

Does cardiac rehabilitation improve left ventricular diastolic function of patients with acute myocardial infarction?

Akut miyokart enfarktüsü sonrası kardiyak rehabilitasyon sol ventrikül diyastolik fonksiyonlarını düzeltir mi?

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ABSTRACT

Objectives: We aimed to observe the effect of cardiac rehabilitation (CR) on left ventricular diastolic function in patients with acute myocardial infarction (AMI) and revascularization by percutaneous coronary intervention (PCI).

Study design: 82 patients were enrolled the study; 42 who were participating in a CR program, and 40 who did not maintain the program as a control group. Measurements of mitral inflow included the peak early filling (E-wave) and late diastolic filling (A-wave) velocities, the E/A ratio, deceleration time (DT) of early filling velocity and mitral A-wave duration. The early diastolic annular velocity has been expressed as e' with PW tissue Doppler imaging. The mitral inflow E velocity to tissue Doppler e' (E/e') was calculated and isovolumic relaxation time (IVRT) was measured. Measurements of pulmonary venous waveforms included peak systolic (S) velocity, peak anterograde diastolic (D) velocity and the time difference between the duration of the atrial reversal (Ar) and mitral A-wave duration (Ar-A).

Results: E/A and septal e' were better with the CR group than the control group. ($p=0.048$ vs $p=0.006$ respectively). The difference between E/e' measurements were not statistically significant ($p=0.138$). The left ventricular diastolic function of patients were partially improved with cardiac rehabilitation. There was no association between infarct-related artery (IRA) and diastolic functional measurements of the left ventricle in the individuals. Only hypertension was found significantly associated with E/A ($p=0.000$).

Conclusion: CR improves septal e' and E/A significantly in patients with AMI and revascularized successfully by PCI, especially in those with hypertension.

ÖZET

Amaç: Bu çalışmada akut miyokart enfarktüsü (AME) geçirmiş ve perkütan koroner girişimle yeniden kanlandırma yapılmış olgularda kardiyak rehabilitasyonun (KR) sol ventrikül diyastolik fonksiyonları üzerine olan etkisi değerlendirildi.

Çalışma planı: Toplam 82 hasta çalışmaya dahil edildi. AME sonrası KR programını tamamlayan 42 olgu hasta grubu ve ilk seanstan sonra sürdüremeyen 40 adet hasta kontrol grubu olarak çalışmaya alındı. Mitral dolum akımlarını oluşturan erken diyastol pik akım hızı (E) ve geç diyastolik pik akım hızı (A), E/A oranı, erken diyastol pik akım hızı azalma süresi (DT) ve mitral A dalgasının süresi ölçüldü. Apikal pencerelerden mitral anulus doku hareket hızları doku Doppler ile değerlendirildi. Erken diyastol hareket hızı e' olarak tanımlandı. E/e' hesaplandı ve doku Doppler incelemesi ile izovolümik gevşeme zamanı (IVGZ) ölçüldü. Pulmoner ven akımı ileri dalga formunun erken sistol pik hızı (S) ve diyastol pik hızı (D) tespit edilerek S/D oranları alındı. Atriyum geri akım süresi (Ar) ile mitral -A dalgası süresi arasındaki fark hesaplandı.

Bulgular: E/A oranı ve septal e' dalgası hızının kardiyak rehabilitasyon ile anlamlı olarak iyileştiği görüldü (sırasıyla $p=0.048$ ve $p=0.006$). E/e' ölçümlerinde istatistiksel olarak anlamlı fark bulunamadı ($p=0.138$). Sol ventrikül diyastolik fonksiyonu kardiyak rehabilitasyon ile kısmen düzelmiş olarak değerlendirildi. Enfarktüstün sorumlu damar ile sol ventrikül diyastolik fonksiyonları arasında herhangi bir ilişki kurulamadı. Hipertansiyon ile E/A arasında istatistiksel olarak anlamlı ilişki bulundu ($p=0.000$).

Sonuç: KR, AME geçirmiş ve yeniden kanlandırma yapılmış olgularda sol ventrikül septal e' ve E/A dalgasında anlamlı iyileşmeye neden olmakta ve bu iyileşme özellikle hipertansiyonu olan olgularda ön plana çıkmaktadır.

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Cardiac rehabilitation is a program of multidisciplinary interventions designed to assist clinically suitable individuals to attain and maintain their optimal level of functioning. In the 1930s, patients with myocardial infarction (MI) were advised to observe 6 weeks of bed rest. Chair therapy was introduced in the 1940s, and by the early 1950s, 3-5 minutes of daily walking was advocated, beginning at 4 weeks. In the 1950s, Hellerstein presented his methodology for the comprehensive rehabilitation of patients recovering from an acute cardiac event.^[1] He advocated a multidisciplinary approach to the rehabilitation program, which was adopted by cardiac rehabilitation (CR) programs throughout the world.

CR is defined as a program that involves medical evaluation, prescribed exercise, education, and counseling of patients with cardiac disease. It has to be comprehensive and, at the same time, individualized. A meta-analysis of randomized, controlled trials showed a 25% reduction in mortality at 3-year follow-up with exercise training in post-MI patients. However, participation in CR was associated with decreased all-cause mortality, although no effect on cardiac death or MI was noted.^[2] Also, the phase II CR programme improves quality of life in patients who have undergone coronary bypass surgery, and the role of CR as one of the most important ingredients of secondary prevention was highlighted in a study by Ciftçi et al.^[3]

The relationship between number of CR sessions attended and cardiovascular outcomes was recently evaluated in an analysis of Medicare claims data including 30,161 patients with coronary artery disease (with recent coronary artery bypass surgery, MI, or acute coronary syndrome) who attended at least 1 CR session. After 4 years of follow-up, patients who attended 36 sessions had a 14% lower risk of death and a 12% lower risk of MI than those who attended 24 sessions; a 22% lower risk of death and a 23% lower risk of MI than those who attended 12 sessions; and a 47% lower risk of death and a 31% lower risk of MI than those who attended 1 session. This dose-dependent improvement further highlights the importance of patient retention in CR programs.^[4]

The assessment of left ventricular (LV) diastolic function is an integral part of an echocardiographic examination. Echocardiographic measurements of diastolic function provide important prognostic infor-

mation after acute MI since E/e' was shown as a powerful predictor of adverse events in several studies, such as one by Hillis and colleagues that demonstrated E/e' as a powerful predictor of survival after acute MI.^[5]

Abbreviations:

CR	Cardiac rehabilitation
DT	Deceleration time
EF	Ejection fraction
HT	Hypertension
Le'	Lateral wall
LV	Left ventricular
MI	Myocardial infarction
PW	Pulsed-wave
RPE	Rate of perceived exertion

The aim of this study was to investigate the effects of phase II comprehensive CR on diastolic function of left ventricle, which plays an important role in mortality of patients with acute MI revascularized by PCI.

PATIENTS AND METHODS

Lower-risk patients following an acute cardiac event were enrolled in this study. High-risk patients with severe residual angina, positive exercise stress test, severe ischemia, poorly controlled hypertension (HT), hypertensive or any hypotensive systolic blood pressure response to exercise and unstable concomitant medical problems (diabetes prone to hypoglycemia) were excluded from the study.^[6] Every attempt was made to recognize the potential effects of factors (age, pre-cardiac event, physical capacity, LV dysfunction, residual myocardial ischemia, skeletal muscle performance, non-cardiac illness, autonomic function such as diabetic neuropathy, peripheral vascular status, pulmonary status, other systemic illnesses, and especially orthopedic problems limiting flexibility and locomotion) on functional capacity in order to minimize risk of the individualized reconditioning program. Very close surveillance was maintained on the patients during their exercise training routines. Patients with severe ventricular arrhythmias and uncontrolled supraventricular arrhythmias, and patients with devices such as pacemakers and defibrillators were not included in the study.

Transthoracic echocardiography and incremental exercise testing with modified Bruce protocol were performed on the trained group before and after 6 weeks of the CR program. Exercise testing was performed to exclude high-risk individuals after AMI, and to determine the exercise capacity of the patients. The control group were those individuals who were accepted as unable to maintain or attend the program because of socio-economic problems. Individuals

with a poor exercise capacity, or who needed revascularisation after AMI or had orthopedic problems that inhibit doing exercises were not included in the control group.

This study complied with the Declaration of Helsinki, was approved by the local ethical committee, and each patient gave written consent before CR.

Cardiac rehabilitation

After 2-6 weeks of recovery at home, the patient was ready to start phase 2 of his/her CR. The phase 2 CR program was initiated based on the result of the exercise testing, and the exercise prescription was individualized. The CR program was performed on the participants with an integrated multidisciplinary team consisting of a cardiologist, an experienced nurse as a coordinator, and a physical therapy and rehabilitation specialist as a medical director in the CR center of our cardiology and cardiovascular surgery education and research hospital. Rehabilitation nurses provided coordination, established good communication with other team members, and despite the individual's physical limitations, attempted to maximize function as independently as possible.^[7] The minimum frequency for exercising to improve cardiovascular fitness was 5 times weekly during the six weeks. Patients allowed 30-60 minutes for each session, which includes a warm-up of at least 10 minutes. The final 10 minutes of cool-down period involved muscular stretching. The intensity prescribed was in relation to the individual's exercise capacity (MetS) and 60-80% of target heart rate. Aerobic conditioning was emphasized in the first few weeks of exercise. Strength training was introduced later. The Borg scale of Rate of Perceived Exertion (RPE) was used; patients exercised at an RPE of 13-15. The Borg scale of perceived exertion at an RPE of 13-15 is somewhat hard. During the training, electrocardiograms were continuously tele-monitored and blood pressures were measured every 3 minutes. (Custo*med rehabilitation systems; custo care 500, Munich, Germany). In addition to exercise, counseling and education on stress management, smoking cessation, nutrition, and weight loss were incorporated into this phase.

Echocardiography

Echocardiography was performed using a Vivid 7 ultrasonographic machine (Vivid 7, GE Vingmed). The LV ejection fraction (EF) was calculated by

Simpson's biplane method of discs according to the American Society of Echocardiography.^[8] A pulsed-wave (PW) Doppler was used in the apical 4-chamber view to obtain mitral inflow velocities to assess LV filling. Peak early and late diastolic transmitral flow velocities (E and A respectively) and the early diastolic wave deceleration time (DT) of the transmitral flow was measured, and the ratio of early to late transmitral flow velocities (E/A) calculated. A PW Doppler of right upper pulmonary venous flow was performed in the apical 4-chamber view. Measurements of pulmonary venous waveforms included peak systolic (S) velocity, peak anterograde diastolic (D) velocity, and the time difference between atrial reversal (Ar) and mitral A-wave duration (Ar-A) was measured and the S/D ratio calculated.

Tissue Doppler echocardiography

An apical four-chamber image of the colour tissue Doppler technique was acquired at a frame rate of 69.8-147.7 frames/s. Tissue Doppler digital data was stored and analysed offline using an EchoPAC. We measured the peak early diastolic velocity at the mitral annuli of the interventricular septum (Se'), lateral wall (Le') sides and IVRT. Mitral inflow E velocity to tissue Doppler Le' ratio was calculated (E/e'). The mean value of measurements were used.

Statistics

We planned a study with 42 experimental subjects and 40 control subjects. In a previous study, the response within each subject group was normally distributed with standard deviation 2.6. The true difference in the experimental and control means is 3.0, and the type I error probability associated with this test of this null hypothesis is 0.05. We reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) 0.99. Statistical analysis was performed using the Statistical Package for Social Sciences version 15.0 software for Windows (IBM, Armonk, NY). Categorical data are expressed as frequencies. Continuous variables were presented as the mean \pm standard deviation. The χ^2 test was applied to compare the influence of the categorical variables. Continuous variables were analysed with Kolmogorov-Smirnov for testing normal distribution. The variances between the groups were compared with One way ANOVA. Associations between the demographic properties of patients and dia-

stolic functional parameters were analysed by linear regression methods. P values <0.05 were regarded as significant.

RESULTS

Table 1 lists the characteristics of the 82 AMI patients included to our study. 40 patients were control subjects who had quit CR after 1 session. There were no significant differences between groups regarding gender, age, cardiovascular risk factors including HT, diabetes mellitus (DM), smoking and hyperlipidemia (HPL), infarct related artery (IRA) and LV EF values. Successful coronary patency was achieved in each case.

There was significant improvement in left ventricle EF of the individuals after CR, and it was better in the trained group than the control group. ($p=0.010$). Also, exercise capacity was improved ($p=0.030$) and mean blood pressure was decreased ($p=0.016$) after CR in the trained group, and the differences were statistically significant from the control group ($p=0.040$ and $p=0.019$, respectively). However, there were no significant differences between the groups in diastolic functional parameters, except E/A and septal e' . ($p=0.048$ and $p=0.006$ respectively.) Although there were significant differences in septal e' measurements after CR, the difference between E/ e' measurements were not statistically significant. ($p=0.138$) DT and IVRT remained unchanged after CR and there was no significant difference from the control group. When

we analysed pulmonary flow measurements, we could not find any statistically significant differences between the groups in Ar-A and S/D with CR, ($p=0.132$ and $p=0.607$ respectively) (Table 2).

The data was analysed according to infarct-related artery. EF and E/A measurements did not show any significant differences, ($p=0.502$ and $p=0.527$ respectively). According to the linear regression analyses, only HT was significantly associated with E/A ($p=0.000$).

DISCUSSION

It is well known that CR programs have favourable effects on left ventricular EF in individuals after AMI.^[9] In many cardiac diseases, diastolic dysfunction develops early and leads to elevation in left ventricular filling pressures. Therefore, we aimed to evaluate whether the left ventricular diastolic function parameters of the individuals are improved with CR in patients with AMI.

Early diastolic mitral annular velocity (e') derived from tissue Doppler imaging (TDI) reflects myocardial relaxation in the long-axis direction. Many investigators have reported the usefulness of the ratio of early diastolic transmitral flow velocity to e' (E/ e') in estimating LV filling pressure. It can be performed easily, and is therefore widely used to evaluate left ventricular (LV) diastolic function.^[10] According to a study by Wang et al., early diastolic mitral annulus velocity, $e' < 3$ cm/s, emerged as the best prognostica-

Table 1. Patient demographics and clinical characteristics

	Cardiac rehabilitation group (n=42)			Control group (n=40)			<i>p</i>
	n	%	Mean±SD	n	%	Mean±SD	
Age (Years)			57±7			58±8	0.474
Gender (Male)	32	76		28	70		0.474
Diabetes	17	40		16	40		0.838
Hypertension	26	61		24	60		0.660
Hyperlipidemia	20	47		13	32		0.323
Smoking	16	38		13	32		0.711
Infarct related artery							0.343
Left anterior descending	16	38		18	45		
Circumflex artery	11	26		13	32		
Right coronary artery	15	35		9	22		

Table 2. The difference of the diastolic functional parameters between groups

	Trained Group (n=42)		<i>p</i>	Control Group (n=40)	
	Before CR	After CR		Mean±SD	
	Mean±SD	Mean±SD			
Ejection Fraction (%)	49±8	54±9	0.011	51±8	0.015
E/A Ratio	1.0±0.2	1.1±0.2	0.047	1.0±0.2	0.048
E/e' Ratio	6.9±1	6.3±1	0.203	6.7±1	0.177
Ar- A (ms)	26±16	21±13	0.193	24±9	0.217
Isovolumic Relaxation Time (ms)	69±11	64±12	0.171	68±11	0.168
Deceleration Time (ms)	203±30	192±27	0.165	197±29	0.192
Septal e' (cm/s)	9±2	10±2	0.012	9±2	0.006
Lateral e' (cm/s)	11±3	12±2	0.356	11±2	0.278
S/D Ratio	1±0.37	1.1±0.34	0.591	1.1±0.30	0.607
Mean Blood Pressure (mmHg)	99±11	92±10	0.016	94±10	0.019
Metabolic Equivalents (METs)	5.2±0.7	5.6±0.8	0.030	5.4±0.6	0.040

CR: Cardiac rehabilitation; n: Number; Ar: Pulmonary a wave duration.

tor in long-term follow-up, incremental to other clinical or echocardiographic variables, including the ratio E/e' in patients with impaired LV systolic function.^[11] Nonetheless, in this study, despite the significant differences in septal e' measurements after CR, the difference between E/e' measurements were not statistically significant.

In fact, the effect of CR on left ventricular diastolic function in patients is not clearly understood. We demonstrated significant improvement in E/A, but not in all echocardiographic parameters of LV diastolic function. However, DT and IVRT were not changed after CR, similar to a study by Golabchi et al., which randomised patients with reperfusion therapy for ST elevation MI into a training group (n=15) and a control group (n=14). They did not demonstrate any improvement in left ventricular diastolic function in post-MI patients with 8 weeks of a CR program.^[12] Conversely, Wuthiwaropas et al. investigated twenty-five outpatients and demonstrated improvement in left ventricular diastolic function at least in half of them with a three-month, exercise-based CR.^[13]

The prognostic role of pulmonary venous flow has been shown in a few studies.^[4,14,15] A decrease in LA compliance and increase in LA pressure decrease the velocity of pulmonary venous inflow S. Pulmonary venous inflow D velocity is influenced by changes

in LV filling and compliance, and changes in parallel with mitral E velocity.^[16] In this study, S/D was found significantly decreased after CR. Pulmonary venous Ar duration is influenced by LV late diastolic pressures, atrial preload and atrial contractility. Ar duration increase as well as the time difference between Ar duration and mitral A wave duration with increased left ventricular end diastolic pressure.^[17,18] To the best of our knowledge, this study is the first to evaluate the difference in pulmonary flow in patients with CR programs. However, we did not find any significant difference in S/D and Ar between groups. Therefore, our study suggests that pulmonary venous flow might not be affected by exercise-based CR.

On the other hand, we demonstrated a significant benefit via CR to left ventricular diastolic function in hypertensive patients with AMI. Schultz et al. reported that after 1 year of lifestyle modifications, the exercise blood pressure significantly diminishes while cardiac size remains the same.^[19] This finding supports our result and suggests that diastolic function in patients may be improved via the improvement in blood pressure with exercise-based CR.

However, a CR program is not only clinically effective, but also cost-effective. In a randomized study in the US, an 8-week trial of rehabilitation beginning 6 weeks following AMI was found more cost-effective

than a cholesterol-lowering strategy for secondary prevention.^[20] The published AHA Presidential Advisory on the referral, enrolment, and delivery of CR programs highlights the patient-oriented, medical, and healthcare system factors associated with suboptimal participation.^[10] In particular, female patients, those who belong to ethnic minorities, the elderly, and those of low socioeconomic status have lower participation rates than white men and represent specific high-risk groups to be targeted for referral.^[21] Addressing factors that limit participation is particularly important. Despite the coverage of health insurance in Turkey, CR programs remain underused in our clinic with an estimated rate of only 10% eligible patients per year who have experienced an acute MI or undergo coronary revascularization, similar to worldwide data.^[22]

Limitations

The mean LVEF of the subjects was relatively favoured and high-risk patients were not included in the study. It was not clearly assessed whether the control group managed risk factors well. A long-term prospective study of larger sample size with group analysis of CR would be beneficial in further evaluating the role of CR in diastolic function of patients as a protector from cardiovascular outcomes.

Conclusion

Cardiac rehabilitation improves septal e' and E/A significantly, especially in hypertensive patients. A CR program is more than just diet and exercise. It is an important component of the current multidisciplinary approach that helps patients recover more quickly after AMI. The wide treatment gap between scientific evidence of the benefits of CR and clinical implementation of rehabilitation programs should be narrowed in our country.

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Key words: Cardiac rehabilitation; cardiovascular diseases; diastolic function; myocardial infarction.

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