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The Assessment of Cardiac Rehabilitation on Echocardiographic Parameters of Left Ventricular Systolic Function in Patients Treated by Primary Percutaneous Coronary Intervention due to Acute ST-Segment Elevation Myocardial Infarction: A Randomized Clinical Trial

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ABSTRACT

Background: The exact effects of cardiac rehabilitation on the left ventricular (LV) systolic function have still remained controversial.

Objectives: The aim of this randomized clinical trial was to assess the effects of cardiac rehabilitation on echocardiographic parameters of LV systolic function in patients treated by Primary Percutaneous Coronary Intervention (PPCI) due to acute ST-segment Elevation Myocardial Infarction (STEMI).

Patients and Methods: After estimating 50 patients as the total sample size according to previous studies and type of the current study, the patients with acute STEMI who were treated by PPCI in our academic centers and had LV ejection fraction (EF) of 35 - 49% were divided into two groups via permuted block randomization method. The first group (n = 25) underwent an 8-week comprehensive cardiac rehabilitation program. Meanwhile, the controls (n = 25) were just instructed on risk factor management. All patients underwent echocardiographic examination during the first week after acute STEMI and 10 weeks later. The measured parameters included LVEF, stroke volume (SV), LV end-diastolic diameter/volume (LVEDD/LVEDV), LV end-systolic diameter (LVESD/LVESV), fractional shortening (FS), LV mass, and mean global longitudinal LV strain (εLL). The SPSS, version 18.0, was used for data analysis and P values less than 0.05 were considered to be statistically significant.

Results: The mean age of the participants was 53.68 ± 6.9, ranging from 38 ± 71 years old; 58% of the patients were men with an approximately similar distribution in both groups. The comparison of changes in variables before and after the rehabilitation period between exercise and control groups illustrated a significant increase in LVEF (mean percentage changes: 13.56 ± 15.98% vs. 2.86 ± 8.46%; P = 0.005) and mean global εLL (16.39 ± 14.97% vs. 2.62 ± 9.98%; P < 0.001) in the rehabilitated individuals. In addition, a significant decrease in LVESD (-7 ± 8.98% vs. -0.53 ± 6%; P = 0.004), LVESV (-10.48 ± 11.86% vs. -2.5 ± 12.34%; P = 0.025) and LV mass (-6.06 ± 6.65% vs. -1.30 ± 6.37%; P = 0.013) was observed in the exercise group as compared with the controls. No significant change in FS, LVEDD and LVEDV was occurred between the groups during the rehabilitation period.

Conclusions: Early exercise-based cardiac rehabilitation program in patients revascularized by PPCI after acute STEMI could have beneficial effects on LV systolic function with no adverse effect on LV remodeling.

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1. Background

Despite growing advances in the management of ST-segment elevation myocardial infarction (STEMI) including shift of reperfusion therapy into catheter-based strategies and the widespread use of guideline-directed medical therapy (GDMT), it is still a major leading cause of death and disability in both industrialized world and developing countries (1-3).

Contemporary recommended management of patients after acute STEMI includes a comprehensive cardiac rehabilitation program which can reduce morbidity and mortality cost-effectively (4, 5). It has also been shown to impact coronary heart disease risk factors by reducing resting blood pressure, managing body weight, improving lipid profile, increasing insulin sensitivity and fibrinolytic activity, decreasing blood clotting, and also helping as a part of smoking cessation strategies (6-9).

Although improvement in echocardiographic left ventricular (LV) systolic function has been reported in several studies, the effects of exercise training on LV systolic function have still remained controversial (10-13). In the LV two-dimensional assessment, improper delineation of endocardial border would result in wrong estimation of cardiac volumes and dimensions leading to problems in the estimation of LV ejection fraction (LVEF) which is the most useful conventional echocardiographic parameter for the assessment of LV systolic function. The difference between the estimated LV volumes in conventional two-dimensional echocardiography and contrast echocardiography has been reported to be up to 30 - 40%.14 Moreover, LVEF has several methods of estimation, all with a relatively high interobserver variability which reduces its reproducibility (14, 15).

Considering the few previous studies; their small sample sizes; the heterogeneous results; and use of conventional, less reproducible parameters, the purpose of this study was to assess the effects of cardiac rehabilitation on echocardiographic parameters of LV systolic function in patients treated by PPCI due to acute STEMI.

2. Objectives

Speckle-tracking Echocardiography (STE) has a sensitive diagnostic potential and reliably measures LV strain; therefore, this novel quantitative technique was used in this study (16, 17). In addition, the cardiac rehabilitation is widely underutilized, and such studies may help to underscore the importance of this neglected necessity.

3. Patients and Methods

3.1. Subjects

This randomized clinical trial was registered in the Iranian Registry of Clinical Trials (code: IRCT2016103130613N1) and also reviewed and approved by our institutional review board. It was conducted on patients with acute STEMI who were treated by PPCI in Shahid Faghihi, Namazi and Alzahra hospitals, Shiraz, Iran, from February 2015 and January 2016. The STEMI was defined according to the third universal definition consensus document (18). Adult individuals with complete revascularization after PPCI with culprit vessel-only approach and LV systolic dysfunction indicated by LVEF of 35 - 49% were included in the study. The patients were selected among those who underwent drug-eluting stent placement within 120 minutes after the first medical contact and reached TIMI (Thrombolysis in Myocardial Infarction) flow of 3 after the procedure. The exclusion criteria were the use of aspiration thrombectomy or intravenous glycoprotein IIb/IIIa antagonists. Also, the patients with atrial fibrillation, more than mild LV hypertrophy in two-dimensional echocardiography (LV septal thickness more than 1.3 and 1.2 in men and women, respectively) and poor echocardiographic window were not included. According to the guidelines of American College of Sports Medicine (ACSM) for exercise testing and prescription, the patients were excluded if they had post-myocardial infarction angina, resting systolic blood pressure > 180 mmHg, resting diastolic blood pressure > 110 mmHg, symptomatic orthostatic change in systolic blood pressure > 20 mmHg, severe aortic stenosis, uncontrolled tachycardia or bradycardia, decompensated heart failure, uncontrolled diabetes mellitus, acute systemic illness, and physical disability (19). After an adequate education on the contents and timing of cardiac rehabilitation program and its necessity, the patients who decided to participate in the study were allocated into exercise and control groups via permuted block randomization method. The exercise group participated in a comprehensive cardiac rehabilitation program including a supervised exercise training course, whereas the control individuals were just instructed about risk factor management.

The sample size of at least 25 participants in each group was considered according to previous studies (20), and the type of the present study, providing study power of 80% and type I error 5% using the following formula:

$d = 3.2$

The excluded individuals were substituted by others who met the inclusion criteria.

The study was approved by the Ethics Committee of Shiraz University of Medical Sciences and all patients signed a predefined written inform consent before entering the trial.

3.2. Cardiac Rehabilitation Program

The cardiac rehabilitation program consisted of 24 sessions and was conducted over an 8-week period (three times per week) in Cardiopulmonary Rehabilitation Center (Shahid Faghihi hospital, Shiraz, Iran). Each session lasted about one hour beginning with a warm-up (10 minutes) and followed by 40 minutes of aerobic exercise training using recumbent upper and lower extremity ergometers. The last 10 minutes was allocated to cooling down and all sessions finished by relaxation. The heart rate reserve (HRR) was calculated on the basis of individualized resting and maximal heart rate obtained by a graded exercise test before the start of cardiac rehabilitation program and the target heart rate was set up between 40 - 60% of the reserve as exercise intensity to achieve a moderate level (19). For the graded exercise test, a symptom-limited method was used by modified Bruce protocol. The blood pressureand heart rate and load were closely monitored in all sessions performed under supervision of an expert physical therapist.

As a comprehensive program, all patients and their families were educated about cardiovascular risk factors and their management including stress reduction methods, smoking cessation and body weight control. Moreover, the importance of medication adherence was emphasized and in order to keep a healthy lifestyle, all patients received psychological, nutritional, and, if needed, smoking cessation consult.

For all patients who completed the whole rehabilitation program, the graded exercise test was repeated at the end of the sessions with the same protocol as the basic one and Metabolic Equivalents (METs) were calculated before and after the cardiac rehabilitation program.

3.3. Echocardiographic Examination

During the first week after acute STEMI, all participants underwent a baseline two-dimensional transthoracic echocardiography including STE, using a vivid E9 (General Electric) system; all measurements were performed by one expert echocardiologist according to the latest recommendations of American Society of Echocardiography (21). Echocardiography was repeated after the completion of the cardiac rehabilitation program in the exercise group and after the same period in the control group. All the follow-up examinations used the same system as basic ones and the same echocardiologist who was blinded to the patient assignment group analyzed them.

The LV end-systolic and diastolic diameters (LVESD and LVEDD) were measured by M-mode and for the calculation of LV end-systolic volume (LVESV), LV end-diastolic volume (LVEDV), LVEF and stroke volume (SV), Simpson's biplane method was used. In addition, LV mass and fractional shortening (FS) were measured via the following formulas: LV mass = (1.04) [(LVEDD + PWT + IVST) 3 - (LVEDD) 3] in which PWT = posterior wall thickness and IVST = interventricular septal thickness and FS = (LVEDD - LVESD) / LVEDD.

Mean global longitudinal LV strain (εLL, %), describing the relative length change of LV myocardium between end-diastole and end-systole, was calculated using STE. On two-dimensional echocardiography, after technical optimizing, the measurement of mid-wall εLL was taken in three standard apical views, averaged by AFI (Automated Function Imaging) application and then demonstrated in Bull's eye.

3.4. Statistical Analysis

All continuous variables were expressed as mean ± standard deviation and categorical variables were expressed as number (n) and percentage (%). The independent t test, paired t test and chi- square test were used to compare the significant differences of the same variables between or within the case and control groups.

The statistical package for social sciences version 18.0 (SPSS Inc., Chicago, IL, USA) for Windows was used for data analysis and P values less than 0.05 were considered to be statistically significant.

4. Results

A total of 56 age and gender-matched eligibility criteria-met individuals were randomly allocated into exercise and control groups. Of 27 participants who completed the course in the exercise group, two patients refused to undergo the follow-up echocardiographic examination. Such an uncooperative behavior was observed in 3 patients in the control group and, finally, data obtained from a total number of 50 patients equally distributed in the case and control groups were collected for statistical analysis (Figure 1).

The mean age of the participants was 53.68 ± 6.9, ranging from 38 - 71 years old. 58% of the patients were men with an approximately similar distribution in both groups. All the patients were taking dual antiplatelets, beta blockers, statins, nitrates and ACEIs/ARBs. Mineralocorticoid receptor antagonists and warfarin were not used by any patient in either group. The baseline characteristics of patients are presented in Table 1.

At the end of the rehabilitation period, the peak exercise

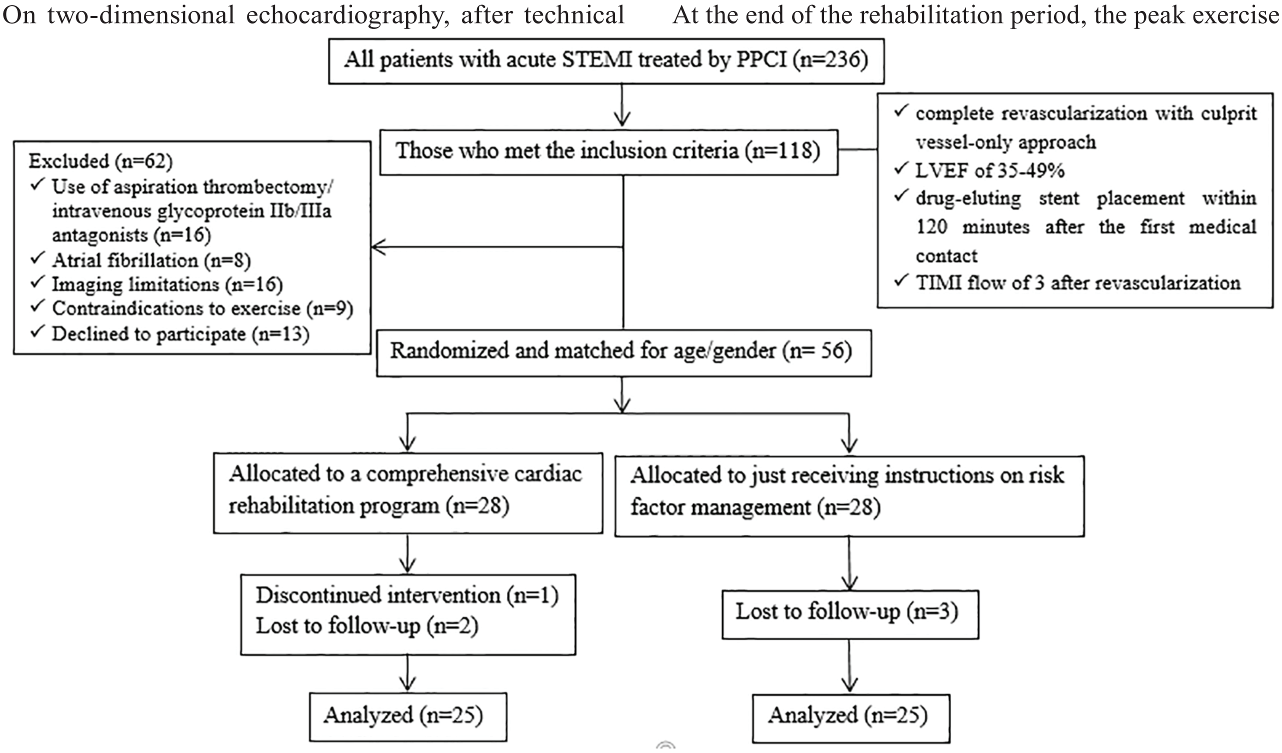

Figure 1. CONSORT Flow Chart of the Clinical Trial

Table 1. Baseline Characteristics of Patients in the Exercise and Control Groups			
Characteristics	**Exercise Group, N=25**	**Control Group, N=25**	**P value**
Demographic data			
Age (years)	53.76 ± 6.96	53.6 ± 6.98	0.936
BMI (kg/m2)	23.84 ± 2.16	23.84 ± 2.15	> 0.99
Gender [Male, n (%)]	14 (56%)	15 (60%)	0.774
Risk factors			
Hypertension	5 (20%)	5 (20%)	> 0.99
Dyslipidemia	5 (20%)	7 (28%)	0.508
Diabetes mellitus	6 (24%)	6 (24%)	> 0.99
Positive family history	7 (28%)	7 (28%)	> 0.99
Smoking	9 (36%)	6 (24%)	0.355
Prior revascularization	2 (8%)	3 (12%)	0.637
Culprit vessel			
RCA	16 (64%)	14 (56%)	0.564
LAD	6 (24%)	9 (36%)	0.355
LCX 2	3 (12%)	(8%)	0.637

Abbreviations: BMI, body mass index; Kg/m2, kilogram per square meter; RCA, Right Coronary Artery; LAD, Left Anterior Descending Artery, LCX: Left Circumflex Artery Data were expressed as mean ± SD or numbers.

capacity increased in the exercise group from 6.54 ± 0.24 to 8.71 ± 0.56 METs (P < 0.001) and diastolic blood pressure decreased from 76.44 ± 3.93 to 74.24 ± 3.49 mmHg (P = 0.006). Such a significant difference was observed in the resting heart rate (P < 0.001). However, other variables showed insignificant changes before and after the cardiac rehabilitation period (Table 2).

According to the results of baseline echocardiographic examination, no significant difference was shown in the LVEF between the exercise (42.96 ± 7.05%) and the control groups (41.8 ± 4.3%) (P = 0.485). In addition, there were no significant differences in the LVESD/LVEDD, LVESV/LVEDV, FS, LV mass and mean global εLL between the two groups (P > 0.05).

After 8 weeks of cardiac rehabilitation program, the LVEF increased significantly in the rehabilitated individuals (42.96 ± 7.05 vs. 48.16 ± 4.3; P = 0.001). Comparison of other variables before and after the rehabilitation period in the exercise group revealed a significant difference in all of them, except for LVEDV and SV. Moreover, the difference in the follow-up LVEF between the exercise and control groups was significant (48.16 ± 4.3 vs. 42.8 ± 3.7; P < 0.001) and such a significant difference was not observed in none of other echocardiographic parameters. The comparison of changes in variables before and after the rehabilitation period between the exercise and control groups illustrated a significant increase in LVEF (mean percentage changes: 13.56 ± 15.98% vs. 2.86 ± 8.46%; P = 0.005) and mean global εLL (16.39 ± 14.97% vs. 2.62 ± 9.98%; P < 0.001) in the rehabilitated individuals. In addition, a significant decrease in LVESD (-7 ± 8.98% vs. -0.53 ± 6%; P = 0.004), LVESV (-10.48 ± 11.86% vs. -2.5 ± 12.34%; P = 0.025) and LV mass (-6.06 ± 6.65% vs. -1.30 ± 6.37%; P = 0.013) was observed in the exercise group as compared with the controls. No significant change in FS, LVEDD and LVEDV was shown between the groups during the rehabilitation period (P > 0.05). The echocardiographic data are summarized in Table 3.

5. Discussion

In this prospective, single-blinded, controlled clinical trial, the 8-week exercise-based cardiac rehabilitation program after acute STEMI did significantly improve the systolic function as indicated by the significant increase in LVEF and global εLL as compared with the controls; this was associated with a significant improvement in exercise capacity. Although the change in FS between the two groups was not statistically significant, a marked improvement was observed in the participants of rehabilitation group during the program. However, the increase in SV before and after the rehabilitation was not significant in the exercise group despite the significant reduction in ESV and this may be at least partially due to insignificant change in the systolic blood pressure or afterload during the course.

In contrast to a relatively comprehensive assessment of the LV systolic performance in our study, most of the previous studies investigating the effects of cardiac rehabilitation in patients after acute myocardial infarction used only LVEF or both LVEF and SV as indicators of the LV systolic function and the use of these parameters contributed to

Table 2. Changes of Exercise Test Parameters before and after the CRP			
Variable	**Initial**	**Follow-up**	**P value**
Resting HR (bpm)	68.8 ± 4.38	65.36 ± 4.13	< 0.001
Resting SBP (mmHg)	121.76 ± 5.29	121.68 ± 5.53	0.981
Resting DBP (mmHg)	76.44 ± 3.93	74.24 ± 3.49	0.006
Maximal HR (bpm)	143.52 ± 5.89	145.12 ± 7.15	0.135
Maximal RPP	24288 ± 2304	24217 ± 2227	0.680
METs	6.54 ± 0.24	8.71 ± 0.56	< 0.001

Abbreviations: CRP, cardiac rehabilitation program; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; RPP, rate pressure product; METs, metabolic equivalents; bpm, beat per minute; mmHg, millimeter of mercury
Data were expressed as mean ± SD.

Table 3. Echocardiographic Changes before and after the Rehabilitation Period in the Exercise and Control Groups

Variables	Exercise Group			Control Group		
	Initial	Follow-up	P	Initial	Follow-up	P
LVESD (mm)	42.76 ± 3.60	39.72 ± 4.77	< 0.001	41.68 ± 4.37	41.4 ± 4.5	0.596
LVEDD (mm)	53.12 ± 5.77	50.88 ± 5.41	0.047	52.84 ± 5.11	52.8 ± 5.39	0.948
LVESV (mL)	49.12 ± 9.31	43.6 ± 8.55	< 0.001	51.12 ± 12.11	49.32 ± 11.56	0.199
LVEDV (mL)	87.07 ± 15.67	83.36 ± 13.08	0.121	89.52 ± 19.62	87.4 ± 18.63	0.480
EF (%)	42.96 ± 7.05	48.16 ± 4.3	0.001	41.8 ± 4.3	42.8 ± 3.7	0.163
SV (mL)	38.8 ± 9.71	39.92 ± 7.92	0.581	39.64 ± 9.97	39.68 ± 7.96	0.986
FS (%)	20.56 ± 3.25	22.59 ± 4.18	0.022	21.03 ± 3.82	21.49 ± 3.47	0.439
LV mass (g)	227.28 ± 21.41	213 ± 21.48	<0.001	232.92 ± 21.65	229.84 ± 25.94	0.325
Global εLL (%)	-13.74 ± 3.15	-15.74 ± 3	< 0.001	-14.12 ± 3.56	-14.35 ± 3.29	0.226

Abbreviations: LVESD, left ventricular end-systolic dimension; LVEDD, left ventricular end-diastolic dimension; LVESV, left ventricular end-systolic volume; LVEDV, left ventricular end-diastolic volume; EF, ejection fraction; SV, stroke volume; FS, fractional shortening; Global εLL, mid-wall global longitudinal left ventricular strain; mm, millimeter; mL, milliliter; g, gram; P, P value
Data were expressed as mean ± SD.

controversial results (20, 22-26). A striking number of these studies were small-sized and one of them lacked a control group. In addition, both LVEF and SV are known to be preload- and afterload-dependent and have several other limitations in the assessment of global LV systolic function. Even in the most currently recommended two-dimensional method to assess the global LV systolic function (Simpson's biplane method), the frequent apex foreshortening, the endocardial dropout and the blindness to shape distortions not visualized in the apical 2- and 4-chamber views would result in inaccurate estimation of both LVEF and SV (21).

The results of our study are inconsistent with the findings of Yu et al., (26) possibly due to low intensity of exercise training and fewer scheduled sessions as well as a relatively longer interval between them. However, the longer period of exercise training (three months) with the same intensity, as ours, also led to discordant results in a small-sized, clinical trial performed by Giallauria et al. in which despite the improvement of exercise capacity and early LV filling, no significant change in the LV volumes or LVEF was observed (23). The confinement of sample volume to only elderly patients may express the inconsistency.

In a recent study, the use of a more sensitive, but angle-dependent parameter, i.e. tissue Doppler systolic velocity at the septal and lateral sides of the mitral annulus, revealed no improvement in the 8-week rehabilitated patients after acute myocardial infarction (27). In contrast, the mean global εLL applied in the current study proved the beneficial effects of cardiac rehabilitation on LV systolic performance, as mentioned before. This parameter is an angle-independent one with the established prognostic value (21), for which the same vendor and the same software were used for measurement in all examinations to eliminate the vendor- and software-dependency of this valuable parameter.

Apart from the significant decrease in LVESD and LVEDV after the rehabilitation course in the exercise group, as compared with the controls, no adverse increase in LVEDD or LVEDV was observed in the exercise group during the rehabilitation period underscoring no disadvantages of early exercise training in patients after acute STEMI. Such a result has been confirmed by other studies (22, 28), and has eliminated the concern about negative consequences of the early use of exercise training in post-myocardial infarction patients which had been stated in former studies (29, 30).

Moreover, a meta-analysis revealed that early exercise-based cardiac rehabilitation not only affected the LV geometry adversely, but also the greatest benefits were seen in earlier programs after acute myocardial infarction (24).

The comparison of the changes in the LV mass between the two groups showed a significant decrease in the exercise group after the cardiac rehabilitation program. Basati et al. and Rodriguez et al. also found such exercise-induced improvement in LV mass (22, 31). In the latter study, increasing the duration of exercise contributed to more decrease in the mean LV mass. Improvement in the LV mass is another clue for the positive effects of exercise-based cardiac rehabilitation on post-myocardial infarction LV remodeling.

The attenuating or reverse LV remodeling induced by exercise training is known to be related to improved balance between matrix metalloproteinase-1 and tissue inhibitor of the matrix metalloproteinase-1, diminished oxidative stress, boosted antioxidant capacity, desirable myosin heavy chain isoform switch, improved mitochondrial calcium handling, enhanced myocardial angiogenesis and mitigation of renin-angiotensin-aldosterone system (RAAS) (32). The latter not only has direct effects on LV remodeling but also influences the afterload which in turn would result in less LV remodeling and better performance.

Despite the mentioned advantages of this study in a highly understudied population for cardiac rehabilitation, it has some limitations such as lack of randomization. In addition, most of the enrolled patients were middle-aged and, therefore, the results cannot be generalized to extremes of age groups in adult population. The graded exercise test was not performed in the control group. Thus, no controlled assessment was possible for the indices of cardiopulmonary motor function to clarify whether the significant changes in the resting heart rate, diastolic BP and exercise capacity were caused by the exercise-based rehabilitation or by natural recovery. Moreover, the potential benefits of cardiac rehabilitation on LV systolic function during exercise were not considered due to performing echocardiographic examinations only at rest; also, the long-term results of cardiac rehabilitation were not determined in this study.

In conclusion, early exercise-based cardiac rehabilitation program in patients after acute STEMI could have beneficial effects on LV systolic function without any adverse effect on LV remodeling. Further well-designed studies worldwide with a larger sample size are required in order to prescribe a safe and optimal exercise training course in patients after acute STEMI.

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Authors' Contribution

Firoozeh Abtahi: Study design, Maryam Tahamtan: data gathering and writing manuscript; Kaynoosh Homayouni: data gathering; Alireza Moaref: data analysis; Mahmoud Zamirian: final revision of manuscript.

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