ARAŞTIRMA MAKALESİ/ORIGINAL RESEARCH

DOI: 10.5505/ktd.2023.81593
KocaeliMedJ2023;12(1):158-165

Egzersize Dayalı Kardiyak Rehabilitasyon Koroner Arter Hastalığı Olan Hastalarda Arter Sertliğini Azalttı, CAVI Yöntemiyle Belirlendi "Kardiyak Rehabilitasyon Arter Sertliğini Azalttı"

Exercise-Based Cardiac Rehabilitation Reduced Arterial Stiffness in Patients with Coronary Artery Disease, determined by CAVI method "Cardiac Rehabilitation Reduced Arterial Stiffness"

Ender Emre[1], Gulay Uzun[1], Ahmet Özderya[1], Mustafa Çetin[2], Muhammet Raşit Sayın[1], Ezgi Kalaycıoğlu[1]

1Türkiye Sağlık Bilimleri Üniversitesi Ahi Evren Göğüs Kalp Damar Cerrahisi Eğitim ve Araştırma Hastanesi, Kardiyoloji Kliniği, Trabzon, Türkiye.
2Tıp Fakültesi, Kardiyoloji Anabilim Dalı, Recep Tayyip Erdoğan Üniversitesi, Rize, Türkiye

ÖZET

GİRİŞ ve AMAÇ: Egzersize dayalı kardiyak rehabilitasyonun (CR), koroner arter hastalığı (KAH) olan hastalarda kardiyovasküler (KV) morbi-mortaliteyi azaltabileceği gösterilmiştir. Artan arteriyel sertliğin KAH'lı hastalarda morbi-mortalitenin bağımsız bir belirleyicisi olduğu gösterilmiştir. Bu çalışmada, stabil KAH'lı hastalarda, kardiyo-ayak bileği vasküler indeksi (CAVI) ile CR'nin arter sertliği üzerindeki etkisini araştırmayı amaçladık.

YÖNTEM ve GEREÇLER: Doktorları tarafından Faz III KR programına sevk edilen ayaktan 202 ardışık stabil KAH olan hasta ve KR programını kabul etmeyen 96 stabil KAH olan hasta çalışmaya dahil edildi. CAVI, VaSera VS-1000 (Fukuda Denshi Co. Ltd, Tokyo) tarafından hesaplandı. <0,05 p değeri istatistiksel olarak anlamlı kabul edildi.

BULGULAR: Çalışma popülasyonu (298 hasta), önce-sonra (Delta) CAVI değerleri arasındaki farka göre 3 eşit persentile göre gruplandırıldı. Grup 1: 1-33 persentil arasında [Delta CAVI ≥ (-0,5)]; Grup 2: yüzde 34-66 arasında [Delta CAVI <(-0,5) - ≥ (-1,3)]; Grup 3: 67-100 persentil arasında [Delta CAVI < (-1.3)]. Çok değişkenli analizde, CAVI-pre (p: <0,001) ve CR'nin (p: <0,001) Delta CAVI'nin bağımsız belirleyicileri olduğu gösterildi.

TARTIŞMA ve SONUÇ: Bu çalışma, egzersize dayalı CR'nin KAH'lı hastalarda arteriyel sertliği iyileştirdiğini gösterdi.

Anahtar Kelimeler: arteriel sertlik, kardiyo-ayak bileği vasküler indeksi, koroner arter hastalığı, egzersize dayalı kardiyak rehabilitasyon

ABSTRACT

INTRODUCTION: It was shown that exercise-based cardiac rehabilitation (CR) might reduce cardiovascular (CV) morbi-mortality in patients with coronary artery disease (CAD). Increased arterial stiffness has been shown to be an independent predictor of morbi-mortality in patients with CAD. In this study, we aimed to investigate the effect of CR on arterial stiffness by cardio-ankle vascular index (CAVI), in patients with stable CAD.

METHODS: We enrolled 202 consecutive stable CAD out-patients who were referred for Phase III CR program by their physicians and 96 stable CAD out-patients who did not have accept CR program. CAVI was calculated by VaSera VS-1000 (Fukuda Denshi Co. Ltd, Tokyo). A p-value of <0.05 was considered statistically significant.

RESULTS: Study population (298 patients) was divided into 3 equal percentile groups according to the difference of post-pre (Delta) CAVI values. Group 1: between 1-33 percentile [Delta CAVI ≥ (-0.5)]; Group 2: between 34-66 percentile [Delta CAVI <(-0.5) - ≥ (-1.3)]; Group 3: between 67-100 percentile [Delta CAVI < (-1.3)]. In multivariate analysis, it was shown that CAVI-pre (p: <0.001) and CR (p: <0.001) were independent predictors of Delta CAVI.

DISCUSSION AND CONCLUSION: This study showed that exercise-based CR improves arterial stiffness in patients with CAD.

Keywords: arterial stiffness, cardio-ankle vascular index, coronary artery disease, exercise-based cardiac rehabilitation

Kabul Tarihi:04.04.2023

Correspondence: Uzm. Dr. Ender Emre, Türkiye Sağlık Bilimleri Üniversitesi Ahi Evren Göğüs Kalp Damar Cerrahisi Eğitim ve Araştırma Hastanesi, Kardiyoloji Kliniği, Trabzon, Türkiye
E-mail:dr.enderemre@hotmail.com

INTRODUCTION

Cardiac rehabilitation (CR) is a comprehensive intervention that entails risk factor management, patient education, and psychosocial counseling in addition to exercise training under medical supervision. According to reports, CR can help individuals with coronary artery disease improve their exertional ischemia symptoms, exercise tolerance, and coronary risk factors (CAD). In addition, it has been shown that exercise-based CR reduces total and cardiovascular (CV) mortality in ranging rate from 20% to 32% in patients with CAD (1). Physical activity may protect against CVD through several ways, including improved endothelial function, decreased sympathetic neural activity and arterial stiffness (2, 3).

It has been widely accepted that changes to the vessel wall's structural integrity cause arterial stiffness (4). Increased arterial stiffness is a marker of CV disease and has been recognized as a key mediator of CV events (5). The pulse wave velocity (PWV) approach is one of the most fundamental techniques for assessing arterial stiffness. However, several factors, such as high fasting serum glucose levels, body weight, blood pressure (BP), and autonomic nerve function, might affect PWV (4). A new measure of the total stiffness of the artery from the aortic origin to the ankle is the cardio-ankle vascular index (CAVI). The most noticeable aspect of CAVI is how independent of blood pressure it is when taking measurements (4,6).

In this study, using the CAVI approach for the first time in the literature, we aimed to examine the impact of exercise-based CR on arterial stiffness in patients with stable CAD.

METHODS

Study population

c CR program by their physicians and 96 stable CAD outpatients who did not accept CR program. Study inclusion criteria were: age between 18-80 years; coronary angiographic documentation of CAD which was defined as having more than 50% stenosis in at least one coronary artery. Patients with decompensated heart failure, chronic renal disease (creatinine>1.6 mg/dL) and a history of malignancy were excluded.

All patients had their baseline clinical and demographic data collected. The formula for calculating body mass index (BMI) is weight (kg)/height (m2).Smoking was defined as current smoking. Blood measurements were made at baseline and after 6 weeks after 12 hours of fasting. We examined the data for fasting blood glucose, lipid parameters, CRP, creatinine, and hemoglobin. According to ASE guidelines, left ventricular ejection fraction was assessed using the biplane Simpson method during echocardiography (VIVID S-5 General Electric Medical System 3,6 MHz).Patients were stable on their optimal medical regimen for at least 4 weeks before participation and none had any medication changes throughout the study.

The local ethics board gave its approval for this study, which was carried out in conformity with the Declaration of Helsinki (Decision Number 2021/88).

CR program

Before the CR program, a step incremental cycle ergometer test was conducted on the patients to ascertain their exercise capacity. The burden was increased by 25W every 2 minutes after a 2-minute break. Throughout the exercise, blood pressure and heart rate were monitored. The maximum exercise capacity was established as the maximum workload.

A multidisciplinary team that included a cardiologist, an experienced physical therapist who served as coordinator, and a physical therapy and rehabilitation specialist who served as medical director supervised the CR program. The CR center of our hospital for cardiology and cardiovascular surgery served as the site of the rehabilitation program.

The rehabilitation program's main component is aerobic activity training. Each person received a customized workout prescription based on the results of the exercise tests. For a total of six weeks, patients continued the program five days each week. Each session lasted 30 minutes, including a 5-minute warm-up and a 5-minute cool-down at the end. The recommended level of aerobic exercise intensity was determined by the person's capacity for exercise. Starting at 40–50% of maximum heart rate reserve, the intensity of the exercise steadily increased to 70–85% of maximum heart rate reserve. The

Karvonen Formula (HRtrain=(HRmax-HRrest)xExerciseIntensity+HRrest) was used to assess heart rate reserve.Heart rate during an aerobic workout is represented by HRtrain, heart rate on a cycle ergometer by HRmax, and heart rate at rest is represented by HRrest. Patients exercised at an RPE of 13 to 15 according to the Borg Scale of Rate of Perceived Exertion (RPE). Throughout the workout, blood pressure was checked every 5 minutes and electrocardiograms were monitored remotely. Patients were also sent to a psychologist, dietitian, and a smoking cessation clinic while they were included in the trial.

CAVI

CAVI was calculated by VaSera VS-1000 (Fukuda Denshi Co. Ltd, Tokyo). It was calculated by using a conventional PWV measurement with the formula: a [q / DP (In Ps / Pd) ca-PWV2] +b, (a and b constants, q: blood density, DP=difference between systolic and diastolic blood pressure, Ps=systolic blood pressure, Pd=diastolic blood pressure and ca-PWV=cardio-ankle pulse wave velocity). The evaluation was carried out after a five-minute period of relaxation. The patient was lying on his back, with cuffs placed briefly over his upper arms and ankles. Brachial and ankle artery pressures and waveforms, as well as electrocardiography and phonocardiography, were all measured. CAVI calculation was automatic3. CAVI measurements were taken by a physician blinded to the patient's CR program.

Statistical Analysis

SPSS statistics software was used to perform the statistical analysis (version 21.0, SPSS, Chicago, IL, USA). Mean and standard deviation were used to depict continuous variables. Categorical variables are shown as percentages and numbers. The normality of the distribution of continuous variables was examined using the Kolmogorov-Smirnov test. Independent sample t-test or the Mann-Whitney U test was performed for continuous variables, and the chi-square test was performed for categorical variables. The independent sample t-test or the Mann-Whitney U test was performed for continuous variables and the chi-square testwas performed for categorical variables. Variables were compared before and after therapy using the Wilcoxon test or related test. The relationship between continuous variables was investigated using Spearman's correlation analysis.A p-value of <0.05 was considered statistically significant

RESULTS

The study population consisted of 298 (77.5% male) patients with the mean age of 56.8□7.7 years. Most of the patients were hypertensive (88.6%) and 203 (67.7%) patients participated exercise-based CR program.

The study population (298 patients) was divided into 3 equal percentile groups according to the difference of post-pre (Delta) CAVI values. Group 1: between 1-33 percentile [Delta CAVI ≥ (-0.5)]; Group 2: between 34-66 percentile [Delta CAVI < (-0.5) - ≥ (-1.3)]; Group 3: between 67-100 percentile [Delta CAVI < (-1.3)]. There was no difference between the groups in terms of baseline characteristics except male gender (p: 0.014) and participation in CR program (p: <0.001). Patients participated in CR-program were 28.3% in Group-1; 84.2% in Group-2 and 100% in Group-3 (p< 0.001). Delta LDL (mg/dL), Delta TG (mg/dL), Delta CRP (mg/dL), Delta WBC (103/3), Delta HDL (mg/dL), CAVI-pre and Delta CAVI values were found to be statistically significantly different between groups (p<0.001 for all) (Table 1).

Univariate analysis was shown that male gender (p: 0.007), CAVI-pre(p<0.001), Delta LDL(mg/dL) (p<0.001), Delta TG(mg/dL) (p< 0.001), Delta WBC(103/□3) (p<0.001), Delta CRP(mg/dL) (p<0.001), Delta HDL(mg/dL) (p<0.001) and CR (p<0.001) were associated with Delta CAVI. In multivariate analysis, it was shown that CAVI-pre (OR: 2.590, 95%CI 1.903-3.524, p: <0.001) and CR (OR: 40.55, 95%CI 8.12-202.4, p: <0.001) were independent predictors of Delta CAVI (Table 2).

A significant correlation was found between Delta CAVI and CR (r=-0.553, p<0.001) (Figure 1).

Table 1: Baseline Characteristics of the Study Population

Variables	Group 1 (n=113)	Group 2 (n=95)	Group 3 (n=90)	All patients (n=298)	p
	Demographic Data				
Age (year)	56.8±7.8	56.8±8.06	56.7±7.3	56.8±7.7	0.984
Cardiac rehabilitation (n, %)	32(28.3%)	80(84.2%)	90(100%)	202(67.7%)	<0.001
Gender (male %)	80(70.8%)	72(75.8%)	79(87.8%)	231(77.5%)	0.014
Hypertension (n, %)	98(86.7%)	83(87.4%)	83(92.2%)	264(88.6%)	0.427
Diabetes mellitus(n, %)	26(23%)	21(22.1%)	27(30%)	74(24.8%)	0.393
Current smoker (n, %)	16(14.2%)	12(12.6%)	10(11.1%)	38(12.8%)	0.811
BMI (kg/m^2)	28.1±3.8	28.1±3.5	28.6±3.5	28.2±3.6	0.514
PCI history (n, %)	62(54.9%)	57(60%)	57(63.3%)	176(59.1%)	0.464
ACS history (n, %)	32(28.3%)	20(21.1%)	26(28.9%)	78(26.2%)	0.386
CABG history (n, %)	23(20.4%)	11(11.6%)	21(23.3%)	55(18.5%)	0.096
LVEF (%)	57.1±5.8	58.4±5.9	58.6±4.4	58.01±5.5	0.104
	Medication				
Beta-blockers (n, %)	94(83.2%)	70(73.7%)	75(83.3%)	239(80.2%)	0.155
Calcium-channel-blockers (n, %)	44(38.9%)	39(41.1%)	49(54.4%)	132(44.3%)	0.031
RAAS inhibitors (n, %)	92(81.4%)	77(81.1%)	74(82.2%)	243(81.5%)	0.978
Statin (n, %)	107(94.7%)	86(90.5%)	85(94.4%)	278(93.3%)	0.426
	Laboratory Data				
Fast plasma glucose (mg/dL)-pre	103.6±30	103.8±27	106.1±33.4	104.4±30	0.823
Creatinine(mg/dl)-pre	0.87±0.21	0.87±0.21	0.9±0.2	0.88±0.21	0.590
Hemoglobin (g/dL)-pre	13.5±1	13.5±1.13	13.7±1.02	13.6±1.05	0.428
LDL-cholesterol (mg/dL)-pre	119.5±33.2	118.9±34	116.4±34	118.4±34	0.803
TG-cholesterol (mg/dL)-pre	151.2±48	156.5±59	156.9±61.5	154.6±55	0.714
HDL-cholesterol (mg/dL)-pre	35.1±4.8	34.9±5.6	35.5±5.8	35.1±5.4	0.748
WBC (10^3/µ^3)-pre	7.4±1.1	7.3±1.2	7.7±1.3	7.5±1.2	0.115
CRP (mg/dL)-pre	3.2±1.2	3.6±1.3	3.4±1.3	3.4±1.3	0.160
Delta LDL (mg/dL)	-10.3±18.8	-20.8±24.3	-31.8±28.9	-20.2±25.5	<0.001
Delta TG (mg/dL)	-16.3±25.1	-30.1±29	-42.1±46.3	-28.4±35	<0.001
Delta CRP (mg/dL)	-0.36±0.72	-0.96±0.9	-1.2±1.01	-0.8±0.96	<0.001
Delta WBC(10^3/µ^3)	-0.34±0.89	-0.64±0.93	-0.99±0.81	-0.63±0.91	<0.001
Delta HDL (mg/dL)	1.66±2.7	3.6±2.7	4.4±2.4	3.1±2.9	<0.001
CAVI-pre	8.7±1.2	9.1±1.2	10.2±1.5	9.3±1.4	<0.001
Delta CAVI	-0.21±0.19	-0.98±0.23	-2.1±0.67	-1.03±0.88	<0.001

BMI: body mass index; PCI: percutaneous coronary intervention; ACS; acute coronary syndrome; CABG: coronary artery by-pass graft; LVEF: left ventricular ejection fraction; RAAS: rennin-angiotensin-aldosterone; LDL: low density lipoprotein; TG: Triglycerides; HDL: high density lipoprotein; WBC: white blood cell; CRP: C-reactive protein; CAVI: cardio-ankle vascular index

Table 2: Multivariate Analysis to Determine the Factors Associated with CAVI Reduction

	Univariate			Multivariate		
Variable	**OR**	**95CI%**	**p**	**OR**	**95CI%**	**p**
Age (year)	0.997	0.966-1.029	0.858			
Gender (male)	2.646	1.312-5.335	0.007	1.958	0.768-4.990	0.159
CABG history	1.558	0.845-2.870	0.155			
CAVI-pre	2.086	1.661-2.619	<0.001	2.590	1.903-3.524	<0.001
Delta LDL (mg/dL)	0.974	0.963-0.985	<0.001	0.998	0.974-1.003	0.128
Delta TG (mg/dL)	0.985	0.977-0.992	<0.001	1.001	0.990-1.011	0.988
Delta WBC ($10^3/\mu^3$)	0.543	0.408-0.722	<0.001			
Delta CRP (mg/dL)	0.561	0.434-0.724	<0.001	1.089	0.770-1.540	0.632
Delta HDL (mg/dL)	1.273	1.155-1.403	<0.001			
Cardiac rehabilitation	37.71	9.045-157.2	<0.001	40.55	8.12-202.4	<0.001

CAVI: cardio-ankle vascular index; CABG: coronary artery by-pass graft; LDL: low density lipoprotein; TG: Triglycerides; WBC: white blood cell; CRP: C-reactive protein; HDL: high density lipoprotein

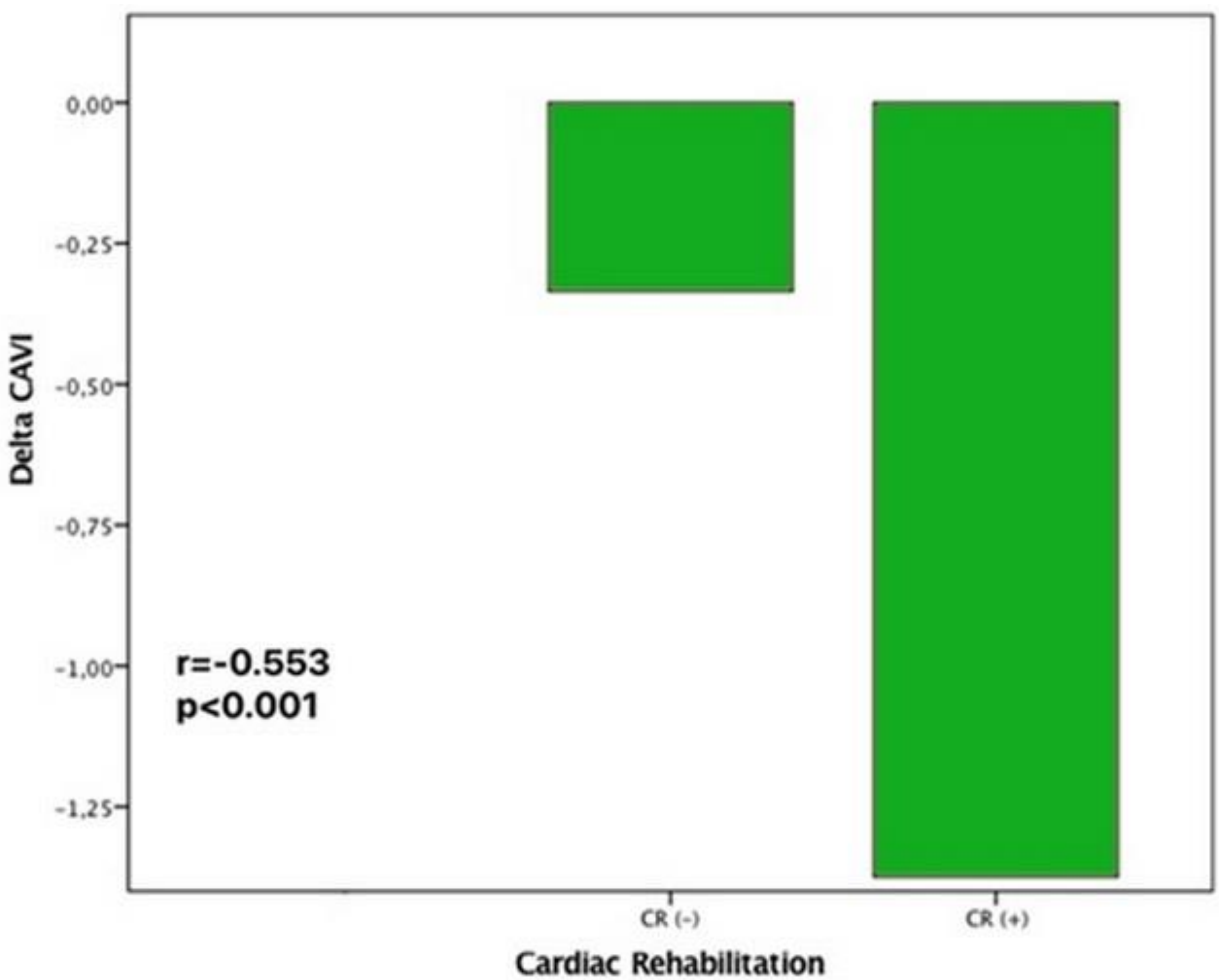

Figure 1:The association between Delta CAVI values and CR

DISCUSSION

To our knowledge, this is the first study that evaluated the effect of exercise-based CR on arterial stiffness in patients with stable CAD, by the CAVI method. Exercise-based CR program was found to be an independent predictor of improved arterial stiffness in these patients.

As the vessels stiffen, left ventricular afterload increases and it can contribute to ventricular hypertrophy, impaired coronary perfusion, increase myocardial oxygen demand, aortic root dilation, valvular dysfunction and heart failure (7). Increased arterial stiffness has been shown to be independently associated with target organ damage and increased CV mortality and morbidity (8). We speculate that one of the mechanisms of exercise-based CR for decreasing CV mortality and morbidity in patients with CAD may be related with its favorable effect on arterial stiffness.

CR program might improve arterial stiffness in several ways. First, increased arterial pressure and heart rate during exercise might cause vessel deformation and this might prevent some of the connective tissue cross-linking. Second, during exercise, skeletal muscles vasodilate and this vasodilatation propagates upstream to large conducting vessels (9). Third, pulsatile flow in the aorta increases with exercise and this might evoke the release of nitric oxide (NO) acutely and also lead to an up-regulation of NO and other vasodilation factors (8,9). Atherosclerosis is characterized by endothelial dysfunction and low-grade inflammation which can contribute to increased vascular stiffness (10). Ribeiro et al. (11,12) showed the anti-inflammatory effects of exercise which was demonstrated by reduction in the levels of pro-inflammatory cytokines and increase in anti-inflammatory cytokines. The anti-inflammatory effect of exercise-based CR may also be related with improvement of arterial stiffness. In concordance with these results, Delta CRP was found to be related with Delta CAVI in our study.

Shimizu et al. (13) demonstrated that after nitroglycerin administration, the stiffness of the arteries as measured by CAVI decreases in CAD patients, indicating that the response of arterial smooth muscle cells to NO is preserved even in CAD patients under medication, like our study population.

Yamamoto et al. (14) analyzed the effect of nitroglycerin on arterial stiffness by the CAVI method in healthy people and also arteriosclerotic patients. They found that, nitroglycerin-induced decrease of arterial stiffness is much more prominent in arteriosclerotic patients than in healthy people. In concordance with this study, we showed that CAVI-pre values were independently associated with Delta CAVI.

Laskey et al. (6) analyzed the effect of CR program on arterial stiffness in 33 patients with established CAD, at their uncontrolled study. In concordance with our study, they found that CR program improves arterial stiffness. But our study includes a larger study population and we have used CAVI, a novel method for arterial stiffness analysis.

Sung et al. (8) suggested that short exercise duration (10 min.) decreases arterial stiffness in patients with CAD. Study population consisted of stable CAD patients who underwent PCI. They found that with short exercise duration, PWV values of CAD patients decreases more than the control group. Because their study population included less extensive CAD patients, they speculated that this may be related to the acute release of NO with exercise in patients which the duration of CAD is not long-term so; the effect of exercise on arterial stiffness in patients with extensive and long-term CAD was unknown. Our study shows that, this was not only acute effect and exercise may improve arterial stiffness in patients with chronic CAD that our study population includes patients with coronary bypass surgery history.

Edwards et al. (7) showed that exercise-based CR for 12 weeks reduced PWV in CAD patients. But their study population included only 20 patients. Although they conducted a total of 12 weeks of CR program including 3 days per week, which is longer than our study, our rehabilitation program was more intense, as 5 days in a week for a total of 6 weeks. The same results were obtained despite the time and intensity differences. It can be said that either the longer duration or more intense exercise improved the stiffness.

In concordance with previous studies, we showed that exercise-based CR program reduces triglyceride levels,low-density lipoprotein-cholesterol and increased high-densitylipoprotein-cholesterol levels (15,16).

It was known that a medication such as statins, renin-angiotensin inhibitors has positive effect on arterial stiffness. But there was no statistically significant difference in medical treatment between groups in our investigation, and we did not change the patient's medications throughout the study.

CR is a cost-effective outpatient program composed of structured exercise training and comprehensive education addressing cardiac risk. Participation has been shown to reduce CV mortality, need for re-hospitalization and re-vascularization procedures and lead to improve functional status when compared with usual care (17,18,19). Currently, the major problem with exercise based-CR is its underutilization by physicians. On the other hand, although data supporting the benefits of CR are highly regarded, they lack the support of large, appropriately powered clinical trials (20). Therefore, randomized controlled trials are needed to assess the impact of CR in higher risk CAD patients and patients with SAP (21). By showing the positive effect of CR on arterial stiffness and safely able to perform in patients with severe CAD and stable angina pectoris, we think that our study can provide a significant contribution to the literature.

Limitations

This study has several limitations. We performed the CR program 5 daysa week for a total of 6 weeks. We could implement a longer CR program, but there is no clear exercise duration or exercise intensity recommended in previous studies or reviews. Since our results are positive, we think this period is enough. The biochemical mechanism of how CR reduces arterial stiffness has not been investigated.

Conclusion

In this study, we have shown that exercise-based CR improves arterial stiffness in patients with CAD. In addition, we have shown that these patients could safely complete the exercise-based CR program.

Acknowledgments: None declared.
Funding sources: None declared.
Conflicts of interest: None declared
Ethics Committee Approval: Ethical approval was obtained by the Local Ethics Committee

REFERENCES

1-Kamakura T, Kawakami R, Nakanishi M, Ibuki M, Ohara T, Yanase M et al. Efficacy of out-patient cardiac rehabilitation in low prognostic risk patients after acute myocardial infarction in primary intervention era. Circ J 2011; 75: 315-21.

2-Guimarães GV, Ciolac EG, Carvalho VO, D'Avila VM, Bortolotto LA, Bocchi EA. Effects of continuous vs. interval exercise training on blood pressure and arterial stiffness in treated hypertension. Hypertens Res 2010; 33: 627-32.

3-Kresnajati S, Lin YY, Mündel T, Bernard JR, Lin HF, Liao YH. Changes in Arterial Stiffness in Response to Various Types of Exercise Modalities: A Narrative Review on Physiological and Endothelial Senescence Perspectives. Cells. 2022;11(22):3544. Published 2022 Nov 9. doi:10.3390/cells11223544

4-Kalaycioğlu E, Gökdeniz T, Aykan AÇ, Gül I, Dursun I, Kiriş G et al. The relationship between dipper/nondipper pattern and cardioanklevascular index in hypertensive diabetic patients. Blood PressMonit2013;18:188-94.

5- Nagayama D, Fujishiro K, Suzuki K, Shirai K. Comparison of Predictive Ability of Arterial Stiffness Parameters Including Cardio-Ankle Vascular Index, Pulse Wave Velocity and Cardio-Ankle Vascular Index0. Vasc Health Risk Manag. 2022;18:735-745. Published 2022 Sep 12. doi:10.2147/VHRM.S378292

6- Laskey W, Siddiqi S, Wells C, Lueker R. Improvement in arterial stiffness following cardiac rehabilitation. Int J Cardiol 2013;167: 2734-8.

7- Edwards DG, Schofield RS, Magyari PM, Nichols WW, Braith RW. Effect ofexercise training on central aortic pressure wave reflection in coronary artery disease. Am J Hypertens 2004; 17: 540-3.

8- Sung J, Yang JH, Cho SJ, Hong SH, Huh EH, Park SW. The effects of short-duration exercise on arterial stiffness in patients with stable coronary artery disease. J Korean Med Sci 2009; 24: 795-9.

9- Joyner J. M. Effect of exercise on arterial compliance. Circulation 2000; 102:1214-15

10- Inflammation, atherosclerosis, and coronary artery disease. N Engl J Med 2005; 352: 1685-95.
11- Ribeiro F, Alves AJ, Duarte JA, Oliveira J. Is exercise training an effective therapy targeting endothelial dysfunction and vascular wall inflammation? Int J Cardiol 2010 11; 141: 214-21.
12-Ribeiro F, Alves AJ, Teixeira M, Miranda F, Azevedo C, Duarte JA et al. Exercise training increases interleukin-10 after an acute myocardial infarction: a randomized clinical trial. Int J Sports Med 2012; 33:192-8.
13- Shimizu K, Yamamoto T, Takahashi M, Sato S, Noike H, Shirai K. Effect of nitroglycerin administration on cardio-ankle vascular index. VascHealth RiskManag 2016; 12: 313-9.
14-Yamamoto T, Shimizu K, Takahashi M, Tatsuno I, Shirai K. The Effect of Nitroglycerin on Arterial Stiffness of the Aorta and the Femoral-Tibial Arteries. J AtherosclerThromb 2017; 24:1048-57.
15-Toyama K, Sugiyama S, Oka H, Iwasaki Y, Sumida H, Tanaka T et al.Combination treatment of rosuvastatin or atorvastatin, with regular exercise improves arterial wall stiffness in patients with coronary artery disease. PLoSOne 2012; 7: 41369
16-Sandesara PB, Lambert CT, Gordon NF, Fletcher GF, Franklin B, Wenger N et al.Cardiac rehabilitation and risk reduction: time to "rebrand and reinvigorate". J Am CollCardiol 2015; 65: 389-95.
17-Alter DA, Zagorski B, Marzolini S, Forhan M, Oh PI. On-site programmatic attendance to cardiac rehabilitation and the healthy-adherer effect. Eur J PrevCardiol 2015; 22:1232-46.
18-Martin BJ, Hauer T, Arena R, Austford LD, Lewin AM, Knudtson ML et al. Cardiac rehabilitation attendance and outcomesin coronary artery disease patients. Circulation 2012; 126: 677-87.
19-Grace SL, Midence L, Oh P, Brister S, Chessex C, Stewart DE et al. Cardiac Rehabilitation Program Adherence and Functional Capacity Among Women: A Randomized Controlled Trial. Mayo ClinProc 2016; 91:140-8.
20-Bonow R. O, Mann D. L, Zipes D. P, Libby P. Braunwalsd’ s HeartDisease2015: 1020
21-Anderson L, Oldridge N, Thompson DR, Zwisler AD, Rees K, Martin N et al. .Exercise-Based Cardiac Rehabilitation for Coronary Heart Disease: Cochrane Systematic Review and Meta-Analysis. J Am CollCardiol 2016; 67:1-12.