Acta Cardiol Sin 2023;39:720–732
Original Article
doi: 10.6515/ACS.202309_39(5).20230306E

Coronary Artery Disease

Effectiveness of Device-Guided Breathing in Chronic Coronary Syndrome: A Randomized Controlled Study

Oguz Akkus,[1] Irem Huzmeli,[2] Taner Seker,[3] Ozkan Bekler,[1] Fatih Sen,[1] Onur Kaypakli,[1] Aysel Yildiz Ozer[4] and Fatih Yalcin[1]

Background: Chronic coronary syndrome (CCS) is one of the most life-restricting coronary artery diseases, and symptom relief is the main goal in CCS patients who suffer from angina.

Objectives: To assess the potential benefits of device-guided breathing in CCS patients with angina in this randomized, controlled, single-blinded study.

Methods: Fifty-one patients with CCS received device-guided breathing for 7 days/8 weeks. Exercise capacity [exercise stress test], cardiac function [transthoracic echocardiography], and angina severity [Canadian Cardiovascular Society Classification] were evaluated initially and after the training. Device-guided breathing was performed at the lowest resistance of the device (POWERbreathe® Classic LR) for the control group (n = 17). The low load training group (LLTG; n = 18) and high load training group (HLTG; n = 16) were trained at 30% and 50% of maximal inspiratory pressure. Baseline characteristics were compared using one-way ANOVA and Kruskal-Wallis test. Categorical data were compared using the chi-square test. ANCOVA was performed to compare changes between three groups. A p value < 0.05 was considered statistically significant.

Results: Metabolic equivalent values were significantly improved in both HLTG and LLTG groups ($p < 0.001$, $p = 0.003$). The Duke treadmill score significantly improved and shifted to low-risk both in the HLTG ($p < 0.001$) and LLTG ($p < 0.001$) groups. Angina severity significantly alleviated after the training in both HLTG and LLTG groups ($p < 0.001$, $p = 0.002$).

Conclusions: An 8-week long program of short-term respiratory muscle training provided positive gains in exercise capacity and angina severity in CCS patients with angina. The effects of long-term training programs on CCS patients should be investigated clinically because of the possibility of helping to decrease the need for invasive treatments.

Key Words: Atherosclerosis • Chronic stable angina • Exercise test • Respiratory muscle training

INTRODUCTION

Coronary artery diseases (CAD) are among the most life-threatening pathological processes despite updated treatment options.[1] Chronic coronary syndrome (CCS) is one of the main components of CAD and can be diagnosed by different clinical manifestations. Patients may be symptomatic (fatigue, weakness, heart failure symptoms, ventricular arrhythmias, etc. which are usually triggered by exercise) or asymptomatic (silent CAD), or they may have stable symptoms after acute coronary syndrome/percutaneous coronary revascularization, vaso-

Received: March 31, 2022 Accepted: March 6, 2023
[1]Department of Cardiology, Tayfur Ata Sokmen Faculty of Medicine; [2]Department of Physiotherapy and Rehabilitation, Faculty of Health Sciences, Hatay Mustafa Kemal University, Hatay; [3]Department of Cardiology, Adana Health Practice and Research Center, University of Health Sciences, Adana; [4]Department of Physiotherapy and Rehabilitation, Faculty of Health Sciences, Marmara University, Istanbul, Turkey.
Corresponding author: Dr. Irem Huzmeli, Department of Physiotherapy and Rehabilitation, Faculty of Health Sciences, Hatay Mustafa Kemal University, Hatay, Turkiye. Tel: +90 (544) 7107160; Fax: 0 (326) 216 06 67; E-mail: fztirem@gmail.com

Abbreviations

CAD	Coronary artery diseases
CCS	Chronic coronary syndrome
DBP	Diastolic blood pressure
DTS	Duke Treadmill Score
ECG	Electrocardiography
ET	Ejection time
HLTG	High load training group
HR	Heart rate
HRR	Heart rate recovery
IQR	Interquartile range
IVCT	Isovolumetric contraction time
IVRT	Isovolumetric relaxation time
LLTG	Low load training group
LVEF	Left ventricular ejection fraction
MET	Metabolic equivalent
METs	Metabolic equivalent of task
MIP	Maximal inspiratory pressure
MPI	Myocardial performance index
OMT	Optimal medical therapy
RMR	Resting metabolic rate
RVOT VTI	Right ventricular outflow tract velocity time integral
SD	Standard deviation
TAPSE	Tricuspid annular plane systolic excursion

spastic angina, microvascular angina or new-onset heart failure, all of which may be diagnosed as CCS.[2,3]

Future cardiovascular event risk (acute coronary syndromes, death) mainly depends on clinical risk factors (age, hypertension, diabetes mellitus, etc.) and primary prevention; angina severity is also associated with increased mortality.[4] In addition to the mortality risk, CCS is one of the most life-restrictive CADs, and symptom relief is the main goal in CCS patients who suffer from angina. Hence, medication is the first approach. Drug therapy in CCS is used with the purpose of preventing future cardiac events and antianginal treatment. Medical treatments include antithrombotic and lipid-lowering therapy for the prevention of future cardiac events such as myocardial infarction and death.[5-8]

The most frequently used antianginal treatments are nitroglycerin, beta blockers, and calcium channel blockers.[2] Coronary revascularization is another alternative; however, there is not yet sufficient evidence supporting the superiority of coronary revascularization over medical treatment.[2] Since angina may be widely defined and is not only the result of the occlusion of epicardial vessels, angina relief may be achieved by secondary improvements in other mechanisms such as oxygen consumption, heart rate, blood pressure regulation, etc. Patients with angina have reduced daily physical activity, reduced muscle strength, and reduced respiratory capacity compared with patients without angina.[9,10] As angina is usually precipitated by increased oxygen demand preceded by decreased muscle strength, these physiological regulations may be achieved by improvements in exercise capacity.[11] Respiratory muscle endurance and walking capacity have been shown to be more significantly improved by the use of breathing devices compared to traditional breathing exercises.[12] Therefore, the aim of the present study was to assess the potential benefits of device-guided breathing training in addition to standard medication treatment in CCS patients with angina. Device-guided breathing can be applied using different methods and intensities.[12,13] Another aim of this study was to compare the effectiveness of device-guided breathing applied in different intensities.

METHODS

Patient population

All patients suffered from angina or an angina equivalent (fatigue, dyspnea, etc.) and underwent coronary angiography; at least one atherosclerotic significant epicardial coronary artery stenosis was proven, and the patients were divided into three groups: high load training group (HLTG), low load training group (LLTG), and control group. Randomization was performed via an online program.

In addition to breathing exercises, all patients received secondary prevention that included lifestyle advice and optimal medical therapy (OMT). The degree of angina was classified into four categories according to the severity of symptoms and whether the symptoms were triggered by strenuous exercise or spontaneously at rest.[14] Patients who presented with an acute coronary episode within 14 days of starting device-guided breathing (post-MI angina) were not included in the study, as they were not considered to be stable. Additional exclusion criteria were: Canadian Cardiovascular Society designations of class I or IV, angina etiology other than atherosclerosis (hypoxia, anemia, thyroid dysfunction, moderate to severe heart valve disease, etc.), coronary heart disease that was clinically unstable during the surveil-

lance period (8 weeks), changes in medication over the surveillance period, uncontrolled comorbid conditions (hypertension, diabetes etc.), newly diagnosed arrhythmias (atrial fibrillation etc.), active infectious disease, orthopedic and neurological diseases restricting inspiration capacity or the ability to undergo a treadmill stress test, obstructive pulmonary diseases (asthma, chronic obstructive pulmonary disease, etc.), hypertrophic cardiomyopathy, symptomatic heart failure, left ventricular EF of < 40%, left main coronary artery stenosis of > 50%, proximal left anterior descending artery stenosis of > 50%, or functional single epicardial vessel.

Coronary angiography was performed in each patient. To create a better classification of follow-up and treatment, we quantified the severity of coronary lesions according to Gensini score and SYNTAX score.[15,16] Gensini severity score was calculated according to degree of 1-25%, 26-50%, 51-75%, 76-90%, and 90-99% coronary lesions, and whether there were any collaterals.[15] Syntax score is related to the severity of CAD and in treatment planning (surgery/coronary artery bypass graft or percutaneous revascularization).[17]

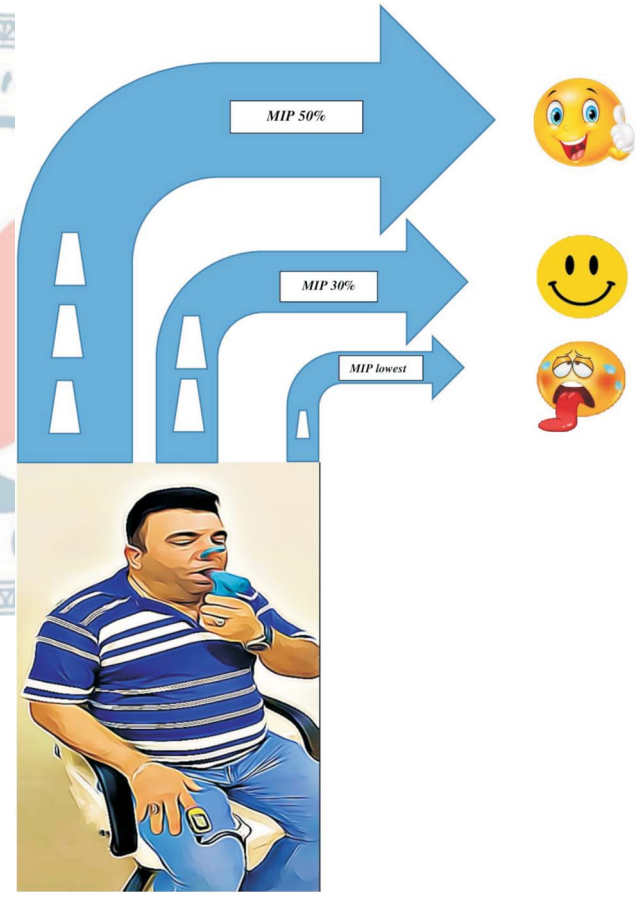
This study was approved by the local ethics committee and performed according to the Declaration of Helsinki. Written informed consent was obtained from all participants.

Device-guided breathing

Device-guided breathing was performed using POWERbreathe® Classic LR devices (HaB Ltd, UK). The loading was set according to the maximal inspiratory pressure (MIP) recorded with a portable electronic mouth pressure measuring device (MicroRPM, Micro Medical, Kent, UK) weekly. Device-guided breathing training was performed at the level of 10 cmH_2O, the lowest resistance of the device, for the control group. The training was performed at a MIP of 30% and 50% of the device in the LLTG and HLTG groups, respectively. The patients performed ambulatory device-guided breathing for 8 weeks (twice a day for 15 minutes or 30 minutes/day and at least five days a week) after initial training by a physiotherapist (Central Illustration). Outpatient visits were performed each week during the surveillance period. Side effects such as shortness of breath, increase in chest pain, discomfort and nausea were not observed during the training. Patients were also informed about possible side effects.

Echocardiographic evaluation

Pre-training and post-training values were obtained by transthoracic echocardiography (GE Vivid S6, USA) at rest. Standard echocardiographic examination of left ventricular EF, pulsed-wave Doppler, and tissue Doppler imaging were performed according to previous recommendations.[18] Left ventricular diastolic functions were evaluated in the apical 4-chamber view using pulsed-wave and tissue Doppler imaging. Pulse-wave Doppler transmittal flow measurements, peak early diastolic filling velocity (E), peak late diastolic filling velocity (A), and their ratio (E/A) were calculated. The E-wave deceleration time, isovolumetric contraction time (IVCT), ejection time (ET), and isovolumetric relaxation time (IVRT) were also calculated. Myocardial performance in-



Central Illustration. *Device-guided breathing. Central illustration demonstrated the efficiency of device-guided breathing in different intensities on patient' symptoms and effort capacity. The level of 10 cmH_2O is the lowest resistance of the device applied for the control group. Maximal inspiratory pressure (MIP) of 30% and 50% of the devices were applied for low load training group (LLTG) and high load training group (HLTG), respectively.*

dex (MPI) was calculated as the sum of IVRT and IVCT divided by the ET.[19] Tricuspid annular plane systolic excursion (TAPSE) was measured in the apical four-chamber view. Pulmonary artery acceleration time was measured between the onset of ejection and the peak flow velocity of the pulmonary artery. At the parasternal short-axis view, right ventricular outflow tract velocity time integral (RVOT VTI) was obtained by pulse-wave Doppler at the level of the RVOT close to the pulmonary valve.[20] Epicardial and pericardial fat thickness/area was measured from the parasternal long-axis window.[21]

Exercise stress test

Exercise testing was performed following the Bruce protocol.[22] Twelve-lead electrocardiography (ECG) was recorded during the procedure. Exercise capacity was measured in metabolic equivalent (MET), and future risk was assessed using the DUKE treadmill score. One MET is defined as the amount of energy expended by a subject while at rest (resting metabolic rate [RMR]), which is 1 kcal per kilogram per hour and 3.5 mL of oxygen per kilogram per minute. By representing the precise level of activity energy expenditure (under steady state conditions) in relative values, i.e., as a multiple of RMR, MET offers a helpful tool to characterize and categorize physical activities. Theoretically, 10 metabolic equivalent of task (METs) would therefore translate to 35 mL O_2 kg^{-1} min^{-1}, or 10 kcal kg^{-1} h^{-1}.[23]

The Duke treadmill score was subclassified as low ($\geq$ 5), moderate (4 to -10), and high risk (< -10) categories using the following formula: Duke Treadmill Score (DTS) = exercise capacity – (5 $\times$ ST depression) – (4 $\times$ exercise-induced angina).[24] In cases of a test-limiting angina symptom, the patients received 2 points; for non-limiting angina, the patients received 1 point, and otherwise, 0 points were given for no angina during exercise. No patient suffered from arrhythmia, blood pressure disturbances, symptoms, or ECG deviation requiring the interruption of exercise testing.

Heart rate recovery (HRR) is a straightforward, non-invasive test for autonomic nervous system impairment that shows a problem with parasympathetic reactivation. Previous research has demonstrated that HRR1, which is defined as a reduction in heart rate (HR) of less than 12 beats per minute from the peak of activity (maximal heart rate) to one minute into recovery, is a predictor of overall mortality.[25,26]

Statistical analysis

IBM SPSS 20.0 statistical analysis software was used (SPSS Inc., USA). Data normality was tested using the Kolmogorov-Smirnov test. Continuous variables were expressed as mean $\pm$ standard deviation (SD) or median and interquartile range (IQR), according to data normality. Baseline characteristics of the three groups were compared using one-way ANOVA and the Kruskal-Wallis test. Categorical data were compared using the chi-square test and presented as count and frequency. ANCOVA was performed to compare changes in cardiac function and exercise capacity between the three groups, accounting for any change in baseline variables. All of the necessary assumptions (normally distributed, homogeneity, homogeneity of regression slope, random independent samples, linearity) for the use of ANCOVA have been verified. Baseline values of each outcome measure were used as covariates. Post-hoc comparisons using the Bonferroni test (syntax) were calculated. The secondary analysis focused on between-group effects and pair-wise comparisons of the remaining study groups. For missing data, intention-to-treat analysis was performed. A p value of < 0.05 was considered to be statistically significant.

Sample size calculation

The G*Power software package (G*Power, Version 3.1.9.4, Franz Faul, Universität Kiel, Germany) was used to calculate the required sample size for the study. According to the MET results of a previous study (Neves et al., 2014)[27] and with type I error α = 0.05, power 95% (1-β error probability), effect size f = 0.6144321, and assuming 20% loss to follow-up and 5% missing data, the sample size was calculated as 54 subjects (n = 18 per group).

RESULTS

Of the 64 consecutive patients who had CCS with angina initially included in the study, 10 patients did not meet the inclusion criteria. After enrollment, the initiation of training was postponed for at least 4 weeks to allow for optimization of the patients' medications. During the follow-up of training, two patients underwent coronary revascularization treatment because of increas-

ing angina severity due to non-adherence to the POWERbreathe®. One patient was excluded because of a newly diagnosed brucella infection, and one patient because of acute atrial fibrillation (Figure 1). The study was concluded with 51 CCS patients. No side effects were observed in any of the groups during the training.

Baseline demographics, clinical characteristics, laboratory, and medication findings are shown in Table 1 and were similar between the groups ($p > 0.05$). More than one coronary artery stenosis was more frequent than single-vessel disease in each group; however, this observation was statistically similar between the groups ($p > 0.05$). The Gensini and Syntax scores were also similar between the groups ($p > 0.05$, Table 1).

The echocardiography and exercise stress test results are shown in Table 2. Clinically, there were no statistically significant changes during the surveillance period regarding echocardiographic findings, and echocardiographic variables were almost similar within and between groups. Significant changes were found only in some echocardiographic findings. Epicardial fat thickness decreased (from 0.83 ± 0.33 to 0.70 ± 0.27 cm, $p = 0.016$) in the LLTG group after training. There was a significant decrease in E/A ratio in the control group ($p =$

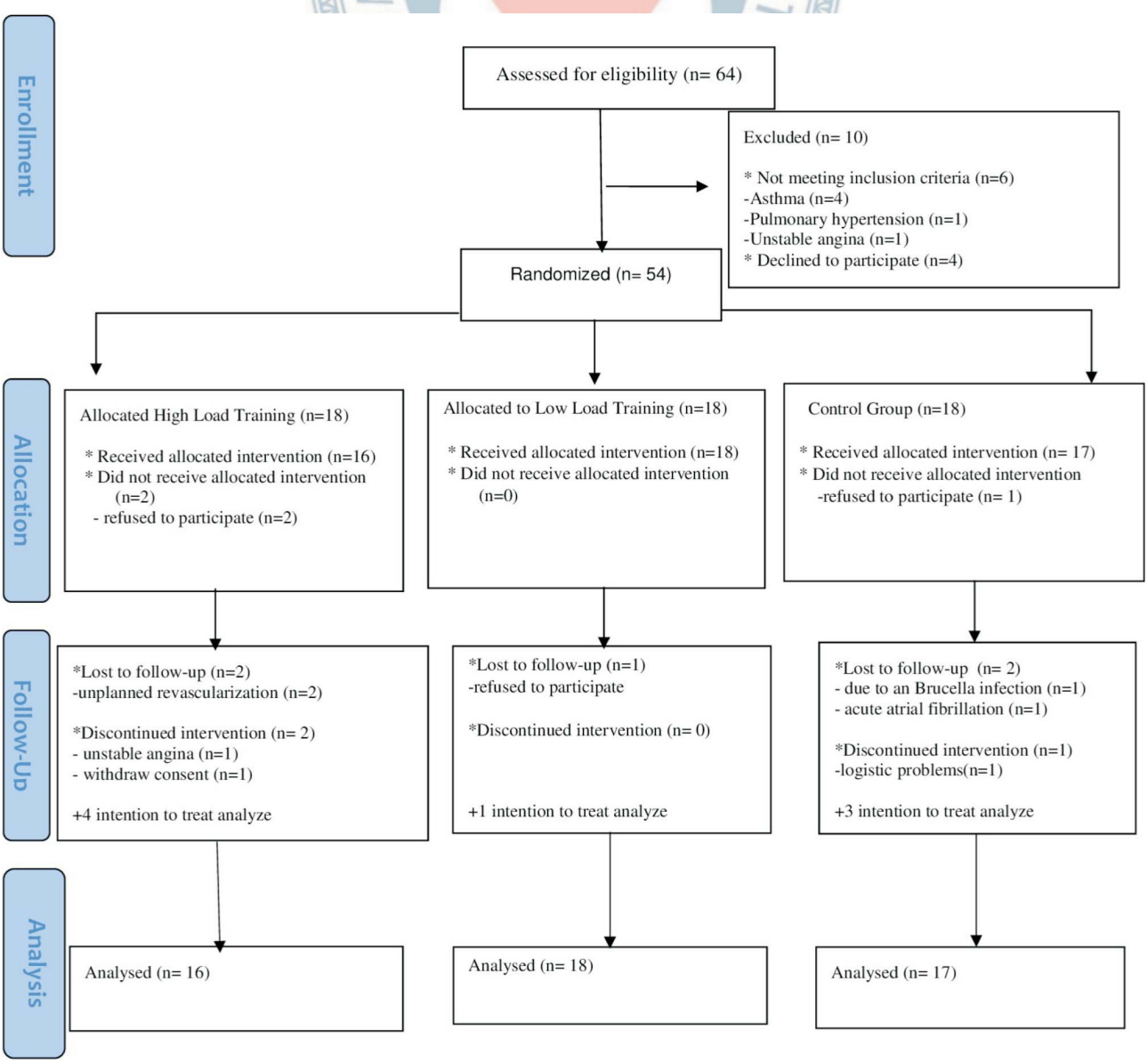


Figure 1. *CONSORT flow diagram of the study.*

Table 1. Demographic, clinical characteristics, laboratory and medication status in patients with CCS

Variables	HLTG (n = 16)	LLTG (n = 18)	CG (n = 17)	p
	Mean ± SD/ median (IQR)/n (%)	Mean ± SD/ median (IQR)/n (%)	Mean ± SD/ median (IQR)/n (%)	
Age (years)	57.31 ± 7.96	54.77 ± 7.06	60.58 ± 6.54	0.067
Body mass index (kg/m^2)	29.03 ± 4.10	29.72 ± 5.12	30.36 ± 4.35	0.708
Female/male, n (%)	3 (18.8%)/13 (81.2%)	1 (5.6)/17 (94.4)	1 (5.9)/16 (94.1)	0.348
Pack × years	23.84 ± 21.46	31.13 ± 35.28	36.05 ± 29.99	0.501
Smoking, n (%)				0.836
Current	3 (18.8)	5 (27.8)	3 (17.6)	
Ex	10 (62.5)	8 (44.4)	9 (52.9)	
Non-smoker	3 (18.8)	5 (27.8)	5 (29.4)	
Alcohol consumption				0.709
Current	3 (18.3)	4 (22.2)	6 (35.3)	
Ex	1 (6.2)	1 (5.6)	0 (0)	
Non-drink	12 (75)	13 (72.2)	11 (64.7)	
Moderate-intensity physical activity, n (%)	4 (25)	9 (50)	10 (58.8)	0.055
Canada Class II/III, n (%)	16 (100)/0 (0)	15 (83.3)/3 (16.7)	17 (100%)/0 (0%)	0.054
Obstructive arteries, n(%)				0.149
> 1	10 (62.5)	5 (27.8)	10 (58.8)	
RCA	3 (18.8)	7 (38.9)	1 (5.9)	
Cx	3 (18.8)	2 (11.1)	3 (17.6)	
LAD	0 (0)	3 (16.7)	3 (17.6)	
IM	0 (0)	1 (5.6)	0 (0)	
Total Gensini Score	36.28 ± 27.89	42.07 ± 13.51	45.33 ± 24.70	0.598
Syntax Score	9 (4-14.12)	10 (6.5-16)	10 (8.25-12.87)	0.829
DM, n (%)	6 (37.5)	7 (38.9)	9 (52.9)	0.371
HG (gr/dL)	14.50 ± 1.45	13.73 ± 1.51	13.28 ± 1.54	0.078
LDL (mg/dL)	117.50 (77.5-157)	85.90 (75.75-115.75)	95 (71-132)	0.308
Creatinin (mg/dL)	0.87 (0.71-1.00)	0.86 (0.72-0.94)	0.92 (0.74-1.00)	0.543
Medication, n (%)				
ASA, n (%)	14 (87.5)	16 (88.9)	15 (88.2)	0.992
P2Y12, n (%)	8 (50)	15 (83.3)	9 (52.9)	0.894
Nitrat, n (%)	8 (50)	5 (27.8)	7 (41.2)	0.623
Trimetazidin, n (%)	5 (31.2)	1 (5.6)	5 (29.4)	0.120
B-bloker, n (%)	15 (93.8)	14 (77.8)	16 (94.1)	0.231
CCB, n (%)	3 (18.8)	4 (22.2)	1 (5.9)	0.381
ACEI/ARB, n (%)	11 (68.8)	16 (88.9)	15 (88.2)	0.226
Statin, n (%)	15 (93.8)	15 (83.3)	14 (82.4)	0.575
Insulin, n (%)	3 (18.8)	2 (11.1)	3 (17.6)	0.799
OAD, n (%)	6 (37.5)	4 (22.2)	9 (52.9)	0.349
Ivabradin, n (%)	0 (0)	2 (11.1)	1 (5.9)	0.389
Ranolazin, n (%)	1 (6.2)	1 (5.6)	3 (17.6)	0.411

ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers; ASA, acetylsalicylic acid; CCB, calcium channel blockers; CCS, chronic coronary syndrome; CG, control group; Cx, circumflex artery; DM, diabetes mellitus; HG, hemoglobin; HLTG, high load training group; IM, internal mammary artery; IQR, interquartile range; LAD, left anterior descending artery; LDL, light density lipoprotein; LLTG, low load training group; OAD, oral antidiabetic; P2Y12, antiplatelet drugs; RCA, right coronary artery; SD, standard deviation.
Chi-Square Tests, One-Way Anova, Kruskal-Wallis Test, $p < 0.05$.

0.026). Figure 2 illustrates the left ventricular ejection fraction (LVEF) values among the groups. METs values were significantly improved in both HLTG and LLTG groups; however, statistical significance was not observed in the control group ($p < 0.001$, $p = 0.003$, $p = 0.821$, Table 2). Hence, METs exhibited a significant difference between the groups ($p < 0.001$, Figure 3). Diastolic blood pressure (DBP) was significantly reduced in the HLTG group (DBP basal from 78.12 ± 11.05 mmHg to 66.82 ± 10.28 mmHg, $p = 0.003$; DBP peak from 77.12 ± 15.44 to 70.00

Table 2. Echocardiographic variables, exercise capacity, angina severity results in patients with CCS

	HLTG			LLTG			CG			Between groups *p**
	Pre-training	Post-training	Within group *p*	Pre-training	Post-training	Within group *p*	Pre-training	Post-training	Within group *p*	
Echocardiographic variables										
TAPSE (cm)	2.10 ± 0.31	2.11 ± 0.29	0.426	2.22 ± 0.40	2.32 ± 0.28	0.347	2.50 ± 0.43	2.38 ± 0.54	0.820	0.445
LVPWs (cm)	1.28 ± 0.18	1.32 ± 0.28	0.811	1.30 ± 0.24	1.38 ± 0.22	0.267	1.41 ± 0.37	1.38 ± 0.22	0.936	0.749
LVIDs (cm)	3.16 ± 0.43	3.06 ± 0.62	0.217	3.33 ± 0.60	3.17 ± 0.62	0.305	3.48 ± 0.81	3.28 ± 0.72	0.158	0.903
ESV (ml)	44.88 ± 13.91	43.17 ± 10.07	0.251	52.13 ± 26.43	48.62 ± 19.63	0.356	56.25 ± 27.15	53.23 ± 24.79	0.780	0.819
LVEF (%)	60.13 ± 6.16	62.03 ± 6.19	0.202	61.16 ± 8.26	63.14 ± 6.79	0.076	58.29 ± 8.34	58.67 ± 8.01	0.732	0.299
FS (%)	32.98 ± 4.07	33.08 ± 4.56	0.894	34.22 ± 5.66	34.42 ± 5.05	0.683	33.40 ± 6.65	34.53 ± 7.58	0.422	0.801
IVSs (cm)	1.57 ± 0.30	1.47 ± 0.21	0.421	1.45 ± 0.19	1.41 ± 0.30	0.370	1.50 ± 0.42	1.34 ± 0.49	0.075	0.702
LVPWd (cm)	1.01 ± 0.15	1.00 ± 0.13	0.532	1.07 ± 0.18	1.08 ± 0.17	0.858	1.11 ± 0.18	1.08 ± 0.33	0.898	0.842
LVIDd (cm)	4.96 ± 0.75	4.84 ± 0.65	0.325	5.03 ± 0.65	5.03 ± 0.57	0.818	4.90 ± 1.42	5.14 ± 0.97	0.108	0.185
EDV (ml)	119.62 ± 40.84	115.61 ± 33.69	0.409	124.44 ± 42.40	125.82 ± 34.92	0.947	137.66 ± 65.77	128.38 ± 62.84	0.510	0.780
IVSd (cm)	1.12 ± 0.32	1.10 ± 0.29	0.741	1.06 ± 0.15	1.08 ± 0.20	0.956	1.17 ± 0.24	1.12 ± 0.23	0.375	0.459
PACT (ms)	101.62 ± 27.24	109.88 ± 25.06	0.464	112.27 ± 24.60	115.13 ± 26.89	0.412	114.37 ± 12.93	112.13 ± 19.75	0.959	0.843
IVCT (ms)	56.60 ± 12.12	62.50 ± 17.40	0.901	70.83 ± 18.43	69.12 ± 16.60	0.833	70.64 ± 23.65	71.00 ± 21.49	0.535	0.927
ET (ms)	265.53 ± 29.42	276.55 ± 37.30	0.095	260.33 ± 44.71	260.65 ± 42.74	0.752	238.06 ± 32.97	234.09 ± 40.95	0.240	0.145
IVRT (ms)	103.80 ± 28.03	103.74 ± 20.74	0.861	100.27 ± 19.01	103.17 ± 32.80	0.778	102.68 ± 23.43	90.38 ± 15.91	0.052	0.201
MPI	0.61 ± 0.16	0.58 ± 0.18	0.140	0.67 ± 0.18	0.68 ± 0.21	0.857	0.74 ± 0.24	0.69 ± 0.19	0.894	0.442
EPI thickness (cm)	0.82 ± 0.36	0.82 ± 0.34	0.924	0.83 ± 0.33	0.70 ± 0.27	0.016*	0.68 ± 0.21	0.67 ± 0.39	0.716	0.142
PERI thickness (cm)	1.38 ± 0.21	1.31 ± 0.27	0.100	1.54 ± 0.43	1.32 ± 0.27	0.066	1.52 ± 0.33	1.33 ± 0.35	0.069	0.605
RVOT VTI (cm)	10.57 ± 5.78	9.46 ± 5.22	0.057	13.93 ± 2.73	12.87 ± 2.36	0.362	13.41 ± 3.12	11.68 ± 4.86	0.062	0.668
Ao diameter (cm)	3.35 ± 0.32	3.39 ± 0.29	0.275	3.20 ± 0.22	3.13 ± 0.28	0.210	3.25 ± 0.39	3.36 ± 0.45	0.195	0.136
LA diameter (cm)	2.86 ± 1.43	3.00 ± 1.43	0.497	3.80 ± 0.51	3.69 ± 0.35	0.450	3.80 ± 0.53	3.52 ± 0.82	0.30	0.157
EPI area (cm^2)	0.75 ± 0.26	0.99 ± 0.36	0.144	0.97 ± 0.36	0.95 ± 0.40	0.990	0.96 ± 0.30	1.07 ± 0.42	0.221	0.453
MWDecT (ms)	220.38 ± 58.76	222.18 ± 57.50	0.701	236.00 ± 148.31	222.78 ± 71.50	0.677	271.00 ± 96.83	284.41 ± 121.98	0.266	0.458
E/A ratio	0.63 ± 0.44	0.75 ± 0.38	0.375	1.37 ± 0.96	1.12 ± 0.36	0.752	0.97 ± 0.13	0.78 ± 0.32	0.026*	0.290
TDe (m/s)	0.09 ± 0.02	0.08 ± 0.02	0.782	0.09 ± 0.02	0.13 ± 0.19	0.363	0.27 ± 0.31	0.24 ± 0.32	0.840	0.643
TDa (m/s)	0.10 ± 0.02	0.18 ± 0.1	0.095	0.12 ± 0.12	0.11 ± 0.03	0.996	0.09 ± 0.02	0.16 ± 0.17	0.141	0.364
Exercise stress variables										
HR bazal (per/min)	80.00 ± 11.24	77.55 ± 13.13	0.404	75.80 ± 13.70	75.56 ± 12.21	0.778	77.43 ± 13.14	78.38 ± 13.62	0.650	0.644
HR maks (per/min)	138.75 ± 16.27	133.98 ± 14.49	0.175	131.66 ± 26.23	138.4 ± 18.15	0.205	147.06 ± 23.62	150.97 ± 25.19	0.059	0.062
SBP basal (mmHg)	140.50 ± 24.11	131.05 ± 22.66	0.146	133.23 ± 18.16	129.90 ± 21.23	0.323	136.33 ± 16.74	128.66 ± 16.74	0.062	0.804
DBP basal (mmHg)	78.12 ± 11.05	66.82 ± 10.28	0.003*	71.15 ± 12.30	72.24 ± 12.21	0.760	79.93 ± 10.72	77.44 ± 11.71	0.635	0.048*
SBP peak (mmHg)	168.62 ± 37.14	165.16 ± 38.19	0.743	134.85 ± 21.28	140.78 ± 25.82	0.315	157.68 ± 18.64	150.89 ± 18.17	0.099	0.202
DBP peak (mmHg)	77.12 ± 15.44	70.00 ± 13.75	0.036*	72.21 ± 14.86	71.55 ± 15.45	0.417	83.00 ± 8.47	77.87 ± 10.41	0.138	0.481
Angina class, n (%)			< 0.001*			0.002*			0.396	0.064*
Class I	0%	43.8%		0%	33.3%		0%	5.9%		
Class II	100%	56.3%		83.3%	61.1%		100%	94.1%		
Class III	0%	0%		16.7%	5.6%		0%	0%		
METs	9.65 ± 2.75	11.91 ± 2.50	< 0.001*	9.20 ± 2.91	10.18 ± 2.72	0.003*	7.93 ± 2.27	8.03 ± 2.26	0.821	< 0.001*
Duke treadmill score, %			< 0.001*			< 0.001*			0.251	0.007*
Low	18.8%	81.2%		22.2%	72.2%		0%	23.5%		
Medium	81.2%	18.8%		77.8%	27.8%		88.2%	64.7%		
High	0%	0%		0%	0%		11.8%	11.8%		
HRR1 min, bpm	23.28 ± 20.25	28.72 ± 31.88	0.568	24.46 ± 13.15	29.41 ± 19.56	0.497	28.64 ± 20.82	24.06 ± 14.44	0.771	0.757
HRR1			0.876			0.243			0.302	0.608
< 12 min, bpm (%)	28.6	20		0	5.9		14.3	7.1		
12 < min, bpm (%)	71.4	80		100	94.1		85.7	92.9		

Ao, aorta; CG, control group; DBP, diastolic blood pressure; E/A, peak early diastolic filling velocity/peak late diastolic filling velocity; EDV, end-diastolic volume; EPI, epicardial fat; ESV, end-systolic volume; ET, ejection time; FS, fractional shortening; HLTG, high load training group; HR, heart rate; HRR1, one minute heart rate recovery; IVCT, isovolumetric contraction time; IVRT, isovolumetric relaxation time; IVSd, interventricular septal thickness at end-diastole; IVSs, interventricular septal end systole; LA, left atrial; LLTG, low load training group; LVEF, left ventricular ejection fraction; LVIDd, left ventricular internal diameter end diastole; LVIDs, left ventricular internal diameter end systol; LVPWd, end diastolic left ventricular posterior wall thickness; LVPWs, left ventricular posterior wall end systole; METs, metabolic equivalent of task (($ml \cdot kg^{-1} \cdot min^{-1}$)); MPI, myocardial performance index; MvDecT, deceleration time of the early mitral inflow velocity; PACT, pulmonary acceleration time; PERI, pericardial fat; RVOT VTI, right ventricular outflow tract velocity time integral; SBP, systolic blood pressure; TAPSE, tricuspid annular plane systolic excursion; TDa, late diastolic mitral annulus velocity; TDe, early diastolic mitral anulus velocity. Ancova tests, $p < 0.05$; * Treatment effect.

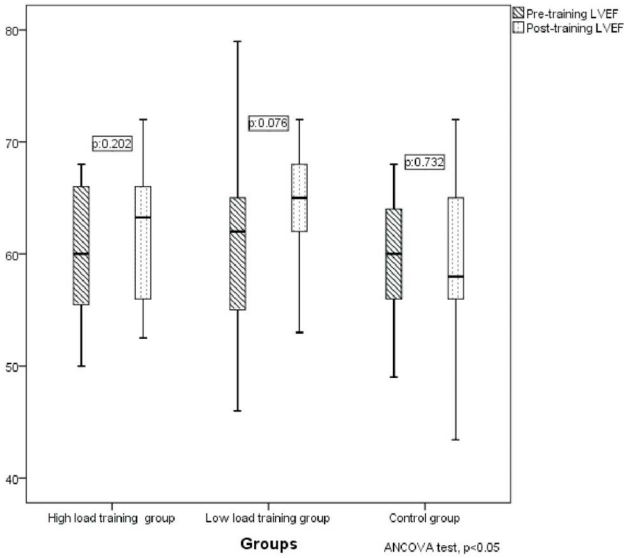


Figure 2. *Comparison of the left ventricular ejection fraction (LVEF) after the training.*

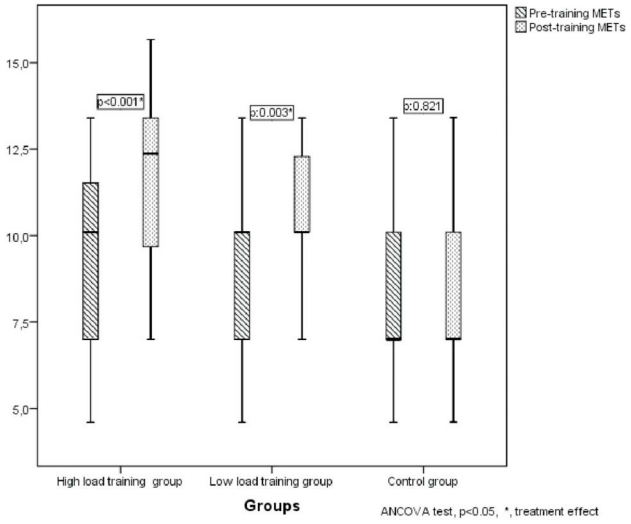


Figure 3. *Comparison of the exercise capacity between the groups.*

± 13.75 mmHg, p = 0.03). Blood pressure changes were similar in the LLTG and the control groups (p > 0.05). Only the reductions in diastolic blood pressure in the HLTG group were significantly different between the groups (p = 0.048). The Duke treadmill score significantly improved and shifted to low-risk in both the HLTG and LLTG groups (p < 0.05). The Duke score was improved in the control group; however, this result was not statistically significant (p = 0.251). The angina severity class was significantly alleviated after training in both the HLTG and LLTG groups (p < 0.001 and p = 0.002) (Table 2).

HRR1 is shown in Table 2. Although there were no significant between and within-group differences in HRR1, the positive increase in HRR1 with device-guided breathing was greater in the training groups than in the control group. The changes in HRR1 in groups according to a cut-off value of ≤ 12/min beats were as follows: HRR1 was increased in 1 patient in the HLTG group and 1 patient in the control group, while the HRR1 in 1 patient was lower than the cut-off value.

DISCUSSION

In the present study, we report the effects of device-guided breathing in CCS patients who suffered from angina. The most important findings were that both high load and low load device-guided breathing were beneficial in relieving angina symptoms, reducing diastolic blood pressure and improving exercise capacity.

Angina has life-limiting effects and diminishes the quality of life despite OMT. Treatment goals for angina include preventing the progression of atherosclerosis, relief of symptoms, mitigation of secondary plaque formation, and improvement in the quality of life.[28] Hence, the initial treatment strategy is crucial both for patient relief and survival. A meta-analysis consisting of 7229 stable angina patients reported that treatment goals (preventing acute coronary syndrome, symptom relief, death) were similar for both percutaneous + OMT and OMT alone. Moreover, further revascularization under the treatment strategies were similar between the groups.[29] The ORBITA study investigated patients with stable angina diagnosed after coronary angiography showed > 70% single coronary artery stenosis.[30] The percutaneous group was revascularized and received OMT, while the other group was treated only by OMT. The primary endpoint of the ORBITA study (increase in exercise time) was similar between the groups. Unlike the ORBITA study, the Duke treadmill score was different between the groups in our study. Hence, a treatment strategy of OMT alone or coronary revascularization (percutaneous or coronary artery by-pass grafting) is controversial in patients with CCS. Several studies have reported the effectiveness of coronary revascularization, however deferral of coronary revascularization is an option, especially in the absence of accelerating angina. Hachamovitch et al.

reported follow-up results over an 8-year period of patients with evidence of ischemia on scintigraphy. Their results showed the benefits on survival by early revascularization only in patients with severe ischemia on scintigraphy (> 20% of myocardium), but not in patients with mild ischemia.[31,32] Hence, in our study we excluded patients with huge ischemia (left main coronary artery and proximal LAD stenosis etc.). The ISCHEMIA trial demonstrated the superiority of a revascularization strategy only in patients with moderate-severe ischemia, persistent anginal symptoms and left main coronary artery disease that was verified by coronary computed tomography angiography. According to the results, patients without these criteria should be directed to medical treatment without urgent intervention, and an intervention should be kept in mind in case of the inefficacy of OMT alone.[33] A recent article reported the exact initial therapy option (initial invasive + OMT and OMT alone) in patients with stable angina with moderate or severe ischemia. The study period was about 3.2 years. At the end of the 1st year, despite a slight increase in primary outcomes (death from cardiovascular causes, myocardial infarction, or hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest) in the percutaneous group, similar results were obtained at the end of the study.[34] Taking the different results and benefits from the mentioned studies into consideration, assessing the appropriate treatment of stable angina, we aimed to treat these patients by increasing their muscle strength and exercise capacity.

Cardiac rehabilitation is recommended for symptom relief in addition to medical therapy in CCS patients. However, cardiac rehabilitation programs mostly include aerobic exercises.[35,36] By slow and regular breathing, for example, less than 10 breaths per minute, tidal volume increases, pulmonary stretch receptors are activated and reflex control of the cardiovascular system is affected in various ways. These include inhibition of sympathetic outflow during exhalation and arteriolar vasodilatation.[37] Thus, increased oxygen uptake and reduced fatigue may improve the symptoms of CCS patients with angina. Adequate respiration and inspiratory phases decrease intrathoracic pressure, decrease pulmonary vascular resistance, and enhance venous return and atrial filling that is essential for myocardial contractility preceded by sufficient ventricular expansion, which is referred to as the Frank-Starling mechanism.[38] In addition, responses to different breathing training exercises have been investigated in previous studies.[39,40] Slow and deep breathing has been reported to promote the modulation of autonomic cardiovascular regulation, which is characterized by increased parasympathetic activity and decreased muscle sympathetic activity. Hamilton et al. addressed the beneficial effects of respiratory and peripheral muscle strength on dyspnea, working capacity, and symptom intensity in patients with cardiorespiratory disorders.[11] In patients with obstructive sleep apnea, device-guided breathing training decreased blood pressure (systolic and diastolic) and circulating plasma catecholamines in the apnea group and ensured better sleep quality.[41] De Abreu et al. reviewed the effects of device-guided breathing from studies investigating patients with diabetes mellitus and heart failure and the influences of device-guided breathing training on cardiac autonomic tone and reflexes (blood pressure, required parasympathetic activation after exercise, etc.), which were emphasized as the predictors of future cardiovascular events and survival. MIP (30%) has been shown to have beneficial effects on cardiac autonomic control, functional capacity, and the quality of life in patients with heart failure.[42-47] An overview evaluating the effectiveness of device-guided breathing exercises in patients with hypertension noted that there was no significant effect on blood pressure.[48] Wang et al. reported a decrease in blood pressure (mean arterial and diastolic blood pressure) and inflammatory marker (TNF-α) after performing 1 and 3 months of device-guided slow breathing exercises in patients with hypertension.[49]

Xu et al. found that combining head movements with device-guided breathing was not effective on 24-hour blood pressure but reduced night-time blood pressure in hypertensive patients.[50] Although a reduction in blood pressure was observed in the study groups ion the present study, the reduction was significant only in the HLTG group in DBP. Similar to the results of the current study, a systematic review and meta-analysis investigating the effects of device-guided breathing exercises on the cardiovascular system through autonomic function modulation,[51] found that device-guided breathing could be considered as a complementary treatment to improve the cardiovascular system, mainly in HR and DBP. In the present study, although there was an improvement in some

cardiac functions, most of them were not statistically significant. Therefore, longer-term studies are needed to show the significant improvement in cardiac function.

Breathing exercises have been reported to provide reductions in retrosternal chest pain,[52] chest pain with normal coronary arteries,[53] and non-cardiogenic chest pain.[54] A recently published study stated that slow deep breathing was effective for relieving pain, but that the underlying mechanisms have yet to be clarified.[55] The results of the current study demonstrated the evident clinical relief of angina in both the HLTG and LLTG groups, and these results were significantly different from the control group. In addition to indicating angina relief, reduced angina class has been shown to be a predictor of decreased mortality.[45] Moreover, long-term studies involving device-guided breathing exercises have investigated the possible effects on mortality. Kodama et al. defined the ability of increased oxygen consumption as increased aerobic capacity and demonstrated cardiorespiratory fitness during a treadmill test.[46] Multivariate analysis of a previous study showed that including the Duke score in traditional clinical evaluations provided the most significant value for the prediction of future cardiovascular events, and that increased Duke score was positively correlated with a higher mortality rate.[47] In the present study, METs and Duke treadmill scores were not improved in the control group; however, the HLTG (METs from 9.65 $\pm$ 2.75 to 11.91 $\pm$ 2.50 ml/kg/min) and LLTG (METs from 9.20 $\pm$ 2.91 to 10.18 $\pm$ 2.72 ml/kg/min) groups gained more benefits from device-guided breathing in terms of METs. Similar to the current study, Muammer et al. reported improvements in exercise capacity with peripheric muscle training and device-guided breathing in coronary artery disease patients with metabolic syndrome. They concluded that different device-guided breathing methods should be used in cardiopulmonary rehabilitation to improve exercise intolerance in coronary artery patients with metabolic syndrome.[56] Current knowledge about the effects of device-guided breathing on functional capacity in patients with CCS is still insufficient. Considering the effects of the current study on functional capacity, it may be recommended to use device-guided respiration to increase functional exercise capacity in CCS patients.

HRR provides a practical, non-invasive way to measure parasympathetic activation after exercise.[57] Device-guided breathing was increased in HRR. Deep slow breathing exercises have been shown to improve heart rate variability in healthy subjects, without altering their cardiac autonomic balance.[58] Similar to the previous study, the current study showed that deep breathing with a device with/without load improved HRR. Deep breathing is a safe noninvasive training method for improving HRR1.

One of the limitations of our study is the sample size. Although sample size measurement was performed by power analysis, an increase in the patient population was halted due to the COVID-19 pandemic. Imaging techniques (scintigraphy, exercise echocardiography, etc.) to clarify ischemia, especially for defining moderate to severe ischemia were not used. The combination of stress testing and an imaging modality for the detection of ischemia may be more valuable to show the benefits of device-guided breathing for alleviating the severity of angina, and also the ischemia degree and myocardial territories in which it was effective. The control group could be trained with traditional breathing exercises.

NEW KNOWLEDGE GAINED

Our study results offer a novel physiological treatment approach to CCS patients. This treatment is a non-invasive approach that improves patients' quality of life. In addition, it will increase the applicability of exercise, which has a place in the secondary treatment of coronary artery disease and CCS.

CONCLUSION

There is still doubt regarding the ideal initial treatment for stable angina. Novel studies have supported initial OMT rather than an invasive approach. Chronic coronary syndrome guidelines recommend aerobic exercise, but there is no information regarding breathing exercises. The current study is the first to show the effect of device-guided breathing exercises on exercise capacity, cardiac function and angina severity in patients with CCS. This study also demonstrated that device-guided breathing exercises with different loads can be added to optimal treatments. High load training was more effec-

tive than low load training and the control group. High load breathing training reduced diastolic blood pressure, relieved angina severity and improved exercise capacity. No side effects (shortness of breath, increased chest pain, etc.) were observed during the training, and this showed the safety of the device-guided breathing exercises. A longer duration and different intensity (medium intensity/high intensity with interval training) of training within controlled groups should be investigated in future studies. Additional studies are needed to find the most effective load of device-assisted breathing exercises in CCS patients with angina. As a result, device-assisted breathing exercises can be added to cardiac rehabilitation programs in patients with CCS and angina.

FUNDING

Mustafa Kemal University scientific research project unit supported this work.

DECLARATION OF CONFLICT OF INTEREST

The authors stated that there is no conflict of interest.

REFERENCES

1. Finucane MM, Stevens GA, Cowan MJ, et al. Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group (Body Mass Index). National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. *Lancet* 2011;12:557-67.
2. Knuuti J, Wijns W, Saraste A, et al. ESC Scientific Document Group. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 2020;14:407-77.
3. Ueng KC, Chiang CE, Chao TH, et al. 2023 Guidelines of the Taiwan Society of Cardiology on the diagnosis and management of chronic coronary syndrome. *Acta Cardiol Sin* 2023;39:4-96.
4. Owlia M, Dodson JA, King JB, et al. Angina severity, mortality, and healthcare utilization among veterans with stable angina. *J Am Heart Assoc* 2019;6:8:e012811.
5. Valgimigli M, Bueno H, Byrne RA, et al. ESC Scientific Document Group; ESC Committee for Practice Guidelines (CPG); ESC National Cardiac Societies. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2018;39:213-60.
6. Davies RF, Habibi H, Klinke WP, et al. Effect of amlodipine, atenolol and their combination on myocardial ischemia during treadmill exercise and ambulatory monitoring. Canadian Amlodipine/Atenolol in Silent Ischemia Study (CASIS) Investigators. *J Am Coll Cardiol* 1995;1:619-25.
7. Mach F, Baigent C, Catapano AL, et al. ESC Scientific Document Group. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2020;41:111-88.
8. Li YH, Hsieh IC, Ueng KC, et al. Antithrombotic treatment of stable coronary artery disease. *Acta Cardiol Sin* 2021;37:574-9.
9. Gardner AW, Montgomery PS, Ritti-Dias RM, et al. Exercise performance, physical activity, and health-related quality of life in participants with stable angina. *Angiology* 2011;62:461-6.
10. Huzmeli I, Ozer AY, Akkus O, et al. Comparison of functional exercise capacity, quality of life and respiratory and peripheral muscle strength between patients with stable angina and healthy controls. *J Int Med Res* 2020;48:300060520979211.
11. Hamilton AL, Killian KJ, Summers E, et al. Muscle strength, symptom intensity, and exercise capacity in patients with cardiorespiratory disorders. *Am J Respir Crit Care Med* 1995;152:2021-231.
12. de Medeiros AIC, Fuzari HKB, Rattesa C, et al. Inspiratory muscle training improves respiratory muscle strength, functional capacity and quality of life in patients with chronic kidney disease: a systematic review. *J Physiother* 2017;63:76-83.
13. McConnell A. Respiratory muscle training: theory and practice. *Respiratory Muscle Training: Theory and Practice*. Elsevier Ltd; 2013:3-224.
14. Smith ER. The angina grading system of the Canadian Cardiovascular Society. *Can J Cardiol* 2002;18:439-42.
15. Rampidis GP, Benetos G, Benz DC, et al. A guide for Gensini Score calculation. *Atherosclerosis* 2019;287:181-3.
16. Serruys PW, Onuma Y, Garg S, et al. Assessment of the SYNTAX score in the Syntax study. *EuroIntervention* 2009;5:50-6.
17. Ong AT, Serruys PW, Mohr FW, et al. The synergy between percutaneous coronary intervention with Taxus and cardiac surgery (SYNTAX) study: design, rationale, and run-in phase. *Am Heart J* 2006;151:1194-204.
18. Schiller NB, Shah PM, Crawford M, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr* 1989;2:358-67.
19. Tei C. New non-invasive index for combined systolic and diastolic ventricular function. *J Cardiol* 1995;26:135-6.
20. Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the Eu-

ropean Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr* 2010;23:685-713.
21. Sicari R, Sironi AM, Petz R, et al. Pericardial rather than epicardial fat is a cardiometabolic risk marker: an MRI vs echo study. *J Am Soc Echocardiogr* 2011;24:1156-62.
22. Bruce RA, Blackmon Jr, Jones JW, et al. Exercising testing in adult normal subjects and cardiac patients. *Pediatrics* 1963;32:742-56.
23. Jetté M, Sidney K, Blümchen G. Metabolic equivalents (METS) in exercise testing, exercise prescription, and evaluation of functional capacity. *Clin Cardiol* 1990;13:555-65.
24. Mark DB, Hlatky MA, Harrell FE Jr, et al. Exercise treadmill score for predicting prognosis in coronary artery disease. *Ann Intern Med* 1987;106:793-800.
25. Chen MS, Blackstone EH, Pothier CE, et al. Heart rate recovery and impact of myocardial revascularization on long-term mortality. *Circulation* 2004;110:2851-7.
26. Ghaffari S, Kazemi B, Aliakbarzadeh P. Abnormal heart rate recovery after exercise predicts coronary artery disease severity. *Cardiol J* 2011;18:47-54.
27. Neves LM, Karsten M, Neves VR, et al. Respiratory muscle endurance is limited by lower ventilatory efficiency in post-myocardial infarction patients. *Braz J Phys Ther* 2014;18:1-8.
28. Walters MA. Management of chronic stable angina. *Crit Care Nurs Clin North Am* 2017;29:487-93.
29. Stergiopoulos K, Brown DL. Initial coronary stent implantation with medical therapy vs medical therapy alone for stable coronary artery disease: meta-analysis of randomized controlled trials. *Arch Intern Med* 2012;172:312-9.
30. Al-Lamee R, Thompson D, Dehbi HM, et al. Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial. *Lancet* 2018;391:31-40.
31. Hachamovitch R, Rozanski A, Shaw LJ, et al. Impact of ischaemia and scar on the therapeutic benefit derived from myocardial revascularization vs. medical therapy among patients undergoing stress-rest myocardial perfusion scintigraphy. *Eur Heart J* 2011; 32:1012-24.
32. Escaned J, Collet C, Ryan N, et al. Clinical outcomes of state-of-the-art percutaneous coronary revascularization in patients with de novo three vessel disease: 1-year results of the SYNTAX II study. *Eur Heart J* 2017;38:3124-34.
33. ISCHEMIA Trial Research Group, Maron DJ, Hochman JS, et al. International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial: rationale and design. *Am Heart J* 2018;201:124-35.
34. Maron DJ, Hochman JS, Reynolds HR, et al. Initial invasive or conservative strategy for stable coronary disease. *N Engl J Med* 2020;382:1395-407.
35. Long L, Anderson L, Dewhirst AM, et al. Exercise-based cardiac rehabilitation for adults with stable angina. *Cochrane Database Syst Rev* 2018;2:CD012786.
36. Long L, Anderson L, He J, et al. Exercise-based cardiac rehabilitation for stable angina: systematic review and meta-analysis. *Open Heart* 2019;6:e000989.
37. de Daly MB. Interactions between respiration and circulation. In: Cheniack NS, Widdicombe JG (eds). *Handbook of Physiology*. American Physiological Society: Bethesda, 1986:529-94.
38. Tyberg JV, Grant DA, Kingma I, et al. Effects of positive intrathoracic pressure on pulmonary and systemic hemodynamics. *Respir Physiol* 2000;119:171-9.
39. Oneda B, Ortega KC, Gusmão JL, et al. Sympathetic nerve activity is decreased during device-guided slow breathing. *Hypertens Res* 2010;33:708-12.
40. Bernardi L, Spadacini G, Bellwon J, et al. Effect of breathing rate on oxygen saturation and exercise performance in chronic heart failure. *Lancet* 1998;351:1308-11.
41. Vranish JR, Bailey EF. Inspiratory muscle training improves sleep and mitigates cardiovascular dysfunction in obstructive sleep apnea. *Sleep* 2016;39:1179-85.
42. de Abreu RM, Rehder-Santos P, Minatel V, et al. Effects of inspiratory muscle training on cardiovascular autonomic control: a systematic review. *Auton Neurosci* 2017;208:29-35.
43. Verrier RL, Tan A. Heart rate, autonomic markers, and cardiac mortality. *Heart Rhythm* 2009;6:68-75.
44. Mello PR, Guerra GM, Borile S, et al. Inspiratory muscle training reduces sympathetic nervous activity and improves inspiratory muscle weakness and quality of life in patients with chronic heart failure: a clinical trial. *J Cardiopulm Rehabil Prev* 2012; 32:255-61.
45. Kaul P, Naylor CD, Armstrong PW, et al. Assessment of activity status and survival according to the Canadian Cardiovascular Society angina classification. *Can J Cardiol* 2009;25:225-31.
46. Kodama S, Saito K, Tanaka S, et al. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. *JAMA* 2009; 301:2024-35.
47. Peteiro J, Monserrrat L, Piñeiro M, et al. Comparison of exercise echocardiography and the Duke treadmill score for risk stratification in patients with known or suspected coronary artery disease and normal resting electrocardiogram. *Am Heart J* 2006;151: 1324.e1-10.
48. van Hateren KJ, Landman GW, Logtenberg SJ, et al. Device-guided breathing exercises for the treatment of hypertension: an overview. *World J Cardiol* 2014;6:277-82.
49. Wang CH, Yang HW, Huang HL, et al. Long-term effect of device-guided slow breathing on blood pressure regulation and chronic inflammation in patients with essential hypertension using a wearable ECG device. *Acta Cardiol Sin* 2021;37:195-203.
50. Xu SK, Chen Y, Liu CY, et al. A randomized cross-over study on the blood pressure lowering effect of the combined passive head-up and -down movement with device-guided slow breathing. *Blood Press* 2019;28:291-9.
51. Cipriano GF, Cipriano G Jr, Santos FV, et al. Current insights of inspiratory muscle training on the cardiovascular system: a systematic review with meta-analysis. *Integr Blood Press Control* 2019;12:1-11.

52. Yoo WG. Effects of combined chest expansion and breathing exercises in a patient with sternal pain. *J Phys Ther Sci* 2017; 29:1706-7.
53. Potts SG, Lewin R, Fox KA, et al. Group psychological treatment for chest pain with normal coronary arteries. *QJM* 1999;92:81-6.
54. Qiu K, Wang J, Chen B, et al. The effect of breathing exercises on patients with GERD: a meta-analysis. *Ann Palliat Med* 2020;9: 405-13.
55. Jafari H, Gholamrezaei A, Franssen M, et al. Can slow deep breathing reduce pain? An experimental study exploring mechanisms. *J Pain* 2020;21:1018-30.
56. Muammer K, Mutluay F, Demir R, et al. Effects of peripheral and different inspiratory muscle training methods in coronary artery disease patients with metabolic syndrome: a randomized-controlled trial. *Respir Med* 2020;172:106119.
57. Kannankeril PJ, Le FK, Kadish AH, et al. Parasympathetic effects on heart rate recovery after exercise. *J Investig Med* 2004;52: 394-401.
58. Tharion E, Samuel P, Rajalakshmi R, et al. Influence of deep breathing exercise on spontaneous respiratory rate and heart rate variability: a randomized controlled trial in healthy subjects. *Indian J Physiol Pharmacol* 2012;56:80-7.