2] It is said that a number of patients not only have not an improvement in their health status after having participated in CR, but even suffer from increased anxiety and depression[3,4] and weight gain.[5] This situation shows that the provision of these services to all patients in a single format, without considering the risk profile of each person, cannot have the same impact on all of them. Because each patient with unique risk factors enters these programs, the risk factors profile of the two patients is not exactly the same. Therefore, we see that patients receive more than a CR program, that the framework of these programs is more in line with their medical condition.

Based on these considerations, we suggest that CR programs be comprehensively tailored to each patient's preferences and needs.[2] In other words, the design of these programs tailored to the profile of each patient's risk factors, and acute consequences could possibly improve the usefulness of it.[6] In the first step, we recommend that patients be classified based on their risk factors and illness consequences profile.[7-10] The types of CVDs risk factors include social (family and friends, residential environment, work, assets, and social support and capital), biological (aging, sex, and genetics), environmental (water and air pollution, and dust), physiological (hypertension, diabetes, and hyperlipidemia), behavioral (lack of exercise, inappropriate nutrition, and smoking), and psychological risk factors (stress and anxiety, grief and depression, and anger). In addition, the consequences of the disease include cognitive impairments.[10] In the framework of this primary comprehensive classification, CR services can be delivered in multi-level modules. Each patient may benefit from one or more levels of care services according to the risk factors/consequences profile. In other words, a patient whose risk factors belongs to just one of these categories, receive level I services for the same risk factor group. For example, an inactive patient with inappropriate nutrition who does not have a problem with the other risk factors can receive I-level services for behavioral risk factors. Level II services are provided to patients risk factors in two separate classes. For example, those who need to be protect in the physiological and psychological fields. Similarly, services of levels III, IV, V, and VI are used for patients that their risk factors are distributed in more classes. Therefore, these patients may receive services and training to quit smoking, control blood pressure or diabetes, and stress management and depression treatment.

According to previous studies that many patients have more than a heart risk factor,[11] it seems that most patients require multidisciplinary services from multiple levels. However, in this comprehensive approach, multiple levels of the services delivery are in line with the needs of patients. Choosing the right exercise, along with providing training on control and management of risk factors based on existing guidelines,[12] can reduce the outcomes of the illness for all patients. Although the services delivery protocol to some patients such as patients with heart failure is specific, we recommend using this method of services delivery for other patients at CR centers of the country.

Conflict of Interests

Authors have no conflict of interests.

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