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SCIENTIFIC INVESTIGATIONS

The beneficial impact of cardiac rehabilitation on obstructive sleep apnea in patients with coronary artery disease

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Study Objectives: To assess the impact of cardiac rehabilitation for decreasing sleep-disordered breathing in patients with coronary artery disease.

Methods: The study included 121 patients aged 60.01 ± 10.08 years, 101 of whom were men, with an increased pretest probability of OSA. The cardiac rehabilitation program lasted 21–25 days. The improvement in cardiorespiratory fitness was assessed using the changes in peak metabolic equivalents, the maximal heart rate achieved, the proportion of the age- and sex-predicted maximal heart rate, and the Six-Minute Walk Test distance. Level 3 portable sleep tests with respiratory event index assessments were performed in 113 patients on admission and discharge.

Results: Increases were achieved in metabolic equivalents (Δ1.20; 95% confidence interval [CI], 0.95–1.40; $P < .0001$), maximal heart rate (–Δ7.5 beats per minute; 95% CI, 5.00–10.50; $P < .0001$), proportion of age- and sex-predicted maximal heart rate (Δ5.50%; 95% CI, 4.00–7.50; $P < .0001$), and the Six-Minute Walk Test distance (Δ91.00 m; 95% CI, 62.50–120.00; $P < .0001$). Sleep-disordered breathing was diagnosed in 94 (83.19%) patients: moderate in 28 (24.8%) patients and severe in 27 (23.9%) patients, with a respiratory event index of 19.75 (interquartile range, 17.20–24.00) and 47.50 (interquartile range, 35.96–56.78), respectively. OSA was dominant in 90.40% of patients. The respiratory event index reduction achieved in the sleep-disordered breathing group was –Δ3.65 (95% CI, –6.30 to –1.25; $P = .003$) and was in parallel to the improvement in cardiorespiratory fitness in the subgroups with the highest effort load and with severe sleep-disordered breathing: –Δ6.40 (95% CI, –11.40 to –1.90; $P = .03$) and –Δ11.00 (95% CI, –18.65 to –4.40; $P = .003$), respectively.

Conclusions: High-intensity exercise training during cardiac rehabilitation resulted in a significant decrease in OSA, when severe, in parallel with an improvement in cardiorespiratory fitness in patients with coronary artery disease.

Keywords: OSA, coronary artery disease, cardiac rehabilitation, cardiorespiratory fitness

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BRIEF SUMMARY

Current Knowledge/Study Rationale: The coexistence of sleep-disordered breathing (SDB) in patients with coronary artery disease is a prognostically negative phenomenon. The early diagnosis and treatment of sleep apnea and lifestyle changes can reduce the morbidity and mortality that result from coronary artery disease.

Study Impact: High-intensity exercise training, when conducted as a part of the cardiac rehabilitation program, results in both improved cardiorespiratory fitness and a reduced respiratory event index in patients with coronary artery disease and accompanying severe OSA. The validity of physical activity in the primary and secondary prevention of cardiovascular diseases has long been established, so an improvement in sleep-disordered breathing because of rehabilitation provides an additional benefit in patients with coronary artery disease.

INTRODUCTION

The presence of sleep-disordered breathing (SDB), which includes both OSA and central sleep apnea (CSA), is common in patients with coronary artery disease (CAD)[1–3] and is independently associated with all-cause mortality and CAD-related mortality.[4–7] OSA, the most commonly diagnosed pathology, contributes to the pathogenesis of CAD[1,8–10] and other cardiovascular (CV) diseases, such as refractory arterial hypertension, arrhythmia and conduction disorders, ischemic stroke, chronic heart failure (HF), and pulmonary hypertension.[9,10]

The treatment of OSA, as evaluated by the reduction of AHI, improves CV outcomes.[7,11,12] However, patients' long-term adherence to treatment with CPAP devices, the gold standard for patients with CV diseases experiencing moderate to severe OSA,[13,14] is often far from optimal.[7]

Physical activity may also improve breathing capacity through its effects on the respiratory rate, a reduced volume of the physiological dead space, increased chest flexibility, strength and endurance of the upper-airway dilators and respiratory muscles, improved oxidative capacity,[15,16] and prevention of lower-extremity fluid accumulation,[3,17,18] which may be conducive to reducing respiratory incidents during sleep.

Thus, supervised exercise training during the cardiac rehabilitation (CR) program could become an effective therapeutic tool in a large group of patients with coexisting CAD and SDB and be crucial to improving the outcome, whether CPAP is applied or not.[19–22] This study aimed to assess the effect of CR on SDB in patients with CAD.

METHODS

The study was conducted between May 2018 and April 2019. It included 185 out of 293 consecutive patients in CR departments from both the day and the inpatient departments among whom an increased risk of OSA was found by using at least 1 of the following standardized risk scales or questionnaires: the STOP-Bang,[23] the 4-Variable Screening Tool,[24] the adjusted neck circumference,[25] and the Epworth Sleepiness Scale.[26] The study exclusion criteria were patients receiving current treatment of SDB with CPAP or intraoral devices and patients with a recent episode of worsening HF as the reason for CR.

Out of 185 participants who met the inclusion criteria, with CAD and a moderate or high pretest probability of OSA, 121 patients aged 60.01 ± 10.08 years, including 101 (83.47%) men and 20 (16.53%) women, were included in the CR program and agreed to undergo polysomnographic diagnostics.

The patients participated in an early CR program.[27] The qualification evaluation for CR was conducted by a cardiology specialist experienced in the field of CR. It was based on (1) the assessment of medical records for the completeness of coronary revascularization, (2) a physical examination with an assessment of the signs and symptoms of circulatory decompensation, (3) an echocardiographic examination with left ventricular ejection fraction (LVEF) assessment, and (4) results of an on-admission treadmill or cyclo-ergometer stress test (EST) with an assessment of coronary flow reserve and exercise capacity. Patients with pulmonary congestion and peripheral edema or signs of ischemia during the EST were referred for retreatment in the cardiology department and did not join the exercise program.

The CR program was carried out in patients with a coronary event and/or coronary revascularization and was started 7–28 days after discharge from the cardiology department. Classes were held 5 (in outpatient settings) or 6 (in inpatient settings) days a week for 21 and 25 days, respectively. Patients qualified for 1 of 4 rehabilitation models (A–D) based on the initial comprehensive assessment of both submaximal cardiorespiratory fitness (CRF)[28] and CV risk and comorbidities according to the recommendations of the Polish Society of Cardiology.[27] The submaximal CRF was defined in metabolic equivalents (METs; 1 MET ≈ 3.5 mL/kg/min)[29] and evaluated using treadmill speed and grade at the end of the submaximal EST. Participants exercised up to an 85% age- and sex-predicted MHR. All tests were conducted using a progressive incremental protocol. For patients who exercised on the cycle ergometer (21.9%), exercise time and final work rate in watts were recorded, and the latter was converted into an estimated MET.[30]

Patients who qualified for model A had a high effort tolerance and achieved a submaximal CRF ≥ 7 METs. They also had a low risk of repeated CV incidents. Patients who qualified for model B had a high or moderate exercise capacity, a moderately high risk of repeated CV incidents, and a submaximal CRF ≥ 5 METs. Patients who qualified for models A and B participated in the CR program in the outpatient rehabilitation department. In the inpatient department, hospitalized patients qualified for models C and D. Rehabilitation model C included patients with a low exercise tolerance, a moderate or high CV risk, and a submaximal CRF ≥ 3 METs. Those who qualified for model D were characterized by advanced HF and an LVEF ≤ 35% of the New York Heart Association (NYHA) performance class III, a low activity tolerance (expressed as < 300 m distance in the 6-Minute Walk Test [6MWT]), a submaximal CRF < 3 METs) or a high risk of repeated CV incidents, and usually numerous comorbidities.

The characteristics of the cardiorespiratory exercise program parameters according to the rehabilitation model are presented in **Table 1.** Both individual and group classes were conducted with a psychotherapist and a dietitian in all models to introduce lifestyle changes. The CR program effect was assessed using the change in CRF expressed in METs, the MHR achieved (measured in beats per minute), and a proportion of the proportion of age- and sex-predicted MHR in the EST, determined at the beginning and end of the exercise cycle. Furthermore, the 6MWT distance and fatigue levels during exercise were evaluated using the Borg Rate of Perceived Exertion scale.

Regardless of which CR model was used, type III portable polysomnography using an Alice PDx (Philips Respironics, Murrysville, PA) or Alice NightOne (Philips Respironics, Murrysville, PA) device was performed twice: upon admission to the department and in the last week of CR. The polysomnographic analysis was conducted per the recommendations of the American Academy of Sleep Medicine.[31]

Sleep apnea was defined as the complete cessation of airflow through the respiratory tract or its reduction by ≥ 90%, with a duration of ≥ 10 seconds. Episodes of apnea with preserved respiratory muscle function were classified as OSA, as opposed to CSA, which was characterized by a lack of both chest and abdominal respiratory movement. A decrease in airflow through the airways by ≥ 30% with a duration of ≥ 10 seconds leading to a decrease in hemoglobin oxygen saturation of ≥ 4% was considered to be an episode of sleep hypopnea. Individuals were diagnosed as having sleep apnea-hypopnea syndrome if the hourly rate of apnea and/or hypopnea (measured using the respiratory event index [REI]) was > 4, with an REI of 5–14 indicating mild, 15–29 indicating moderate, and ≥ 30 indicating a severe form of the disease.

The institutional review board of the Medical University of Silesia in Katowice, Poland, approved the study. All patients gave their informed written consent to participate in the research project.

The results were statistically analyzed using MedCalc version 19.0.3 software (MedCalc, Ostend, Belgium). The quantitative parameters were presented by arithmetic mean and standard deviation or median and interquartile range (IQR). Qualitative data were expressed in percentages. The univariate analysis was carried out using (1) an assessment of the significance of differences for samples of dependent variables with the Student *t* test/univariate analysis of variance and the

Table 1—Characteristics of the cardiorespiratory exercise program parameters, according to the rehabilitation model.

	Rehabilitation Model			
	A	B	C	D
Number of patients	39 (32.5%)	49 (40.8%)	28 (23.3%)	4 (3.3%)
Baseline CRF	≥ 7 METs/100 W during EST	≥5 METs/75 W during EST	≥3 METs/50 W during EST	< 300 m in 6MWT
Type of training	Continuous exercises in cyclo-ergometric physical training	Continuous/interval exercises in cyclo-ergometric physical training	Interval exercises in cyclo-ergometric physical training	Individual exercises only
	Series of resistance exercises	Elements of resistance training		
	General fitness, breathing exercises, individual training			
Frequency	5 d/wk	5 d/wk	6 d/wk	6 d/wk
Total duration of physical training	60 min/d	45–60 min/d	45–60 min/d	30 min/d
Intensity of physical exercises	50%–70% of maximum effort load during initial EST	50% of maximum effort load during initial EST	40%–50% of maximum effort load during initial EST	10%–15% increase in baseline heart rate

CRF = cardiorespiratory fitness, EST = exercise stress test, METs = metabolic equivalents, 6MWT = 6-Minute Walk Test, W = watts.

Wilcoxon test/Kruskal-Wallis test, respectively, for the number and distribution of variables; and (2) linear and logistic regression analyses, according to the nature of the variables. The change in respiratory parameters was analyzed jointly for the whole group and in subgroups, depending on the baseline SDB severity and exercise effort load (according to the rehabilitation model). A P value < .05 was used as the significance level limit in the tests conducted.

RESULTS

The anthropometric parameters and characteristics of the population studied in terms of coexisting diseases and the pharmacological treatment applied, for the entire group and for those divided by CR model, are presented in **Table 2.** At admission, the average LVEF in the whole group was 55.0% (45.0–60.0), and 109 (90.08%) patients were in NYHA functional classes I or II. The definition of ischemic heart failure with an LVEF reduced below 40% (HFrEF) was met by only 8 (6.8%) participants. Data on the LVEF and mean baseline exercise capacity parameters of patients undergoing rehabilitation according to each model are presented in **Table 3.**

Level 3 portable sleep tests were performed in 113 patients. Sleep apnea was diagnosed in 94 (83.19%) patients, including 39 (34.51%) patients with sleep apnea of a mild nature with a median REI of 9.1 events/h (IQR, 6.83–11.18), 28 (24.8%) patients with sleep apnea of a moderate nature with an REI of 19.75 events/h (IQR, 17.20–24.00), and 27 (23.9%) patients with sleep apnea of a severe nature with an REI of 47.50 events/h (IQR, 35.96–56.78). OSA was dominant and was found in 90.40% of patients with SDB. The dominant type of SDB was OSA in the subgroup of patients with HFrEF, which accounted for 71.4% of patients with apnea. **Table 4** presents the characteristics of the SDB.

There were no differences in the baseline objective and self-reported parameters of CRF evaluation between the group of patients with moderate/severe sleep apnea and the patients in the entire study group. The maximal level of oxygen usage in METs was 7.6 in patients with moderate/severe sleep apnea (IQR, 6.1–9.5) vs 7.4 in the patients in the entire study group (IQR, 6.4–9.5; P = .82), respectively; the distance in the 6MWT was 638.5 meters (IQR, 496.0–798.5) vs 654.0 meters (IQR, 536.0–798.5; P = .47), respectively; and fatigue in the RPE scale was 14.0 (IQR, 14.0–16.0) vs 14.0 (IQR, 14.0–15.0; P = .79), respectively.

In the whole study group, significant improvements in CRF were achieved: from 7.45 (IQR, 5.85–9.50) to 9.00 METs (IQR, 6.90–10.65) with P < .0001 (Δ1.20; 95% CI, 0.95–1.40); MHR increasing from 119.00 (IQR, 108.00–131.50) to 128.00 beats per minute (IQR, 118.50–141.00) with P < .0001 (Δ7.5 beats per minute; 95% CI, 5.00–10.50); proportion of age- and sex-predicted MHR increasing from 78.00% (IQR, 70.00–85.00) to 83.00% (IQR, 78.00–87.00) with P < .0001 (Δ5.50%; 95% CI, 4.00–7.50); the 6MWT increasing from 654.00 (IQR, 534.50–818.00) to 729.00 meters (IQR, 580.25–930.25) with P < .0001 (Δ91.00 meters; 95% CI, 62.50–120.00), and a change in NYHA classification by 1 level in 28 participants (P < .0001; **Figure 1A, Figure 1B, Figure 1C, Figure 1D**). The increase in CRF was visible in the group of patients from the A, B, and C models: from 9.5 (IQR, 9.0–10.2) to 10.9 METs (IQR, 9.8–12.1) with P < .0001 (Δ1.4; 95% CI, 1.10–1.80) for model A; from 6.9 (IQR, 6.6–7.7) to 8.5 METs (IQR, 7.3–9.5) with P < .0001 (Δ1.20; 95% CI, 0.85–1.50) for model B; and from 4.20 (IQR, 3.70–4.60) to 4.70 METs (IQR, 4.20–6.50) with P = .004 (Δ0.80; 95% CI, 0.30–1.50) for model C. The number of patients in model D, in whom the follow-up load tests were performed, was insufficient for statistical analysis.

In parallel to the growth in CRF, there was also a reduction in REI achieved in all patients with SDB, from 19.05 (IQR, 9.80–35.50) to 16.95 events/h (IQR, 8.80–26.40) with P = .003 (–Δ3.65; 95% CI, –6.30 to –1.25; **Figure 2A**); in the subgroup with severe apnea, from 47.50 (IQR, 35.70–55.80) to 38.35 events/h (IQR, 23.10–47.40) with P = .03 (–Δ11.00; 95% CI, –18.65 to –4.40; **Figure 2B**); and in the subgroup with SDB rehabilitated according to model A who underwent a high-intensity

Table 2—Characteristics of anthropometric parameters, coexisting diseases, and treatment applied, according to rehabilitation model.

	All Participants	Rehabilitation Model				*P* Value*
		A	B	C	D	
Number of patients	121	39 (32.5)	49 (40.8)	28 (23.3)	4 (3.3)	
Age (y)	60.0 ± 10.1	56.7 ± 8.5	60.3 ± 10.4	63.6 ± 11.1	62.8 ± 5.7	.045 [1]
Sex (male)	100 (82.6)	39 (100)	36 (73.5)	22 (78.6)	3 (75.0)	.008
Height (m)	1.72 ± 0.08	1.74 ± 0.07	1.71 ± 0.08	1.71 ± 0.08	1.75 ± 0.10	.20
Body weight (kg)	88.7 ± 14.9	85.5 ± 12.8	90.9 ± 17.0	88.1 ± 13.7	99.5 ± 8.4	.18
BMI (kg/m^2)#	29.3 (26.3–33.3)	27.3 (26.0–30.0)	30.2 (26.6–34.9)	29.5 (26.1–34.6)	31.0 (29.8–35.7)	.05 [2]
Neck (cm)#	42.0 (40.9–44.5)	42.0 (41.0–45.5)	42.0 (41.0–45.0)	43.0 (40.0–44.0)	42.5 (41.0–43.5)	> .99
MI	109 (90.1)	38 (97.4)	43 (87.8)	24 (83.9)	4 (100.0)	.35
Hypertension	95 (78.5)	28 (71.8)	43 (87.8)	21 (77.8)	3 (75.0)	.31
HFrEF	8 (6.6)	0 (0.0)	1 (2.1)	4 (15.4)	3 (75.0)	< .0001
AF	10 (8.3)	0 (0.0)	2 (4.1)	8 (29.6)	0 (0.0)	< .0001
CNS stroke	4 (3.3)	2 (5.1)	0 (0.0)	2 (7.4)	0 (0.0)	.31
COPD	6 (5.0)	0 (0.0)	4 (8.2)	2 (7.4)	0 (0.0)	.31
Diabetes	31 (25.6)	4 (10.3)	13 (26.5)	11 (40.7)	3 (75.0)	.005
Beta-blockers	109 (90.1)	35 (89.7)	47 (97.9)	23 (95.8)	4 (100)	.36
ACE-I/ARB	108 (89.2)	37 (94.9)	48 (100)	21 (87.5)	2 (50.0)	.0004
MRA	33 (27.3)	5 (12.8)	12 (25.0)	14 (58.3)	2 (50.0)	.001
Loop diuretics	18 (14.9)	2 (5.1)	4 (8.3)	9 (37.5)	3 (75.0)	< .0001
Thiazide diuretics	15 (12.4)	4 (10.3)	6 (12.5)	5 (20.8)	0 (0.0)	.54

All items in parentheses are percentages except as noted. #Continuous variables presented as median and interquartile range. **P* value for differences between models A–D. [1]*P* < .05 for A vs. C. [2]*P* < .05 for A vs. B. ACE-I = angiotensin-converting enzyme inhibitors, AF = atrial fibrillation, ARB = angiotensin receptor antagonists, BMI = body mass index, CNS = central nervous system, COPD = chronic obstructive pulmonary disease, HFrEF = heart failure with left ventricular ejection fraction < 40%, MI = myocardial infarction, MRA = mineralocorticoid receptor antagonists, neck = neck circumference.

Table 3—Characteristics of LVEF and baseline exercise capacity parameters, according to rehabilitation model.

	All Participants	Rehabilitation Model				*P* Value*
		A	B	C	D	
Number of patients (%)	121	39 (32.5)	49 (40.8)	28 (23.3)	4 (3.3)	
LVEF#	55.0 (45.0–60.0)	55.0 (52.0–60.0)	55.0 (48.0–57.5)	45.0 (42.0–55.0)	22.5 (17.5–32.5)	< .001 [1]
NYHA I class (%)	47 (38.8)	27 (69.2)	13 (26.5)	7 (25.0)	0 (0.0)	< .001
NYHA II class (%)	62 (54.2)	12 (30.8)	33 (67.3)	16 (57.1)	1 (33.3)	
NYHA III class (%)	10 (8.3)	0 (0.0)	3 (6.1)	5 (17.9)	2 (66.7)	
6MWT (m)#	627.0 (514–794)	840.0 (753–948)	583.5 (527– 661)	325.0 (247–451)	218.0 (146–290)	< .001 [2]
METs#	7.2 (5.9–9.5)	9.5 (9.0–10.4)	6.9 (6.6–7.6)	4.2 (3.8–4.9)	3.2 (3.1–3.2)	< .001 [2]
Fatigue levels in RPE scale#	14.0 (14.0–16.0)	14.0 (14.0–16.0)	14.0 (14.0–16.0)	14.0 (12.0–15.5)	11.05 (9.5–13.5)	.01 [3]
MHR (bpm)	120 ± 16.5	130 ± 14.5	117 ± 13.1	112.2 ± 17.7	98.0 ± 16.5	< .001 [4]
MHR% (%)	77.6 ± 9.8	81.5 ± 8.5	74.8 ± 9.0	77.3 ± 11.8	76.3 ± 9.0	0.01 [4]

All items in parentheses are percentages except as noted. #Continuous variables presented as median and interquartile range. **P* value for differences between groups A–D. [1]*P* < .05 for A vs. B vs. C vs. D. [2]*P* < .05 for A vs. B vs. C. [3]*P* < .05 for C vs. D. [4]*P* < .05 for A vs. B. bpm = heartbeats per minute, LVEF = left ventricular ejection fraction, METs = metabolic equivalents, MHR = maximal heart rate, MHR% = proportion of age- and sex-based predictions of maximal heart rate, NYHA = New York Heart Association, RPE scale = Borg Rate of Perceived Exertion scale, 6MWT = 6-Minute Walk Test.

exercise training program with a load of 5.0–6.5 METs or 50%–70% of the maximum effort load during the initial EST, from 20.0 (IQR, 11.8–29.6) to 15.2 events/h (IQR, 8.6–19.9) with $P = .003$ (–Δ6.4; 95% CI, –11.40 to –1.90; **Figure 2C**), with no baseline difference in REI between the A–D subgroups, $P = .73$.

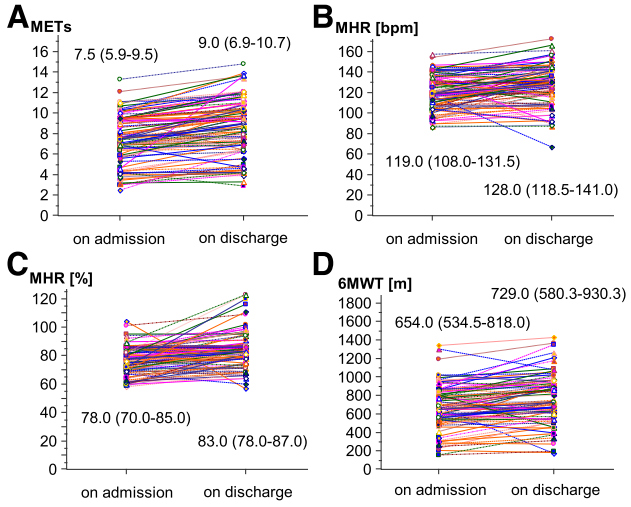
In the subgroup with moderate apnea, a trend toward an improvement in REI was observed, from 20.00 (IQR, 17.90–23.95) to 17.90 events/h (IQR, 13.58–22.35) with $P = .08$ (–Δ3.35; 95% CI, –4.50 to 0.45). There was no significant change in REI events/h in the group of patients with mild sleep apnea (–Δ0.40;

Table 4—Characteristics of SDB, according to rehabilitation model.

	All Participants	Rehabilitation Model				*P* Value*
		A	B	C	D	
Number of patients (%)	113	38 (33.6)	46 (40.7)	25 (22.1)	4 (3.5)	—
REI (events/h)#	14.1 (6.8–29.4)	14.8 (9.3–29.2)	11.4 (5.9–33.6)	17.6 (6.7–26.3)	17.3 (8.5–36.8)	.73
Participants with OSA/CSA (%)	85 (75.2%)/8 (7.1%)	32 (84.2)/1 (2.6)	31 (67.4)/4 (8.7)	20 (95.2)/1 (4.8)	2 (50.0)/2 (50.0)	.05
Average episode duration (sec)#	21.0 (18.1–25.5)	21.3 (19.3–24.7)	19.7 (16.9–24.5)	24.0 (19.8–27.2)	24.5 (21.2–28.5)	.11
Maximum episode duration (sec)#	59.3 (43.3–87.8)	67.8 (44.0–90.0)	54.5 (35.8–82.1)	58.5 (45.8–89.6)	79.3 (55.0–116.8)	.36
Average SpO_2 (%)#	93.0 (91.0–94.0)	93.0 (91.0–94.0)	92.0 (91.0–94.0)	92.0 (89.8–93.2)	93.5 (92.5–94.5)	.24
Minimal SpO_2 (%)#	84.0 (80.5–88.0)	850.0 (82.0–88.0)	85.0 (78.8–88.0)	83.0 (79.5–84.5)	82.0 (70.0–84.0)	.09
Time spent with SpO_2 < 90% (minimum)#	14.6 (3.2–40.6)	11.2 (2.2–35.2)	18.2 (1.3–45.5)	18.8 (5.6–87.0)	50.8 (21.2–80.3)	.36
TST 90 (%)#	4.5 (0.3–18.9)	2.9 (0.3–10.7)	5.1 (0.1–18.4)	6.8 (1.1–35.6)	2.4 (0.9–5.6)	.42
Time spent with SpO_2 < 85% (minimum)#	0.1 (0.0–2.9)	0.0 (0.0–1.2)	0.1 (0.0–3.6)	0.2 (0.0–16.3)	0.0 (0.0–0.0)	.24
TST 85 (%)#	0.0 (0.0–0.7)	0.0 (0.0–0.2)	0.0 (0.0–0.9)	0.1 (0.0–5.5)	0.1 (0.0–0.1)	.12
Sleepiness on ESS#	7.0 (3.0–10.0)	6.5 (3.0–9.0)	6.5 (4.0–9.0)	7.0 (4.3–10.0)	11.5 (7.00–14.0)	.49

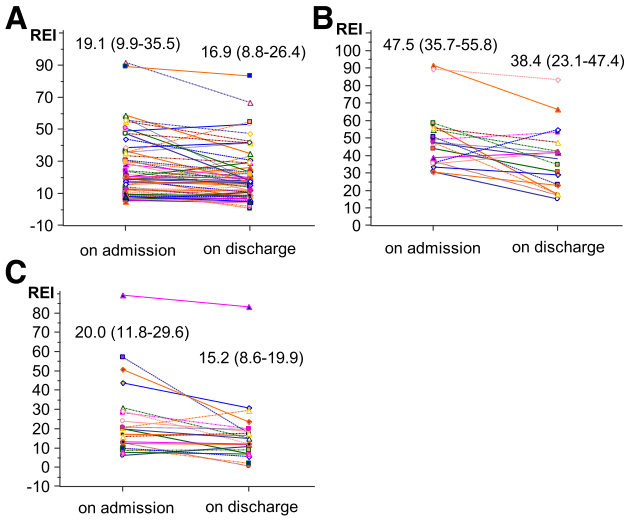
#Continuous variables presented as median and interquartile range (in parentheses). **P* value for differences between groups A–D. [1]*P* < .05 for A vs. B vs. C vs. D. [2]*P* < .05 for A vs. B vs. C. [3]*P* < .05 for C vs. D. [4]*P* < .05 for A vs. B. CSA = central sleep apnea, ESS = Epworth Sleepiness Scale, REI = respiratory event index, SpO_2 = arterial oxygen saturation estimated by pulse oximetry, TST 85 = percentage of total sleep time with oxyhemoglobin saturation below 85%, TST 90 = percentage of total sleep time with oxyhemoglobin saturation below 90%.

Figure 1—Improvement in CRF parameters (entire group of patients).



(A) ΔMET. **(B)** ΔMHR. **(C)** ΔMHR%. **(D)** Δ6MWT. The lines show the changes in parameters over time for each of the patients. The values given reflect the median and interquartile range (in parentheses) for the parameter under study at two time points. CRF = cardiorespiratory fitness, METs = metabolic equivalents, MHR = maximal heart rate, MHR% = proportion of the age- and sex-predicted maximal heart rate, on admission = the start of the rehabilitation program, on discharge = the end of the rehabilitation program, 6MWT = 6-Minute Walk Test.

Figure 2—Reduction in REI.



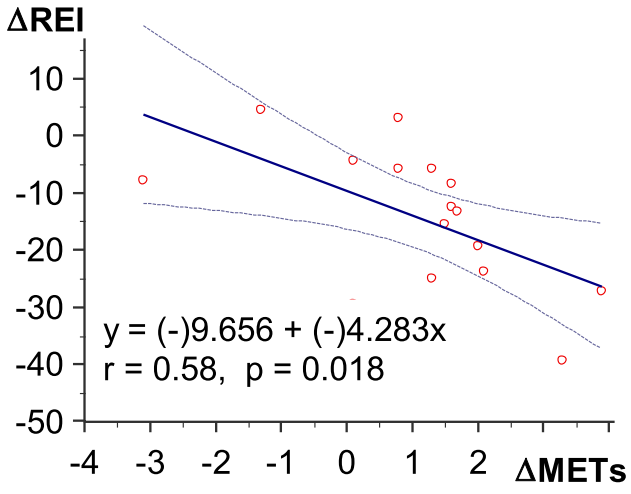
(A) The entire group. **(B)** Severe SDB group. **(C)** Model A group. The lines show the changes in parameters over time for each of the patients. The values given reflect the median and interquartile range (in parentheses) for the REI at two time points for the entire group, the group with severe SBD, and the group rehabilitated by model A, respectively. on admission = the start of the rehabilitation program, on discharge = the end of the rehabilitation program, REI = respiratory event index, SDB = sleep-disordered breathing.

95% CI, –2.40 to 1.95), *P* = .69. Similarly, patients undergoing exercise with less effort load did not achieve a significant REI reduction: –Δ2.65 events/h (95% CI, –6.75 to 1.50; *P* = .20) for model B, and –Δ1.00 events/h (95% CI, –7.10 to 4.15; *P* = .84) for model C. As with the CFR assessment, the number of patients in model D was insufficient for statistical analysis.

In 65 patients who underwent both EST with METs assessment and polysomnography at the beginning and end of the CR program, a directly proportional relationship between improvements in sleep apnea respiratory parameters (expressed in REI) and CRF (expressed in METs) was found in the subgroup with initially severe sleep apnea (*P* = .004; **Figure 3**). In 7 patients (ie, 25.96% of the patients with severe apnea), the improvement resulted in a change in their sleep apnea qualifications from severe to moderate.

The participants' ages did not influence the initial REI value or its degree of improvement after CR: *P* = .33 and *P* = .49, respectively.

Figure 3—The relationship between the improved REI and METs in patients with initially severe sleep apnea.



METs = metabolic equivalents, REI = respiratory event index.

In the entire study group, there were no differences between the percentage of OSA and CSA and mixed sleep apnea episodes in relation to the number of all apnea episodes on admission and on discharge: for OSA, –Δ0.55 (95% CI, –8.15 to 3.20; $P = .70$); for CSA, Δ0.65 (95% CI, –1.61 to 5.23; $P = .47$); and for mixed sleep apnea, Δ0.00 (95% CI, –1.49 to 2.39; $P = .87$), respectively. Only in the subgroup of patients with HFrEF who were rehabilitated according to models C or D was there a trend toward a reduction in the percentage of central episodes, from 7.32% (IQR, 3.47–46.09) to 0.00% (IQR, 0.00–4.43; $P = .06$), but without improvement in REI ($P = .63$).

In the observed group, after the CR cycle, there was no difference in the severity of daytime sleepiness (–Δ0.5; 95% CI, –2.0 to 0.5; $P = .30$) and other respiratory parameters, such as the mean and minimum oxygen saturation of the blood (Δ0.00%; 95% CI, –0.50 to 0.50; $P = .89$ and Δ0.50%; 95% CI, 0.00–1.50; $P = 1.17$, respectively) or the percentage of total sleep time with oxyhemoglobin saturation below 85% and below 90% (Δ0.00%; 95% CI, –0.02 to 0.02; $P = .86$ and –Δ0.39%; 95% CI, –2.25 to 0.68; $P = .45$, respectively). However, there was significantly lower minimal saturation during sleep (79.00%; IQR, 74.25–84.00; $P = .0004$), and there was a higher percentage of total sleep time with oxyhemoglobin saturation below 90% (17.06%; IQR, 5.92–34.16; $P = .001$) and below 85% (0.64%; IQR, 0.02–3.75; $P = .00008$) in the group of patients with severe SDB as compared with the patients with mild/moderate apnea. No body weight loss was observed in the studied patients during rehabilitation ($P = .13$).

DISCUSSION

Numerous mechanisms associated with endurance exercise training have a beneficial effect on the cardiovascular system. Examples of such adaptations are, inter alia, nitric oxide–mediated changes in coronary and peripheral vascular resistance, reduction in sympathetic nerve tone, improvement in endothelial function, suppression of inflammation, and blood clotting.[32] These mechanisms lead to an improvement in systolic and diastolic left ventricular function and cardiac output, reduce resting heart rate and blood pressure, and reduce the risk of cardiac arrhythmias. Therefore, physical activity seems to be a crucial element in reducing CV risk in the secondary prevention of CV diseases.[33,34] The National Health Fund, the obligatory health insurer in Poland, makes early CR available after a CV incident as part of a program for patients with CAD.

We found that in patients with CAD and severe OSA, 4 weeks of exercise training, conducted as a part of the CR program, resulted in both improvement in CRF and in a reduction of REI. Furthermore, REI reduction was achieved in parallel with improvement in CRF in subgroups with the highest effort load. The coexistence of severe OSA in patients with CAD is a prognostically negative phenomenon.[4,5,7] One cannot exclude the possibility that a reduction in the severity of OSA caused by CR contributes to the rehabilitation-induced improvement of patients' prognosis in CAD.

The assumption of causation in the improvement of exercise capacity by exercise rehabilitation in different clinical settings, including recovery from a cardiac event, has been presented in earlier research.[35–37] In a meta-analysis of international studies involving 3,827 patients by Sandercock, Hurtado, et al,[35] CR produced a Δ1.6 MET (95% CI, 1.22–1.89) increase in fitness ($P < .001$). A significant improvement was also observed in groups of patients rehabilitated for ≤ 12 weeks and amounted to Δ1.0 MET (95% CI, 0.81–1.18; $P < .001$). In a multicenter study conducted in the United Kingdom[36] during a standard CR program lasting 6–8 weeks, an increase in CRF of 0.4–0.7 METs was obtained, depending on the clinical center. A Polish study[37] conducted on the basis of a standard CR program after myocardial infarction (4–6 weeks) documented a significant increase in energy expenditure during the cardiopulmonary exercise test from 9.4–11.8 METs and an increase in peak oxygen uptake (VO_2 peak) from 32.3 to 39.3 mL/kg/min ($P < .001$). The above results are in line with our study, in which as a result of the CR program we obtained a Δ1.20 increase (95% CI, 0.95–1.40; $P < .0001$) in METs with an average of 11.35% (IQR, 6.42–21.30). The increased activity tolerance was also reflected in an increase in the 6MWT distance of Δ91.00 meters (95% CI, 62.50–120.00; $P < .0001$) with an average of 11.38% (IQR, 1.62–23.00), and an improvement in NYHA performance class by 1 level in 23.14% of patients (28 patients).

In parallel, a significant reduction in REI was achieved in the whole group with SDB, mostly experiencing OSA (–Δ3.65 events/h; 95% CI, –6.30 to –1.25; $P = .003$; a 13.10% reduction in AHI from baseline: IQR, –10.79 to 40.14) and in patients with severe sleep apnea (–Δ11.00 events/h; 95% CI, –18.65 to –4.40; $P = 0.03$; a 23.92% reduction in AHI from baseline: IQR, 6.61 to [minus symbol]50.65. Notably, a positive CR effect was found in patients eligible for CPAP therapy. In 25.96% of patients with severe OSA, the improvement resulted in the reclassification of their apnea from severe to moderate. This finding bolsters the hope of reducing CV mortality.[4–6] The REI reduction in this group of patients was directly proportional to the improvement of CRF expressed in METs. It is worth noting that the REI decrease in the presented study was observed

only in the model A rehabilitation group (patients with an exercise capacity ≥ 7 METs and the ability to do continuous exercise with a minimal load of 50–70 watts). In addition, in the study by Hupin et al,[3] a reduction in AHI was obtained in the group of patients with the greatest improvement in VO_2 peak of 24.9% and good adherence to the CR program. This finding suggests the need to implement intensive physical training to improve SDB.

Our observations are consistent with the results of 4 meta-analyses assessing the impact of rehabilitation programs and the promotion of daily physical activity outside medical facilities on OSA severity.[19–22] In the Iftikhar et al[22] meta-analysis of research from 2000–2011, a significant effect of exercise on CRF and the severity of OSA was achieved through 12 and 24 weeks of training on average for 3 days/week. The authors reported a 32% postintervention reduction in AHI (–Δ 6.3 events/h; 95% CI, –8.54 to –3.99; $P < .001$) related to a 17.7% increase in VO_2 peak (Δ3.9 mL/kg/min; 95% CI, 2.44–5.42; $P < .001$). In a systematic review including 354 patients from 8 subsequent studies (2011–2015) by Bollens and Reychler,[20] an observed reduction in AHI ranged from 2–17.4 events/h in one 12-week exercise program conducted 3–7 times a week. An increase in VO_2 peak, MET, and muscle strength was shown as a result of physical exercise. The effect of exercise training on sleep apnea was also shown in the Aiello et al[21] analysis of 182 participants as an odds ratio for improving AHI of 72.3 (95% CI, 27.91–187.49) in patients receiving exercise as treatment. Mendelson, Bailly, et al[19] described a mean decrease in AHI of 8.9 events/h (95% CI, –13.4 to –4.3; $P < .01$; a 28% reduction in AHI from baseline) with a parallel increase in VO_2 peak of 3.4 mL/kg/min (95% CI, 0.4–6.3; $P = .03$) in the largest group of participants (502) included in 8 studies in the years 2011–2016. In all these analyses,[19–22] AHI reduction was accompanied by an improvement in terms of daytime sleepiness, sleep efficiency, and/or quality of life, which is an added value to the exercise program.

The beneficial effect of 1 month of CR in patients with CAD and moderate-to-severe OSA also confirmed the findings of Redolfi, Bettinzoli, et al[17]; Mendelson, Lyons, et al[18]; and Hupin et al.[3] This group's respiratory parameter improvement during sleep can be associated with reduced fluid accumulation in the lower parts of the body during the day, thus reducing the amount of fluid shifting rostrally overnight. The diameter of the upper airway lumen was reduced by fluid accumulating in the cervical region, which increases resistance and predisposes the patient to obstructive apnea.[38] In healthy sedentary people, fluid accumulation is the result of venous stasis in the lower limbs while standing/sitting[39]; therefore, the overnight rostral fluid shift from the legs to the neck and lungs can be reduced by the work of the calf muscle pump during CR.[3,17,18] In turn, for people with HF, the rostral fluid shift may be exacerbated by ankle swelling. Therefore, one must consider the resolution of pulmonary congestion/edema connected with LVEF recovery and assisted by diuretic therapy as a cause of the improvement in sleep apnea in the HF group.[40–43]

In the presented group of patients, the best CR effect in terms of the reduction of respiratory events was obtained in the subgroup of patients rehabilitated according to model A. At the time of qualifying for the CR program, these patients had a very good exercise capacity of 9.5 METs (IQR, 9.0–10.4), a normal LVEF of 55.0% (IQR, 52.0–60.0), and no comorbidities. All patients in model A were in NYHA functional class I (27 patients; 69.2%) or II (12 patients; 30.8%). The percentage of use of loop diuretics was 5.1% (2 patients). However, the patients underwent a 21-day high-intensity exercise training program with a load of 5.0–6.5 METs, or 50%–70% of the maximum effort load during the initial EST and with REI reduction directly proportional to the improvement of CRF expressed in METs. Therefore, we concluded that the reduction of REI did not result from the recovery process associated with improvement of LVEF or with the resolution of pulmonary congestion and the use of diuretic therapy but rather was associated with improvement of exercise capacity as a result of CR.

In patients with HF, lung receptor irritation from the accumulating fluid caused hyperventilation and decreased partial CO_2 pressure, which favors the occurrence of CSA.[40–42] The lack of significant weight loss during the CR program furthermore speaks against the hypothesis of the resolution of circulatory decompensation features in connection with intensive diuretic treatment. In addition, no differences were found between the percentage of OSA and CSA episodes in relation to the number of all apnea episodes upoon admission and upon discharge in the whole study group and in a group of patients with HFrEF using loop diuretics, contradicting just such an explanation of the changes observed.

Similar to the study by Lombardi et al,[44] the majority of our patients with HFrEF rehabilitated according to models C and D had obstructive apnea, not central apnea. In this group, there was no reduction in REI achieved during the 4-week rehabilitation. In their study, Yamamoto et al[45] documented a significant reduction in AHI from 24.9 (IQR, 19.2–37.1) to 8.8 events/h (IQR, 5.3–10.1; $P < .01$) resulting from a decrease in the number of central apnea episodes rather than obstructive apnea, parallel to an improvement in CRF in a spiroergometric test and a decrease in the brain's natriuretic peptide levels in patients with stable HF and SDB after 6 months of aerobic training. On the contrary, Ueno et al[46] described a 36% reduction in AHI and a 5% improvement in the levels of minimum O_2 saturation during sleep only in patients with HF and OSA but also after a 4-month rehabilitation period. These periods of regular exercise are much longer than in our study, which may explain the lack of the effect of CR in our subgroup with HFrEF.

The combination of obesity/overweight and a sedentary lifestyle, which often occurs with CAD, is another reason for the reduction of exercise capacity[47] and the increase in SDB.[48,49] Obesity control remains the most effective long-term intervention to support SDB treatment, especially the treatment of OSA.[48] The loss of adipose tissue that has accumulated in the throat and neck contributes to the increase of lumen in the upper respiratory tract, and in parallel, the reduction of abdominal obesity reduces the pressure in the peritoneal cavity and improves the function of the diaphragm.[49] In addition, such a group of patients also has a chance to improve CRF and modify body composition (decrease fat mass but increase muscle mass) under the influence of exercise.[47] Although no weight loss was achieved in the short term in the present population, a meta-analysis of previous studies indicated that weight loss is not a prerequisite for improving respiratory parameters.[19,20,22] Patients with OSA

because of chronic fatigue, increased daytime sleepiness, and the accompanying low capacity of skeletal muscles have a lower chance of maintaining an active lifestyle without simultaneous intervention in terms of SDB. We found no differences in baseline maximal CRF in patients with moderate/severe SDB and others in the presented group. However, some researchers[50,51] have documented such differences in the population with OSA. Similarly, we did not find increased daytime sleepiness in patients after a CV incident and with significant OSA, as also described by Mehra et al[2] and Hupin et al.[3]

In our study, the achieved CR program REI reduction was not age-dependent, as reported by Torres-Castro et al[52] in their study based on an urban-walking program. We did not observe a significant reduction in REI in the subgroup of patients with mild sleep apnea but only a trend toward improvement in REI in the group with moderate severity of SDB. In a patient population with a small number of respiratory events, the variability in the number of apnea and hypopnea episodes on subsequent nights may be large enough and close to the variability in the number of episodes obtained as a result of physical rehabilitation; hence, rehabilitation's effect is difficult to show in a short period of time. Similar reports from Redolfi, Bettinzoli, et al[17]; Desplan et al[53]; and Hupin et al[3] on the effect of physical rehabilitation from SDB have indicated the highest reduction of AHI in groups with the highest intensity of disorders.

In the observed group, as in the meta-analysis by Bollens and Reychler[20] after the end of the rehabilitation cycle, there was no difference in respiratory parameters, such as the mean and minimum oxygen saturation of the blood. Unfortunately, the current study revealed significantly lower minimum saturation during sleep (79.00%; IQR, 74.25–84.00; $P = .0004$) and a higher percentage of total sleep time with oxyhemoglobin saturation below 90% (17.06%; IQR, 5.92–34.16; $P = .001$) in patients with severe SDB than in patients with mild/moderate apnea. These results may be of significant clinical importance because nocturnal desaturation, especially below 72%–78%, is a risk factor for the occurrence of ischemic events, arrhythmias and conduction disturbances, and sudden cardiac death.[54–56] Furthermore, the percentage of total sleep time with oxyhemoglobin saturation below 90% greater than 2.7% has been described as a significant predictor of mortality (odds ratio, 1.83; 95% CI, 1.31–2.52) in men younger than age 70 years.[4]

The presence of SDB that required medical treatment was confirmed in a total of 48.7% of our patients with CAD and an increased risk of OSA (defined through the use of simple questionnaires), which suggests that routine SDB diagnosis should be introduced in patients with CV diseases. Although the improvement in SDB that is achieved through physical activity is lower than when using CPAP,[57] the former promotes a healthy lifestyle and is a prerequisite for lowering total CV and metabolic risks.[58,59]

Limitations

The most important limitation of the study was the relatively short duration of the supervised rehabilitation program and the lack of follow-up in terms of both maintaining lifestyle changes and survival without cardiac events. Furthermore, because the inclusion criteria assumed the high pretest probability of OSA calculated from risk scales, the study omitted patients with CSA. The dominant group consisted of patients after a coronary incident with preserved LVEF who had been rehabilitated on an outpatient basis. This participant distribution also meant that patients with severe HF and at high risk of CSA were less well represented. This kind of group selection could affect (1) the observed high and comparable percentage of patients with SDB in the models, and (2) the proportion of the number of patients with OSA and CSA within the groups. However, even in the population with a small percentage of patients with HFrEF, the impact of resolving pulmonary congestion or reducing rostral fluid shift caused by recovery and assisted by diuretic therapy on improving sleep apnea may have reduced the REI and affected the final results.

Because of the documented impact of CR on the prognosis, cardiovascular mortality, and risk of hospitalization of patients after coronary events (Class I recommendation from the European Society of Cardiology, the American Heart Association, and the American College of Cardiology[33,34]), the study was not randomized. All of the patients who were included were consecutive.

CONCLUSIONS

When carried out as a part of a comprehensive CR program, high-load cardiorespiratory exercises resulted in an increase in CRF and a reduction of apnea and hypopnea breathing incidents during sleep in patients with CAD and coexisting severe OSA. Because of the documented role of physical activity in the prevention of primary and secondary cardiovascular diseases, this type of intervention could reduce cardiovascular and metabolic risks regardless of CPAP use.

ABBREVIATIONS

CAD, coronary artery disease
CI, confidence interval
CR, cardiac rehabilitation
CRF, cardiorespiratory fitness
CSA, central sleep apnea
CV, cardiovascular
EST, exercise stress test
HF, heart failure
HFrEF, heart failure with reduced ejection fraction
IQR, interquartile range
LVEF, left ventricular ejection fraction
MET, metabolic equivalents
MHR, maximal heart rate
6MWT, 6-Minute Walk Test
NYHA, New York Heart Association
REI, respiratory event index
SDB, sleep-disordered breathing
VO_2 peak, peak oxygen uptake

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DISCLOSURE STATEMENT

All authors have seen and approved the manuscript. Work for this study was performed at the Department of Electrocardiology and Heart Failure, Medical University of Silesia, Katowice, Poland. The authors report no conflicts of interest.