Title: Effect of Cardiac Rehabilitation on Atrial Conductions Following Isolated Coronary Artery Bypass Surgery

Running Title: P wave Dispersion and Cardiac Rehabilitation

Ahmet Anıl Şahin[1], Omer Tasbulak[2], Serkan Kahraman[2], Gokhan Demirci[2], Hicaz Zencirkıran Agus[2], Cigdem Altun[3], Ali Kemal Kalkan[2], Mehmet Erturk[2]

[1]Department of Cardiology, Halic University, Faculty of Medicine, Istanbul, Turkey

[2]Department Cardiology, University of Health Sciences, Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital, Istanbul, Turkey

[3]Department of Physical Medicine and Rehabilitation, University of Health Sciences, Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital, Istanbul, Turkey

Funding Status: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Conflict of interest: Authors declare that they have no conflict of interest.

Corresponding Author: Ahmet Anıl Şahin

Address: Sutluce Mahallesi, Imrahor Caddesi No: 82 Beyoglu / Istanbul

Phone: +905532227627

Fax Number: +902124719494

e-mail: aanilsahin@hotmail.com

Introduction

Coronary artery bypass grafting (CABG) is one of the treatment choices for revascularization in ischemic heart disease[1]. Cardiac Rehabilitation (CR) is a structured program, which includes exercises, lifestyle modifications, psychosocial support and education compatible with special conditions of each patient. CR is associated with improved clinical outcomes in a broad spectrum of cardiac disease[2,3,4]. The beneficial effect of CR has been proven in patients with ischemic heart diseases[5,6].

Post-operative atrial fibrillation (AF) and atrial arrhythmias are common complications following CABG surgery[7]. Electrocardiography (ECG) is the method of choice to detect electrical instability of atrial conduction abnormalities. For this purpose, P wave dispersion (PWD), P wave maximum duration (Pmax) and P wave minimum duration (Pmin) were calculated in ECG to provide information about inhomogeneous and discontinuous atrial conduction which in turn closely related to supraventricular arrhythmias and AF[8].

There are studies, in which CR program improves atrial and ventricular functions in patients with ischemic heart disease[9,10]. The aim of this study was to evaluate the effect of CR on atrial conductions in patients who underwent isolated CABG surgery.

Materials and Methods

The investigation conforms with the principles outlined in the Declaration of Helsinki. The study was approved by the local ethics committee. All participants gave written informed consent before inclusion.

Patients were selected among cases that underwent isolated CABG surgery in a community tertiary hospital between July 2016 and July 2019. Exclusion criterion were; patients who had AF or atrial flutter in their ECG during pre- or post-operative

follow-up, unsuitable ECG to read, history of pacemaker implantation, post-operative junctional rhythm, patients under hemodialysis during follow-up, myocardial infarction during follow-up, and pre-excitation syndromes. After the exclusion criterion was applied 545 patients were included in the study, retrospectively. The demographic characteristics, concomitant diseases and cardiovascular risk factors of the patients were recorded.

Patients were than divided into two groups. One group (Rehab +) included patients who participated in CR program after isolated CABG surgery. The other group (Rehab -) included patients who did not want to participate or could not be participated in CR program after isolated CABG surgery. ECG data of the both groups before operation and six months after the operation [in the end of CR program for Rehab (+) and in the routine follow-up for Rehab (-) group] were evaluated from the computer system of the hospital.

All the patients are routinely invited to CR program after full recovery of the surgery (~3 months after surgery) in our hospital. CR program was performed 3 days per week for 10 weeks in the hospital. Patients who accepted to be enrolled in CR program first underwent exercise tolerance test in cardiac rehabilitation unit. Exercise capacities of the patients were assessed with Cycle Ergometer (Ergoline Ergoselect 2 model 600 and Opticare software program). Target heart rate and maximum heart rate were calculated using Karvoneen formula [(Maximal heart rate - resting heart rate) × Intensity% + resting heart rate] individually for every patient according to their age and gender. At the beginning of the test, cycling with 30 watts of pedal load and 15 watts increment was applied every two minutes with constant pedaling speed of 55-65 per minute. The test was stopped if the patients reached to target heart rate or if the patients wanted to stop due to fatigue. Initially the ratio of maximum load to patient's

body weight (watt/kg) was calculated. This ratio was used as an indicator of physical fitness. The values lower than 1.4 watt/kg indicated an untrained person or patients with moderate to high risk for cardiac complications during physical stress according to the recommendations of the American Heart Association[11]. If the ratio was lower than 1 watt/kg, the patients started the program with low-intensity intermittent training to provide a better 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. After cycle ergometer training, each exercise session was finished with stretching and strengthening exercises. After the program, the patients were encouraged to perform aerobic exercises by themselves during their daily life.

12- lead Surface ECG (Nihon Kohden Corporation, Cardiofax M Model ECG-1250, Tokyo, Japan) were performed in the supine position, with a 25 mm/sec paper speed and a voltage of 10 mm/sec for each patient. All ECGs were taken after the patient rested in supine position for 15 minutes in a quiet room at ideal room temperature and were stored in a digital system. Analyses were performed by two cardiologists who were blinded to the patients' data via using the software of Adobe Photoshop (Adobe Systems, Inc., San Jose, California, USA) with *400% magnification. Heart rate and PR interval was recorded for each patient. For each lead, P-wave durations and PWD were calculated manually according to previous studies[12]. Pmax and Pmin were detected in any of the measured leads. PWD was defined as the difference between Pmax and Pmin. The inter-observer and intra-observer co-effiencients of variation were 2.0% and 2.4%, respectively.

Statistical Analysis

Statistical analyses were performed using the SPSS version 24.0 (SPSS Inc., Chicago, Illinois, USA). Whether the variables show normal distribution; visual (histograms, probability curves) and analytical methods (Kolmogorov-Simirnov and Shapiro-Wilk) were evaluated. Numerical variables showing normal distribution were mean ± standard deviation (SD), numerical variables not showing normal distribution were expressed as median (interquartile range) and categorical variables as percentage (%). Chi Square or Fisher exact test were used to compare categorical variables in between groups. Since the distributions of the differences in the dependent variables (ECG parameters) were non-normally distributed, the Wilcoxon signed-rank test was used to assess the changes in ECG parameters. The distribution of differences between the ECG parameters were assessed using histogram pilots to ensure they were symmetrical in shape since the Wilcoxon signed-rank test requires dependent variables with symmetrical distribution. The McMemar's test was used to compare the differences in categorical variables. Throughout the present study, a p-value of <0.05 was considered significant.

Results

Among 545 patients, rehab (-) group included 255 patients and rehab (+) group included 290 patients. Table 1 showed demographic information of the both groups. Rehab (+) group had significantly higher rate of patients with peripheral artery disease (PAD) and hypertension. However, there was no significant difference between groups in terms of ECG findings before the surgery.

Table 2 showed ECG findings for rehab (+) group. The table included comparison of ECG findings before operation and after CR program. There was significant difference in ECG findings of all parameters. Heart rate [Before CR: 78

(71-87) vs. After CR: 71 (65-79); P<0.001], PR interval [Before CR: 148 (132-164) vs. After CR: 154 (140-170); P<0.001], Pmax duration [Before CR: 94 (88-102) vs. After CR: 94 (86-100); P=0.033], Pmin duration [Before CR: 71 (65-77) vs. After CR: 78 (74-86); P<0.001], and PWD [Before CR: 23 (19-27) vs. After CR: 12 (10-16); P<0.001] were significantly changed after CR program.

ECG findings of rehab (-) group were given in table 3. The table included comparison of ECG findings of the group before and six months after operation. Heart rate [Preoperative: 81 (71-89) vs. Postoperative: 72 (65-83); P<0.001], PR interval [Preoperative: 144 (130-160) vs. Postoperative: 148 (134-167); P<0.001] were significantly changed after the operation. There was no significant difference in terms of Pmax duration, Pmin duration, and PWD.

Table 4 included comparison of ECG findings between Rehab (+) and Rehab (-) group. There was no significant difference in terms of heart rate and PR interval between groups. However, there was significant difference in terms of Pmax duration [Rehab (-) group: 96 (90-102) vs. Rehab (+) group: 94 (86-100); P<0.001], Pmin duration [Rehab (-) group: 72 (66-76) vs. Rehab (+) group: 78 (74-86); P<0.001], and PWD [Rehab (-) group: 24 (20-30) vs. Rehab (+) group: 12 (10-16); P<0.001].

Discussion

In this study, we aimed to evaluate the effect of CR program on atrial conductions in patients who underwent isolated CABG surgery. Our study demonstrated that after CR program following CABG surgery, Pmax duration and Pmin duration significantly changed when compared to control group who did not underwent CR program following CABG surgery. As a result, PWD, which is one of the main parameters of an indirect indicator of impairment of atrial conduction, was decreased significantly.

In literature, close relationship between atrial conduction and PWD was shown by previous studies. Dilaveris et al. [13] compared patients with a history of paroxysmal AF with healthy controls and found that paroxysmal AF patients had higher PWD than healthy controls. Based on previous studies, Centurion commented that PWD was associated with an abnormality in atrial conduction, and increased PWD might lead to AF shortly[14].

There are several reasons related to impairment in atrial conductions. One of the reasons is ischemia. Dilaveris et al.[15] showed that PWD was higher in patients with stable angina when compared to the patients without stable angina. Additional to that, Ozmen et al.[16] showed that PWD was significantly higher during ischemia created by occlusion of the vessel with balloon angioplasty compared to baseline measurements. Other etiologic factor for atrial conduction abnormality is increased afterload which then leading to diastolic dysfunction. Even without diagnosis of hypertension, afterload increase might lead to atrial conduction abnormalities[17]. Another factor related to atrial conduction abnormality is the imbalance between sympathetic and parasympathetic control of the cardiac conduction. May et al.[18] showed that the autonomic dysfunction might lead to atrial conduction abnormalities. For all these etiologic factors, previous studies showed beneficial effect of CR program. CR program could increase myocardial perfusion[19,20], might decrease arterial stiffness and aortic afterload[21] and might have beneficial effects on autonomic control of cardiac conduction[22]. Improvement of atrial conduction and decrease in PWD after CR program in our study might be explained based on this information.

Another finding of our study was change of heart rate and PR interval in post-operative follow up. In both groups, post-operative heart rate significantly decreased and PR interval significantly increased. However, there was no significant difference

between the groups in post-operative ECG findings. These findings suggested that, heart rate and PR interval might change after isolated CABG surgery and these changes were independent whether patient participated in CR program or not. Therefore, it is not possible to comment that CR program might effect the heart rate or PR interval in post-operative follow up.

In conclusion, patients should be encouraged to participate in CR program after CABG surgery. Our findings referred that atrial conduction could be improved by CR program following CABG surgery; thereby improvement in atrial conduction could reduce atrial arrhythmias.

Study Limitations

There are several limitations in our study. First, because parameters identified retrospectively, this study included limitations inherent in any retrospective analysis. Second, we did not follow up the patients in long-term to evaluate long-term outcomes of ECG findings. Third, we did not have follow up of patients about atrial arrhythmias that at least 24-hour rhythm monitoring could be applicable to detect atrial arrhythmias. Therefore we could not evaluate direct association between atrial arrhythmia with ECG findings.

References

[1] Serruys PW, Morice MC, Kappetein AP, et al.; SYNTAX Investigators. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med. 2009 Mar 5;360(10):961-72.

[2] Karapolat H, Durmaz B. [Exercise in cardiac rehabilitation]. Anadolu Kardiyol Derg. 2008 Feb;8(1):51-7.

[3] Beauchamp A. Attendance at cardiac rehabilitation is associated with lower all-cause mortality after 14 years of follow-up. Heart. 2013 May;99(9):620-5.

[4] McMahon SR, Ades PA, Thompson PD. The role of cardiac rehabilitation in patients with heart disease. Trends Cardiovasc Med. 2017 Aug;27(6):420-425.

[5] Malfatto G, Facchini M, Bragato R, Branzi G, Sala L, Leonetti G. Short and long term effects of exercise training on the tonic autonomic modulation of heart rate variability after myocardial infarction. Eur Heart J. 1996;17(4):532-538.

[6] O'Connor GT, Buring JE, Yusuf S, et al. An overview of randomized trials of rehabilitation with exercise after myocardial infarction. Circulation. 1989;80(2):234-244.

[7] Echahidi N, Pibarot P, O'Hara G, Mathieu P. Mechanisms, prevention, and treatment of atrial fibrillation after cardiac surgery. J Am Coll Cardiol. 2008;51(8):793-801.

[8] Hari KJ, Nguyen TP, Soliman EZ. Relationship between P-wave duration and the risk of atrial fibrillation. Expert Rev Cardiovasc Ther. 2018;16(11):837-843.

[9] Acar RD, Bulut M, Ergün S, Yesin M, Eren H, Akçakoyun M. Does cardiac rehabilitation improve left ventricular diastolic function of patients with acute myocardial infarction?. Turk Kardiyol Dern Ars. 2014;42(8):710-716.

[10] Deniz Acar R, Bulut M, Ergün S, Yesin M, Alıcı G, Akçakoyun M. Effect of cardiac rehabilitation on left atrial functions in patients with acute myocardial infarction. Ann Phys Rehabil Med. 2014;57(2):105-113.

[11] Thomas RJ, Balady G, Banka G, Beckie TM, Chiu J, Gokak S, Ho PM, Keteyian SJ, King M, Lui K, Pack Q, Sanderson BK, Wang TY. 2018 ACC/AHA Clinical Performance and Quality Measures for Cardiac Rehabilitation: A Report of the American College of Cardiology/American Heart Association Task Force on Performance Measures. J Am Coll Cardiol. 2018 Apr 24;71(16):1814-1837.

[12] Pérez-Riera AR, de Abreu LC, Barbosa-Barros R, Grindler J, Fernandes-Cardoso A, Baranchuk A. P-wave dispersion: an update. Indian Pacing Electrophysiol J. 2016;16(4):126-133

[13] Dilaveris PE, Gialafos EJ, Sideris SK, et al. Simple electrocardiographic markers for the prediction of paroxysmal idiopathic atrial fibrillation. Am Heart J 1998;135:733

[14] Centurión OA. Clinical implications of the P wave duration and dispersion: relationship between atrial conduction defects and abnormally prolonged and fractionated atrial endocardial electrograms. Int J Cardiol. 2009;134(1):6-8.

[15] Dilaveris PE, Gialafos EJ, Andrikopoulos GK, et al. Clinical and electrocardiographic predictors of recurrent atrial fibrillation. Pacing Clin Electrophysiol. 2000;23(3):352-358.

[16] Ozmen F, Atalar E, Aytemir K, et al. Effect of balloon-induced acute ischaemia on P wave dispersion during percutaneous transluminal coronary angioplasty. Europace. 2001;3(4):299-303.

[17] Kim SJ, Choisy SC, Barman P, et al. Atrial remodeling and the substrate for atrial fibrillation in rat hearts with elevated afterload. Circ Arrhythm Electrophysiol. 2011;4(5):761-769.

[18] May AM, Van Wagoner DR, Mehra R. OSA and Cardiac Arrhythmogenesis: Mechanistic Insights. Chest. 2017;151(1):225-241.

[19] Szot W, Zając J, Kubinyi A, Kostkiewicz M. The effects of cardiac rehabilitation on overall physical capacity and myocardial perfusion in women with microvascular angina. Kardiol Pol. 2016;74(5):431-438.

[20] Kissel CK, Nikoletou D. Cardiac Rehabilitation and Exercise Prescription in Symptomatic Patients with Non-Obstructive Coronary Artery Disease-a Systematic Review. Curr Treat Options Cardiovasc Med. 2018;20(9):78. Published 2018 Aug 18.

[21] Brozic AP, Marzolini S, Goodman JM. Effects of an adapted cardiac rehabilitation programme on arterial stiffness in patients with type 2 diabetes without cardiac disease diagnosis. Diab Vasc Dis Res. 2017;14(2):104-112.

[22] Gambassi BB, Almeida FJF, Almeida AEAF, et al. Acute Response to Aerobic Exercise on Autonomic Cardiac Control of Patients in Phase III of a Cardiovascular Rehabilitation Program Following Coronary Artery Bypass Grafting. Braz J Cardiovasc Surg. 2019;34(3):305-310.

Table 1. Pre-operative demographic, clinical, and electrocardiographic findings of both groups before isolated coronary artery bypass surgery

	Patients who did not undergo Cardiac Rehabilitation (n=255)	**Patients who underwent Cardiac Rehabilitation (n=290)**	**P value**
Age (years)	59.2 ± 9.5	59.9 ± 8.4	0.332
Gender (male -%)	196 (76.9)	225 (77.6)	0.841
HFrEF (n-%)	19 (7.5)	16 (5.5)	0.358
PAD (n-%)	14 (5.5)	34 (11.7)	**0.010**
Smoking (n-%)	93 (36.5)	93 (32.1)	0.280
DM (n-%)	144 (56.5)	163 (56.2)	0.951
Hypertension (n-%)	189 (74.1)	240 (82.8)	**0.014**
Previous MI (n-%)	33 (12.9)	52 (17.9)	0.109
LVEF (%)	59 (50-60)	60 (50-60)	0.059
Stroke (n-%)	21 (8.2)	17 (5.9)	0.278
Creatinine (mg/dL)	0.87 (0.74-1.04)	0.90 (0.77-1.05)	0.350
Heart Rate (/min)	81 (71-89)	78 (71-87)	0.132
PR interval (ms)	144 (130-160)	148 (132-164)	0.136
P wave max (ms)	96 (90-102)	94 (88-102)	0.104
P wave min (ms)	72 (66-76)	71 (65-77)	0.205
P wave dispersion (ms)	24 (20-28)	23 (19-27)	0.079

HFrEF: heart failure with reduced ejection fraction, PAD: peripheral artery disease, DM: diabetes mellitus, MI: myocardial infarction, LVEF: left ventricular ejection fraction

Table 2. Electrocardiographic findings of the patients in Rehab (+) group before surgery and after cardiac rehabilitation following isolated coronary artery bypass surgery.

Rehab (+) group (n=290)	**Before CABG surgery**	**After Cardiac Rehabilitation**	**P value**

Table 3. Preoperative and postoperative (6 months after surgery) ECG findings of the patients who did not undergo cardiac rehabilitation after isolated coronary artery bypass surgery (Rehab – group).

Rehab (-) group (n=255)	**Preoperative**	**Postoperative**	**P value**
Heart Rate (/min)	81 (71-89)	72 (65-83)	**<0.001**
PR interval (ms)	144 (130-160)	148 (134-167)	**<0.001**
P max (ms)	96 (90-102)	96 (90-102)	0.214
P min (ms)	72 (66-76)	72 (66-76)	0.970
P wave dispersion (ms)	24 (20-28)	24 (20-30)	0.428

Table 4. Comparison of ECG findings of the patients between rehab (-) and rehab (+) groups six months after coronary artery bypass surgery.

	Rehab (-) group	**Rehab (+) group**	**P value**
Heart Rate (/min)	72 (65-83)	71 (65-79)	0.305
PR interval (ms)	148 (134-167)	154 (140-170)	0.058
P max (ms)	96 (90-102)	94 (86-100)	**<0.001**
P min (ms)	72 (66-76)	78 (74-86)	**<0.001**
P wave dispersion (ms)	24 (20-30)	12 (10-16)	**<0.001**