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The effect of cardiac rehabilitation on left ventricular diastolic functions assessed by exercise stress echocardiography in patients with acute coronary syndrome

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ABSTRACT

Objective: The aim of our study is to investigate the impact of cardiac rehabilitation on left ventricular (LV) diastolic function in acute coronary syndrome (ACS) patients.

Patients and Methods: Patients were selected consecutively among ACS patients who underwent primary percutaneous intervention and were found eligible for cardiac rehabilitation program from May 2014 to May 2015. Forty-four patients were included in cardiac rehabilitation group and recruited to 30 sessions of Phase 3 cardiac rehabilitation program six weeks after discharge. Twenty consecutive patients were included as control group. LV diastolic functions were assessed by resting and stress echocardiography.

Results: There were not any significant differences in characteristics between the groups. Resting and stress E velocities and resting lateral e' velocity significantly increased after rehabilitation program. Left atrial volume index, resting and stress A velocities and average E/e' ratios were significantly lower while stress lateral e' velocity was significantly higher in rehabilitation group after program compared to controls. The number of patients with diastolic dysfunction decreased after rehabilitation program. Final resting and stress echocardiography revealed significantly lower frequency of diastolic dysfunction in rehabilitation group.

Conclusion: Cardiac rehabilitation improves diastolic functions in ACS patients, which may be detected by stress echocardiography.

Keywords: Acute coronary syndrome, Cardiac rehabilitation, Diastolic function, Diastolic stress echocardiography

1. INTRODUCTION

Acute coronary syndrome (ACS) is the most leading cause of mortality worldwide [1]. ACS affects not only physical but also psychological and social life of the patients, which have highlighted the importance of a multidisciplinary approach to ACS patients.

Cardiac rehabilitation is a structured program which includes exercises, lifestyle modifications, psychosocial support and education compatible with special conditions of each patient. Cardiac rehabilitation is associated with improved clinical outcomes in a broad spectrum of cardiac diseases. Participation in a cardiac rehabilitation program after ACS and coronary artery bypass grafting is associated with reduced mortality [2]. The meta-analysis of exercise training trials in patients with chronic heart failure has provided evidence that exercise training is associated with significant decreases in mortality and hospitalizations [3]. Therefore, current guidelines support cardiac rehabilitation for ACS patients after revascularization either by coronary artery bypass grafting or stent implantations, after valve surgery, and in patients with stable chronic systolic heart failure [4].

Both systolic and diastolic functions may be impaired in patients with ACS. Due to its significant benefits in heart failure with reduced ejection fraction, cardiac rehabilitation is strongly recommended and its reimbursement is approved. On the other hand, for patients with heart failure with preserved ejection fraction is not endorsed by clinical guidelines [4]. A randomized exercise training study of 54 patients with cardiomyopathy demonstrated a reduction in left ventricular (LV) diastolic stiffness in the exercise training group suggesting that cardiac rehabilitation improves diastolic function [5]. Exercise training resulted in a decrease in E/e´ in patients with heart failure with preserved ejection fraction [6].

Echocardiographic examination has a crucial role in diagnosis of ventricular systolic and diastolic functions. Diastolic

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stress testing might be superior to resting echocardiography in showing diastolic dysfunction especially in patients with exertional dyspnea.

The aim of this study was to investigate the effects of cardiac rehabilitation on LV diastolic functions assessed by bicycle stress echocardiography in ACS patients.

2. PATIENTS and METHODS

The study was approved by the Marmara University School of Medicine Research Ethics Committee on 28.06.2013 (approval number: 09.2013.0215). Written informed consent was obtained from all patients before entering the study.

Study Population

In this prospective study, the data were collected in Department of Cardiology, Marmara University School of Medicine, Turkey, from May 2014 to May 2015. Power analysis was performed by an online calculator (https://clincalc.com/stats/samplesize.aspx). Assuming a power of 90 % and α=0.05, a study population including at least 44 individuals was needed. Patients were selected consecutively among patients who were hospitalized in our coronary intensive care unit with the diagnosis of ACS, underwent successful primary percutaneous intervention (PCI) with thrombolysis in myocardial infarction (TIMI) 3 grade flow, discharged with optimal medical therapy (including dual antiplatelet therapy with an angiotensin converting enzyme inhibitor, beta blocker and statin unless there was a contraindication) and were found eligible for cardiac rehabilitation program after discharge. The diagnosis of ACS was based on symptoms, electrocardiography and cardiac markers. ST segment elevation myocardial infarction (STEMI) was defined as the presence of chest pain with persistent ST segment elevation of at least 0.1mV in at least two contiguous leads. Non ST segment elevation myocardial infarction (NSTEMI) was defined as the presence of chest pain during the previous 48 hours with ST segment and/or T wave changes on electrocardiography indicating ischemia and a positive troponin test. Exclusion criteria were presence of multi-vessel disease, PCI in coronary arteries other than infarct-related artery, arrhythmias (atrial fibrillation, atrial flutter, ventricular arrhythmias), bundle branch blocks, significant valvular disease (any stenosis and/or regurgitation greater than mild in severity), severe renal, hepatic or lung disease and malignancy. Seventy-five consecutive patients were invited to the study and were informed about Phase 1 rehabilitation program during hospitalization and Phase 2 rehabilitation program during the 6 weeks following discharge. Twenty patients refused to participate in the cardiac rehabilitation program due to socioeconomic conditions and were included in the study as control group. Exercise test was performed to the remaining 55 patients to assess their eligibility for cardiac rehabilitation program six weeks after discharge. After the exclusion of the patients who developed chest pain (6 patients), syncope/presyncope (2 patients) and significant ST segment depression (3 patients) in the exercise test, the remaining 44 patients who did not have contraindication for Phase 3 cardiac rehabilitation were included as cardiac rehabilitation group.

All patients were evaluated in terms of demographic characteristics, concomitant diseases and cardiovascular risk factors. Hypertension was defined as systolic and/or diastolic blood pressure ≥140/90mmHg, previously diagnosed hypertension, or use of any antihypertensive medications. Diabetes was defined as fasting plasma glucose levels of more than 126mg/dL in ≥3 measurements, previously diagnosed diabetes, or use of antidiabetic medications such as oral anti-diabetic agents or insulin. Hyperlipidemia was defined as serum total cholesterol ≥200mg/dl, serum triglyceride ≥150mg/dl, low-density lipoprotein cholesterol ≥130mg/dl, previously diagnosed hyperlipidemia, or the use of lipid-lowering medication. Smoking status was defined as the history of tobacco use at admission or in the 6 months prior to the visit. Detailed physical examination was performed to all patients. Body mass index (BMI) was calculated from measurements of height and weight. The N-terminal pro brain natriuretic peptide (NT-proBNP) levels of the patients during hospital stay and follow-up were noted [7].

Echocardiographic Examination

All patients underwent transthoracic echocardiography and diastolic stress echocardiography before the cardiac rehabilitation program and within the following five days after the cessation of cardiac rehabilitation program. Control group underwent echocardiographic evaluation 6-8 weeks following discharge and echocardiography was repeated three months later.

Standard transthoracic echocardiography was performed by a single, experienced cardiologist with a Philips iE33 echocardiography device (Philips Medical Systems, Andover, MA, USA). Patients were positioned in the left lateral decubitus position. Data acquisition was performed with a 3.5 MHz transducer at a depth of 16-17 cm in the parasternal and apical views (standard parasternal short-axis from mid-ventricular level; apical long-axis; two, three, and four-chamber images). Standard M-mode, 2D, Doppler and color-coded tissue Doppler images (TDI) were obtained during breath hold, stored in cine loop format from three consecutive beats, and transferred to a workstation for further offline analysis. Gain settings, filters, and pulse repetition frequency were adjusted to optimize color saturation, and a color Doppler frame scanning rate of 100–140 Hz was used for color TDI and a frame rate of 44–82 frames/s for grayscale images. Conventional echocardiographic measurements were performed in accordance with the recommendations of the American Society of Echocardiography guidelines [8,9]. The diagnosis of LV diastolic dysfunction was based on mitral flow velocities (E/A), mitral annular e′ velocity, E/e′ ratio, peak velocity of tricuspid regurgitation jet, and left atrium maximum volume index. The abnormal cutoff values were septal e′ velocity < 7cm/sec, lateral e′ velocity <10cm/sec, average E/e′ ratio >14, left atrial volume index (LAVI) >34mL/m^2, and peak tricuspid regurgitation velocity >2.8m/sec. LV diastolic dysfunction was present if more than half of the available parameters met these cutoff values.

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After baseline echocardiography, all the patients underwent diastolic stress echocardiography using the supine bicycle protocol (General Electric eBike EL tilt-table ergometer). Patients pedaled at constant speed beginning at a workload of 25 Watts (W), with an increment of 25 W every 3 minutes. Subsequently, with continuous electrocardiographic monitoring and interval blood pressure monitoring, patients exercised on the supine bicycle to achieve target heart rate (85% of maximum predicted for age). During the supine bicycle stress, 2D images and Doppler diastolic parameters were acquired in the apical four-chamber views at each stage including peak exercise and recovery. From the apical window, a 1 – to 2-mm pulsed Doppler sample volume was placed at the mitral valve tip, and mitral flow velocities from 5 to 10 cardiac cycles were recorded. The mitral inflow velocities were traced and the following variables were obtained: peak velocity of early (E) and late (A) filling, and deceleration time (DT) of the E velocity. The tricuspid regurgitant jet velocity was also obtained to estimate pulmonary artery systolic pressure using continuous wave Doppler. Mitral annulus velocity was measured by TDI using the pulsed wave Doppler mode. The filter was set to exclude high frequency signals, and the Nyquist limit was adjusted to a range of 15 to 20 cm/s. Gain and sample volume were minimized to allow for a clear tissue signal with minimal background noise. E´ was measured from the apical 4-chamber view with a 2 – to 5-mm sample volume placed at the septal and lateral corner of the mitral annulus. The test was considered definitely abnormal indicating diastolic dysfunction when all of the following three conditions were met: average E/e′ >14 or septal E/e′ ratio >15 with exercise, peak TR velocity >2.8m/sec with exercise and septal e′ velocity <7cm/sec or lateral e′ velocity <10cm/sec at baseline (Figures 1 and 2). The results were normal when average (or septal) E/e′ ratio was <10 with exercise and peak TR velocity was <2.8m/sec with exercise [**9**].

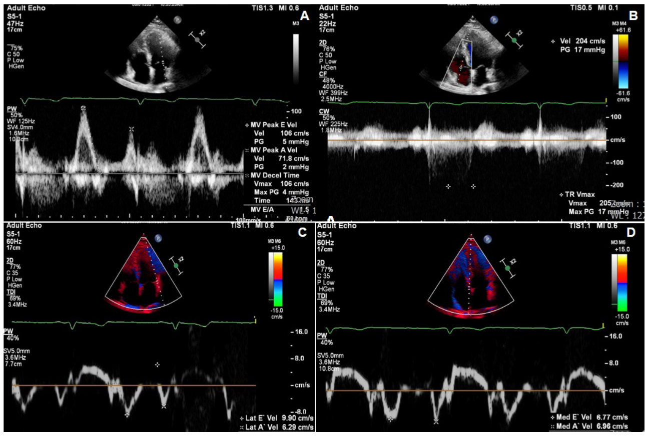

Figure 1. *Baseline Doppler echocardiographic measures of a patient – heart rate is 60/min (A. Mitral inflow velocities (peak velocity of early (E) and late (A) filling and deceleration time of the E velocity); B. tricuspid regurgitant jet velocity; C. mitral annular lateral e′ and a′ velocities; D. mitral annular septal e′ and a′ velocities)*

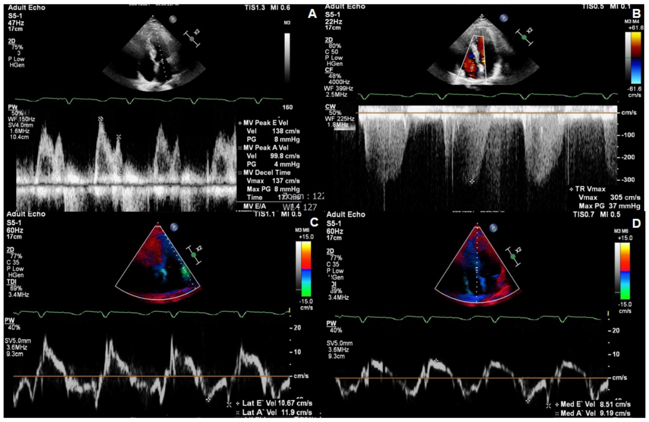

Figure 2. *Exercise Doppler echocardiographic measures of the same patient – heart rate is 104/min (A. Mitral inflow velocities (peak velocity of early (E) and late (A) filling and deceleration time of the E velocity); B. tricuspid regurgitant jet velocity; C. mitral annular lateral e′ and a′ velocities; D. mitral annular septal e′ and a′ velocities)*

Cardiac Rehabilitation Program

Cardiac rehabilitation program included supervised exercise training together with patient education about secondary prevention from cardiovascular diseases [10]. Advices for lifestyle modifications including a healthy, balanced diet with salt restriction, smoking cessation, moderation of alcohol consumption, dealing with stress, regular sleep and maintaining an ideal body weight with regular physical activity were given to each patient and adherence to these advices were checked regularly each week by a trained nurse.

Exercise tolerance test was applied in Cardiac Rehabilitation Unit two days after the first assessment. Contraindications for exercise test were assessed by a cardiologist. Cycle ergometer (Ergoline Ergoselect 2 model 600 and Opticare software program) was used to assess exercise capacity. Patients wore comfortable clothes, stopped eating/drinking three hours before their arrival and did not smoke before the test. Maximum heart rate was calculated according to age and gender. Target heart rate range was calculated according to Karvoneen method [(Maximum heart rate – resting heart rate) × 60-80% + resting heart rate)]. During the test, the patient started cycling with 30 W pedal load and 15 W increment was applied every two minutes with a constant pedaling speed of 55-65 per minute. If target heart rate was reached or the patient wanted to stop due to fatigue, the test was stopped. Maximum pedal load in watts, maximal oxygen consumption in minutes per kg or the metabolic equivalent of task (MET) (ml/kg/minutes) and maximal energy consumption (kcal/minutes) reached were recorded. The data were used to develop individualized rehabilitation program for patients in cardiac rehabilitation group and also used as a follow-up criteria of fitness parameters.

Initially the ratio of maximum load to patient body weight (watt/kg) was calculated. The ratio was used as an indicator of physical fitness. The values lower than 1.4 W/kg indicated

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an untrained person or a patient with moderate to high risk for cardiac complications during physical stress according to the recommendations of the American Heart Association. If the ratio was lower than 1 watt/kg, the patients started the program with low-intensity intermittent training to provide their compliance with the program. When the ratio was 1.4 and over, exercise program was continued with constant heart rate (endurance training) method. Individual exercise programs were revised by weekly assessments according to improvements in physical fitness.

Each training session included reduced load warming and cooling periods for five minutes in the beginning and the end of the training. In the intermittent training program, the patients performed low load for 1 minute and maximum load for 1 minute consecutively for 20 minutes. In constant heart rate method, the maximal load at target heart rate was recorded with the exercise testing. In the program, the patients exercised without exceeding target heart rate. The target heart rate was kept constant with changing the load automatically by cycle ergometer.

After cycle ergometer training, each exercise session was finished with stretching and strengthening exercises. Biceps, triceps, deltoid, quadriceps, hamstrings, abductor muscle groups were trained in the muscle strengthening program. Strengthening exercises were planned with calculation of 1 repetition maximum (RM) method. The maximum load which could be hold by 3 different large muscle groups of lower and upper extremities was determined. Each muscle was strengthened with 3x10 repetitive isotonic contractions with up to 75% resistance of 1 RM. This program was performed 3 days per week for 10 weeks in the hospital (30 sessions lasting approximately 2.5 months). After the program, the patients were encouraged to perform aerobic exercises by themselves in their daily life.

Statistical Analysis

All statistical tests were performed with a commercially available software program (Statistical Package for the Social Science (SPSS) 20.0 for Windows, Chicago, IL, USA). All continuous variables were checked for normal distribution by the Kolmogorov-Smirnov test and presented as mean±standard deviation (SD) while categorical variables were expressed as numbers or percentages. Chi-square test or McNemar test was used to compare categorical variables. Student's *t* test or paired sample test were used to compare continuous variables with normal distribution while Mann-Whitney *U* test or Wilcoxon test were used to compare the continuous parameters without normal distribution. P <0.05 was considered statistically significant.

3. RESULTS

The baseline characteristics, LV size and ejection fraction of the 44 patients in cardiac rehabilitation group and the 20 patients in control group are shown in Table I. There were not any significant differences in age, sex and comorbidities between the cardiac rehabilitation group and controls. In the cardiac rehabilitation group, 20 patients had anterior STEMI while 2 patients had lateral STEMI and 10 patients inferior STEMI. In the control group, 8 patients had anterior STEMI and 6 patients had inferior STEMI. LV size and ejection fraction of the rehabilitation group and controls were similar. Nine patients in the cardiac rehabilitation group and 4 control patients had LV ejection fraction <50%. None of the patients had dilated LV. There were not any significant changes in the LV diameters (for LV end diastolic diameter 47.2 ± 4.7mm to 46.4 ± 4.9mm, P=0.286 in cardiac rehabilitation group and 48.8 ± 5.9mm to 48.6 ± 5.1mm, P=0.242 in controls; for LV end systolic diameter 32.5 ± 5.4mm to 31.8 ± 4.9mm, P=0.314 in cardiac rehabilitation group and 35.6 ± 5.8mm to 35.1 ± 5.4mm, P=0.342 in controls) and EF (56.5 ± 8.5% vs 56.9 ± 8.1%, P=0.614 in cardiac rehabilitation group and 53.8 ± 5.4% vs 55.2 ± 6.8%, P=0.156 in controls) in control echocardiographies. The NT-proBNP values of the cardiac rehabilitation group and controls were similar before the rehabilitation program (410.9±529.4pg/mL vs 445.2±601.8pg/mL P= 0.142). The NT-proBNP values decreased significantly in cardiac rehabilitation group to 218.8±274.1pg/mL (P<0.001) after rehabilitation program whereas the decrease in NT-proBNP levels was not significant in controls (396.7±456.8pg/mL, P= 0.112).

Table I. *Patient characteristics and baseline left ventricular size and ejection fraction*

	Cardiac Rehabilitation Group (n= 44)	Control Group (n= 20)	P
Age (year)	53.2 ± 9.9	57.1 ± 14.1	0.274
Male gender (n-%)	40 (90.9%)	15 (75%)	0.124
Hypertension (n-%)	29 (65.9%)	9 (45%)	0.114
Diabetes (n-%)	13 (29.5%)	7 (35%)	0.663
Hyperlipidemia (n-%)	33 (75.0%)	14 (70%)	0.675
Smoking (n-%)	26 (59.1%)	15 (75%)	0.219
Body mass index (kg/m^2)	27.6 ± 3.7	26.5 ± 2.9	0.300
Left atrium (mm)	37.4 ± 4.0	40.3 ± 6.5	0.127
Left ventricular end diastolic diameter (mm)	47.2 ± 4.7	48.8 ± 5.9	0.399
Left ventricular end systolic diameter (mm)	32.5 ± 5.4	35.6 ± 5.8	**0.014**
Interventricular septum thickness (mm)	10.5 ± 1.8	11.4 ± 1.9	**0.033**
Posterior wall thickness (mm)	10.0 ± 1.3	9.4 ± 1.3	0.054
Left ventricular ejection fraction (%)	56.5 ± 8.5	53.8 ± 5.4	0.191

The resting diastolic parameters and diastolic stress echocardiographic parameters of the cardiac rehabilitation group and controls are shown in Table II. Among the baseline resting and stress echocardiographic parameters; only LAVI was significantly different between the cardiac rehabilitation group and controls. Resting and stress E velocities and resting

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lateral e' velocity increased significantly in cardiac rehabilitation group after rehabilitation program while comparison of control group's baseline and third month echocardiography revealed no significant change in resting and stress echocardiographic diastolic parameters except from resting A velocity; which increased significantly. LAVI, resting and stress A velocities were significantly lower while stress lateral e' velocity was significantly higher in cardiac rehabilitation group after rehabilitation program compared to control. Although, there were not any significant differences in resting and stress E/e' parameters between cardiac rehabilitation group and controls, cardiac rehabilitation group had significantly lower resting and stress E/e' measures after rehabilitation program compared to third month echocardiography measures of control group (Figure 3).

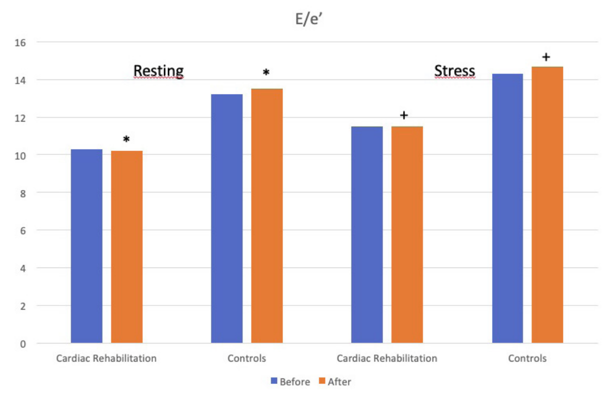

Figure 3. *Bar graph showing resting and stress E/e' measures of the cardiac rehabilitation group and controls before and after (* and + denote statistically significant differences in resting and stress E/e' between cardiac rehabilitation group after rehabilitation program and controls after three months, respectively).*

Table II. *The resting and diastolic stress echocardiography parameters of the cardiac rehabilitation group and controls*

	Cardiac Rehabilitation Group (n= 44)			Control Group (n= 20)				
	Before rehabilitation	After rehabilitation	P1	Baseline	At 3rd month	P2	P3	P4
LAVI (mL/m²)	25.4±6.4	24.3±6.6	0.165	33.5±12.5	33.0±12.1	0.586	**0.005**	**0.002**
Rest E (m/s)	0.85 ± 0.15	0.92 ± 0.15	**0.007**	0.93 ± 0.19	0.98 ± 0.17	0.225	0.101	0.137
Stress E (m/s)	1.06 ± 0.18	1.15 ± 0.14	**0.002**	1.14 ± 0.21	1.21 ± 0.17	0.135	0.088	0.166
Rest A (m/s)	0.68 ± 0.15	0.71 ± 0.15	0.200	0.73 ± 0.16	0.81 ± 0.17	**0.019**	0.246	**0.039**
Stress A (m/s)	0.79 ± 0.17	0.77 ± 0.16	0.436	0.82 ± 0.18	0.91 ± 0.25	0.103	0.323	**0.038**
Rest DT (ms)	192 ± 31	178 ± 27	**0.003**	180 ± 28	184 ± 34	0.636	0.183	0.727
Stress DT (ms)	162 ± 35	175 ± 26	**0.011**	166 ± 23	170 ± 38	0.840	0.506	0.190
Rest Septal e′ (cm/s)	7.8 ± 2.4	8.4 ± 2.1	0.074	7.4 ± 2.8	7.3 ± 2.5	0.879	0.445	0.102
Stress Septal e′ (cm/s)	8.4 ± 2.8	9.1 ± 2.2	0.118	7.4 ± 3.1	7.9 ± 2.5	0.453	0.103	0.070
Rest Lateral e′ (cm/s)	9.5 ± 2.3	10.7 ± 3.1	**0.005**	9.1 ± 3.6	9.3 ± 3.4	0.717	0.326	0.115
Stress Lateral e′ (cm/s)	11.5 ± 3.2	11.9 ± 2.7	0.406	10.6 ± 3.9	10.3 ± 3.4	0.720	0.209	**0.044**
Rest Average E/e′	10.3 ± 2.7	10.2 ± 2.6	0.963	13.2 ± 6.7	13.5 ± 5.2	0.363	0.151	**0.041**
Stress Average E/e′	11.5 ± 4.0	11.5 ± 3.0	0.815	14.3 ± 6.0	14.7 ± 4.9	0.820	0.063	**0.041**
Rest TR velocity (m/sec)	2.2 ± 0.4	2.2 ± 0.3	0.054	2.4 ± 0.6	2.5 ± 0.5	0.058	0.092	0.054
Stress TR velocity (m/sec)	2.5 ± 0.4	2.5 ± 0.4	0.646	2.7 ± 0.6	2.8 ± 0.5	0.119	0.237	**0.030**
Patients with diastolic dysfunction by resting echocardiography (n – %)	5 (11.4%)	3 (6.8%)	0.625	5 (25%)	7 (35%)	0.500	0.263	**0.008**
Patients with diastolic dysfunction by stress echocardiography (n – %)	12 (27.3%)	8 (18.2%)	0.344	10 (50%)	9 (45%)	1.0	0.076	**0.024**

LAVI: left atrial volume index; E= early diastolic mitral flow velocity; A= late diastolic mitral flow velocity; DT: deceleration time; e´= early diastolic velocity of the lateral mitral annulus; TR: tricuspid regurgitation
P1: comparison of cardiac rehabilitation group before and after rehabilitation program
P2: comparison of control group's baseline and third month echocardiography parameters
P3: comparison of baseline echocardiographic parameters between cardiac rehabilitation group and controls
P4: comparison of final echocardiographic parameters between cardiac rehabilitation group and controls

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Although, in resting echocardiography, diastolic dysfunction was detected in 5 patients in cardiac rehabilitation group and in 5 patients in controls; stress echocardiography revealed diastolic dysfunction in 12 patients in cardiac rehabilitation group and in 10 control patients. Diastolic dysfunction assessed by stress echocardiography improved in 7 patients after rehabilitation program while 5 patients remained to have diastolic dysfunction and 3 new patients had worsened diastolic function. On the other hand, only 3 patients had improved diastolic function while 7 patients remained to have diastolic dysfunction and 2 new patients had worsened diastolic function in the control group. The number of the patients with diastolic dysfunction decreased after cardiac rehabilitation program. And the frequency of diastolic dysfunction assessed by either resting or stress echocardiography was lower in cardiac rehabilitation group after the rehabilitation program compared to controls (6.8% vs 35% P=0.008 and 18.2% vs 45% P=0.024).

4. DISCUSSION

Diastolic dysfunction and elevated LV filling pressures are associated with poor prognosis in patients with acute myocardial infarction even in patients with relatively preserved systolic function [11]. Cardiac rehabilitation is associated with reduced mortality after myocardial infarction, after percutaneous coronary intervention and in patients with LV systolic dysfunction [3,12-14]. However, the effects of exercise training on diastolic function are less definite. In our study, we showed that cardiac rehabilitation program improved diastolic parameters in ACS patients with relatively preserved LV systolic function. The novelty of our study was the demonstration of the improvement in diastolic parameters by also stress echocardiography.

High intensity aerobic treadmill exercise has been shown to improve early diastolic relaxation in patients with stable coronary artery disease, measured by the mean LV early diastolic strain rate [15]. Similarly, in our study, resting and stress E velocities and resting lateral e' velocity increased significantly after cardiac rehabilitation program. However, another study did not show any improvement in LV diastolic indices including E, A, E/A ratio and deceleration time after an 8-week cardiac rehabilitation program in post-myocardial infarction patients revascularized with coronary artery bypass grafting or percutaneous coronary intervention although exercise capacity improved [16].

E/e' ratio can be used to predict LV filling pressures and is a powerful predictor of survival after acute myocardial infarction [17]. In our study, although the baseline E/e' were not significantly different between the groups, after cardiac rehabilitation program the difference became statistically significant. Cardiac rehabilitation program is associated with improved LV diastolic function. Similar to our study, Acar et al., explored the effect of cardiac rehabilitation on LV diastolic function in ACS patients revascularized by percutaneous coronary intervention and found that although E/e' decreased with cardiac rehabilitation, the difference was not statistically different **[18]**. They showed better E/A and septal e' in the cardiac rehabilitation group after the rehabilitation program compared to the controls and concluded that cardiac rehabilitation partially improved LV diastolic function in these patients. In another study conducted prospectively in 24 patients, a 3-month exercise-based cardiac rehabilitation program improved E/e' ratio and diastolic function in 12 patients while 9 patients remained at the same grade of diastolic dysfunction and one patient had worsened diastolic function [19]. Similarly, in our study among the 12 patients who has diastolic dysfunction assessed by stress echocardiography; diastolic function improved in 7 patients after rehabilitation program.

The improvement of diastolic dysfunction may also be explained by the revascularization procedure and the effect of optimal medical therapy initiated in these patients. However; a study exploring the effect of cardiac rehabilitation in 146 patients undergoing percutaneous coronary intervention revealed that cardiac rehabilitation improved diastolic functions and the distribution of diastolic dysfunction was changed significantly only in the cardiac rehabilitation group [20]. The most prominent improvement was observed in the patients with grade I diastolic dysfunction.

Diastolic stress echocardiography is superior to resting echocardiography in evaluation of patients with concealed diastolic dysfunction. Although, diastolic parameters are normal with resting echocardiography, augmentation of myocardial relaxation may be limited and E/e′ ratio increases with exercise in these patients. Diastolic stress echocardiography is recommended in patients with indeterminate or grade 1 diastolic dysfunction [9]. In our study, most of the patients had normal LV ejection fraction with normal or indeterminate LV diastolic function. We evaluated diastolic functions of the patients also with stress echocardiography and found more patients to have diastolic dysfunction with stress echocardiography. Although, there was not any significant decrease in the stress E/e′ ratio or tricuspid regurgitation velocity in cardiac rehabilitation group, the final E/e′ ratio and tricuspid regurgitation velocity of the cardiac rehabilitation group were significantly lower than that of controls.

Study Limitations

The major limitations of our study were the relatively small sample size and being a single center study. Most of the patients had preserved LV function and the results might be different in a population with more pronounced LV systolic dysfunction. Non-randomized design of the study and the inclusion of the patients who refused cardiac rehabilitation as control group were also major limitations. Adherence to medication and lifestyle modifications were not evaluated in patients who refused cardiac rehabilitation. Adherence might be poor in these patients which might affect study results. The follow period was short and many patients discontinued cardiac rehabilitation program due to socioeconomic status and various other reasons which limited the analysis of prolonged effect of cardiac rehabilitation in these patients.

Conclusion

Cardiac rehabilitation improves diastolic parameters in ACS patients. Although, resting echocardiographic parameters are useful in assessing the response in diastolic functions; diastolic stress echocardiography may reveal concealed LV diastolic dysfunction and its response to cardiac rehabilitation in these patients. Larger studies with longer follow up periods are necessary to elucidate the temporal changes in diastolic parameters in these patients.

Compliance with the Ethical Standards

Ethics Approval: The study was approved by the Marmara University School of Medicine Research Ethics Committee on 28.06.2013 (approval number: 09.2013.0215). Written informed consent was obtained from all patients before entering the study.

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Authors contributions: MS, OY and NS: Concept and design, YB, KT and BO: Supervision, FB and JM: Data collection and/or processing, FB, IY and AC Analysis and interpretation. All authors read and approved the final version of the manuscript.

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