The impact of obstructive sleep apnea on exercise capacity in a cardiac rehabilitation program

C. Sonners[1,2], **C. N. Schmickl**[1,2], **J. Raphelson**[1,2], **A. V. Sykes**[1,2], **E. G. Roberts**[1,2], **I. Swiatkiewicz**[1,2], **A. Malhotra**[1,2], **P. R. Taub**[1,2]

[1]Department of Cardiology and Internal Medicine, Collegium Medicum Bydgoszcz, Nicolaus Copernicus University, Torun, Poland

[2]Internal Medicine, Critical Care, Sleep Medicine and Physiology, Cardiovascular Medicine, UC San Diego, PulmonaryLa Jolla, CA 92037, USA

Abstract

Purpose—Cardiac rehabilitation (CR) improves clinical outcomes in patients with cardiovascular disease (CDV). Patients with CVD often have multiple comorbidities, including obstructive sleep apnea (OSA), potentially affecting their ability to participate and achieve functional improvement during CR. We aimed to test the hypothesis that OSA reduces peak exercise capacity (EC) in patients undergoing CR and to explore if OSA treatment modifies this relationship.

Methods—Data from a retrospective cohort of CR patients was analyzed. OSA was defined as a respiratory event index > 5/h or physician diagnosis. Patients with OSA were considered "treated" if using continuous positive airway pressure regularly during the CR period. Change in METs was the primary study outcome.

Results—Among 312 CR patients, median age of 67 years, 103 (33%) had known OSA (30 treated, 73 untreated). Patients with OSA vs. those with no OSA were more likely to be obese and male; otherwise, groups were similar. Compared with the no OSA group, patients with OSA had lower pre-CR METs (3.3 [2.9–4.5] vs. 3.9 [3.1–5], $P = .01$) and lower post-CR METs (5.3 [4–7] vs. 6 [4.6–7.6], $P = .04$), but achieved a similar increase in METs post-CR (1.8 [0.6–2.6] vs. 2.0 [0.9–3], $P = .22$). Furthermore, compared to no OSA, pre-CR and post-CR METs tended to be similar in patients with treated OSA, but lower in untreated patients, with similar increases in METs across all groups, even when adjusting for covariates via multivariable regression.

Conclusion—OSA is prevalent in patients with CVD undergoing CR. CR substantially improves exercise capacity independent of OSA status, but screening for—and treatment of—OSA may improve the absolute exercise capacity achieved through CR.

C. Sonners csonners@health.ucsd.edu.

Introduction

Obstructive sleep apnea (OSA) is intricately linked with cardiovascular disease (CVD) outcomes [1–5]. Previous studies have shown that OSA impacts important cardiovascular endpoints such as blood pressure, left ventricular ejection fraction, vascular parameters, and risk of arrhythmias as well as increases the risk of cardiovascular events [6–9]. Although prospective observational cohort studies have shown an increased incidence of fatal and non-fatal cardiovascular events with untreated OSA [6], definitive data from randomized controlled trials showing the benefit of OSA therapy for hard cardiovascular outcomes are currently lacking [10]. On the other hand, treatment of OSA has been shown to improve daytime sleepiness and function which may be important determinants of how fully patients engage in medical interventions such as cardiac rehabilitation (CR) programs [11, 12]. Importantly, CR improves hard clinical outcomes such as hospital readmissions, quality of life, and mortality in patients with CVD and is thus a class I recommendation [13–16]. However, despite literature implicating OSA as a modulator of CVD risk and data linking CR to improved CVD outcomes, there remains a lack of rigorous studies regarding the impact of OSA on CR outcomes. We, and others, have observed that OSA is common in patients with CVD [17–20]. OSA has been associated with impaired exercise capacity (EC) in some, but not all, studies [21–24]. However, the mechanism underlying exercise impairment in OSA patients remains unclear, although endothelial dysfunction and deconditioning have been suggested. Thus, it remains unclear whether a diagnosis of OSA affects CR outcomes or whether treatment of OSA (e.g., continuous positive airway pressure [CPAP] which is the standard of care and most used treatment for OSA) influences CR outcomes. At least in theory, if OSA adversely affects CR outcomes, then treatment of OSA would be predicted to be beneficial from the standpoint of improved exercise capacity which could translate into improved outcomes following CR. This finding would also imply that patients planning to participate in CR would benefit from assessment of OSA status (sleep study or questionnaires [25]) prior to initiation of the CR program. Based on this framework, our objective was to test the hypothesis that OSA reduces exercise capacity in CVD patients undergoing CR and to explore if OSA treatment modifies this relationship.

Methods

We performed a retrospective chart review on a cohort of 312 consecutive adult patients with CVD who underwent CR at UCSD between 1/1/2018 and 3/15/2019 (IRB #190,538). Although some of our participants were involved in other as-yet unpublished analyses, none of the present findings has been previously published.

Patients were eligible for CR due to at least one of the following: acute myocardial infarction within the last twelve months, stable angina, coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI), heart valve repair or replacement, stable

chronic systolic heart failure, heart transplant, and peripheral artery disease. Patients went through either standard CR (SCR) or the Ornish intensive CR (ICR) program [1, 26]. The details about both CR programs were presented previously [1]. Briefly, the ICR program (specifically, the Ornish program, Sharecare, Inc., Atlanta, GA, USA) included a structured class model twice a week (4 h) over nine weeks (18 sessions, 72 h in total) comprising supervised exercise training, a specialized plant-based diet, education on nutrition and a healthy lifestyle, stress management, and social support. Nutritional counseling about a specific plant-based diet along with written instructional materials was provided to patients. A whole food, low-fat, low in refined carbohydrates, nutritionally adequate, plant-based diet (consisting of fruits, vegetables, whole grains, legumes, and soy products) without caloric restriction was recommended. Stress management included stretching exercises, breathing techniques, meditation, progressive relaxation, and imagery. Social support was provided through regular group meetings led by a clinical psychologist. The SCR program involved exercise and educational sessions on nutrition and healthy lifestyle (1 h) 3 days per week over 12 weeks (36 sessions, 36 h in total). Healthy food choices were recommended, such as saturated fatty acids < 10% of total energy intake, 2–3 servings of fruit/day, 2–3 servings of vegetables/day, fish 1–2 times/week, < 5 g of salt/ day, 30–45 g of fiber/day (preferably from wholegrain products), and limited sugar-sweetened soft drinks and alcoholic beverages. The structured and supervised exercise included regular, moderate aerobic, and resistance/ strength training. The exercise component was the same in both CR programs. Patients were individually prescribed exercise levels (typically walking) according to baseline exercise treadmill testing (ETT) results. The target training heart rate (HR) was 50–70% of the HR, at which symptoms and/or ECG changes occurred or 55–70% of predicted age-adjusted maximum HR based on patient conditioning level. Three of the 312 patients participated in CR twice, but we included only data from their first encounter in the analyses (i.e., 312 unique CR encounters). There were no other exclusion criteria.

Charts were manually reviewed, and data were collected on baseline demographics, comorbidities, and medications. In addition, characteristics related to CR were collected including the diagnosis that prompted a referral to CR, participation in SCR versus ICR, duration of CR (days), CR adherence (% of all attended CR sessions), and smoking status/ alcohol use at the time of CR. For patients classified as having OSA, adherence/ treatment status was assessed by obtaining adherence data remotely through online cloud-based databases during the dates of the patient's CR dates. If no data were found, physicians' notes indicating treatment were used if available. The peak exercise capacity (EC) was quantified as metabolic equivalents (METS) during exercise treadmill testing (ETT) that was performed according to the standard Bruce protocol. Patients exercised as long as possible, depending on the conditioning level, to achieve at least 70–85% of the predicted age-adjusted maximum HR or until symptoms (such as dyspnea, fatigue, and chest pain), 1 mm ST depression in ECG, abnormal BP response, or ventricular ectopy occurred. The maximum METs value was calculated using a standard formula, and the person's performance on a treadmill as the workload was increased.

OSA was defined as a respiratory event index (REI) > 5/h on in-laboratory polysomnography, home sleep study, or a physician diagnosis of OSA. OSA patients were considered "treated" if using continuous positive airway pressure (CPAP) > 4 h/night on >

70% of nights during the CR period, or if physician notes indicated treatment adherence and objective CPAP data were unavailable [27]. METs were assessed on treadmill exercise testing to peak exercise (70–85% of their age-adjusted maximum heart rate based on level of conditioning or until symptoms), which is consistent with standardized measurement methods in other cardiac rehabilitation studies [28]. Changes in METs were calculated by subtracting the METs documented on the first day of CR ("pre-CR") from the METs documented on the last day of CR ("post-CR").

Categorical data were summarized as percent (number) and compared using Fisher's exact tests. Continuous data were summarized using the median (interquartile range [IQR]); for univariable analyses, we used Wilcoxon rank-sum tests for comparisons by OSA status and Kruskal–Wallis tests (followed by pairwise Wilcoxon rank-sum tests with p-values adjusted based on the method by Hochberg and Benjamini [29]) when making comparisons across OSA treatment groups. Given a large number of candidate covariates, we used multivariable regression with backward selection (based on Bayes' information criterion) to adjust for major covariates. Pre/post-CR METs were log-transformed for multivariable analyses to increase normality. Candidate variables for all regression models included age, sex, body mass index (BMI), race, self-reported Hispanic status, underlying cardiac condition, smoking, alcohol use, asthma, and COPD. For post-CR METs and changes in METs, we further considered CR adherence, CR duration, and participation in the Ornish vs. standard program. All analyses were performed in R (3.6.1; R Foundation, Vienna, Austria), using P-values < 0.05 to judge statistical significance.

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request (Table 1).

Results

Among 312 CR patients, 103 (33%; 95% confidence interval [CI]: 28 to 39) had known OSA (30 treated, 73 untreated). Of the 103 patients classified as OSA, the majority (82) had sleep studies available (either home sleep test or polysomnogram) and 21 had an OSA diagnosis based on physician notes. CR patients were mostly older (67 [59 to 73] years) men (72%). Patients with OSA were more likely to be male (83% vs. 66%, $P = 0.001$) and had a higher body mass index (BMI) (28.5 vs. 26.1 kg/m^2, $P < 0.001$) than patients without OSA (no OSA); otherwise, groups were clinically similar (Table 2). Furthermore, in the subgroup of patients with OSA, those with treated OSA were more obese (BMI 32 kg/m^2 vs. 27.6 kg/m^2, $P = 0.002$) and had more severe OSA based on the available REI (43/h vs. 19/h, $P = 0.002$) than untreated OSA patients, but otherwise had similar baseline characteristics (Supplementary Table E1).

Primary analyses: the effect of OSA diagnosis on exercise capacity

Compared with the no OSA group, OSA patients had lower median pre-CR (baseline) METs (3.3 vs. 3.9, $P = 0.01$) and lower post-CR METs (5.3 vs. 6, $P = 0.04$), but achieved a similar increase in METs during CR (1.8 vs. 2.0, $P_{\text{between-group}} = 0.22$; $P_{\text{within-group}} < 0.001$). In sensitivity analyses, results were similar when comparing (log-transformed) means using t-tests, suggesting the robustness of the results. Furthermore, results were also similar when

adjusting for covariates: Compared to no OSA patients, OSA patients had 11.3% lower pre-CR METs ($P = 0.003$) and 8.7% lower post-CR METs ($P = 0.06$) which did not reach statistical significance, while the change in METs was similar in both groups ($P = 0.51$; for more details, see Table 2, Fig. 1).

Exploratory analyses: the effect of OSA treatment status on exercise capacity

Compared with the no OSA group, untreated OSA patients had significantly lower median pre-CR (baseline) METs (3.3 vs. 3.9, $P = 0.03$) and lower post-CR METs (5.3 vs. 6, $P = 0.052$) which did not reach statistical significance, whereas treated OSA patients had similar pre-CR and post-CR METs as patients without OSA ($P > 0.5$). Both treated and untreated OSA patients achieved a clinically relevant increase in METs [30] during CR which was similar to patients without OSA (2.0 vs. 1.7 vs. 2, $P_{\text{between-groups}} = 0.18$; $P_{\text{within-group}} < 0.001$). Results were similar when adjusting for covariates: Compared with no OSA patients, untreated OSA patients had 11.7% lower pre-CR METs ($P = 0.007$) and 11.9% lower post-CR METs ($P = 0.02$), while changes in METs were similar across both groups ($P > 0.2$; for more details, see Table 3, Fig. 1). Key findings are illustrated in Fig. 2.

Discussion

Our results add to the literature with several novel findings. First, we found that clinical OSA was highly prevalent (33%) in the population of patients with CVD undergoing the comprehensive CR program, even with the limitation of using clinical diagnosis, as discussed below. In comparison, *Spielmanns* et al. screened for OSA (using an REI > 15/h) in their study of post-cardiac surgery patients entering CR and found a prevalence of 59% [31]. But to our knowledge, our study is the first to define this prevalence in a more generalizable cohort as it included all applicable referral types to CR (e.g., post-myocardial infarction, post-coronary revascularization, and heart failure). Second, the group with untreated OSA had substantially reduced exercise capacity at baseline and at the completion of CR as assessed by METs, whereas interestingly, patients with treated OSA tended to have a similar exercise capacity as those without OSA. Third, OSA diagnosis or treatment status did not impact on the post-CR change in METs implying that the CR intervention was still impactful. Taken all together, these findings suggest that identifying patients with OSA prior to initiation of CR with the intention of treating them prior to and during CR could be important to help patients realize optimal exercise capacity and CR outcomes.

Fourth, the above-mentioned results also support the notion that OSA itself does have effects on exercise capacity (EC), as suggested in previous studies. A few previous studies examining OSA and exercise training were typically small or focused on the relationship of exercise on sleep apnea and not vice versa. For example, *Awad* et al. showed that exercise duration was positively associated with protection from sleep-disordered breathing in a longitudinal epidemiologic study of 1521 adults [22]. Furthermore, in a study by *Beitler* et al. including 34 subjects, OSA was associated with impaired EC as defined by decreased peak VO_2 [23]. Similarly, *Przyby-lowski* et al. found in 111 OSA patients that a greater REI was associated with decreased peak VO_2, elevated blood pressure response during exercise,

and delayed recovery of blood pressure post-exercise [32]. A subsequent meta-analysis of studies that evaluated peak VO_2 in OSA confirmed by a sleep study vs. no OSA controls found that peak VO_2 was preserved in patients with moderate to severe OSA based on a patient-level meta-analysis while the study-level meta-analysis showed lower peak VO_2 in severe OSA [33]. Of note, prior studies have shown some improvement in sleep apnea following cardiac rehabilitation, even in the absence of important weight loss, although the underlying mechanisms are unclear [34]. Thus, despite interesting findings, the literature in this area is relatively sparse, with some mixed results, and would likely benefit from larger-scale systematic studies.

Despite our study's strengths including a substantial sample size of patients with CVD undergoing CR, we acknowledge a number of limitations. First, we relied on clinically diagnosed OSA, and thus, we likely missed subclinical disease, potentially biasing results toward the null. Moreover, we relied on physician diagnosis of OSA in a subset of our participants, recognizing that polysomnography would be the gold standard in this context. Nonetheless, our goal was to do a real-world study of clinical OSA, but we recognize that further work will be required to characterize the impact of subclinical OSA on the EC in patients with CVD more definitively. Second, we assessed EC by measuring METs using a treadmill stress test before and after CR which has been an-established clinical tool. However, we recognize that gold standard measurements would require more detailed exercise testing such as cardiopulmonary exercise testing [35]. Thus, again, we advocate for further research to understand the mechanisms underlying our new findings. Third, we conducted a retrospective analysis, and thus, we did not prospectively assign therapy or have the ability to randomize which patients might receive PAP therapy. Thus, we may suffer from the so-called healthy user effect, whereby CPAP may well ameliorate underlying OSA but may also be a marker of a patient who is motivated, affluent, and/or educated. Indeed, *Platt* et al. have shown that CPAP use is a marker of statin therapy, and thus, we advocate for randomized trials to draw firm conclusions in the future [36]. Fourth, the null finding for the change in METs could reflect a power issue. But reassuringly, based on post-hoc analyses, we had a power of > 0.98 to detect a medium effect size (Cohen's $d = 0.5$) of 0.87 METs, and still a reasonable power of > 0.69 to detect even a small effect size (Cohen's $d = 0.3$) of 0.52 METs. Despite these limitations, we believe that our findings are novel and will facilitate and stimulate further research in this area.

Our main conclusions from these findings are that sleep apnea is common in patients participating in cardiac rehabilitation, contributes to impaired exercise capacity, and patients might benefit from OSA screening prior to cardiac rehabilitation to optimize post-cardiac rehabilitation peak exercise capacity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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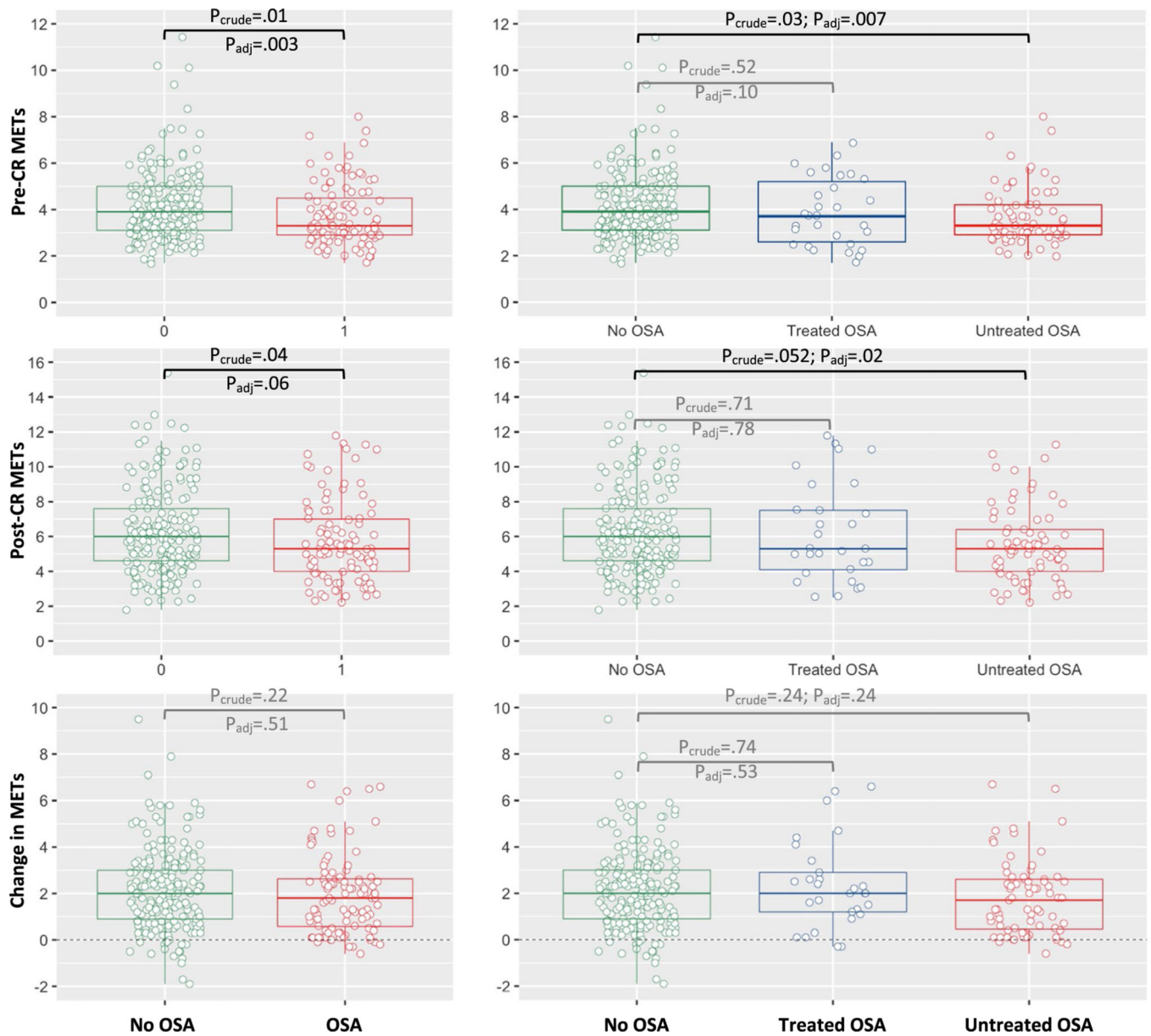
Fig. 1.

Comparison of METs based on OSA diagnosis and treatment status. Compared to untreated OSA patients, patients with treated OSA had change in METs similar to patients without any OSA
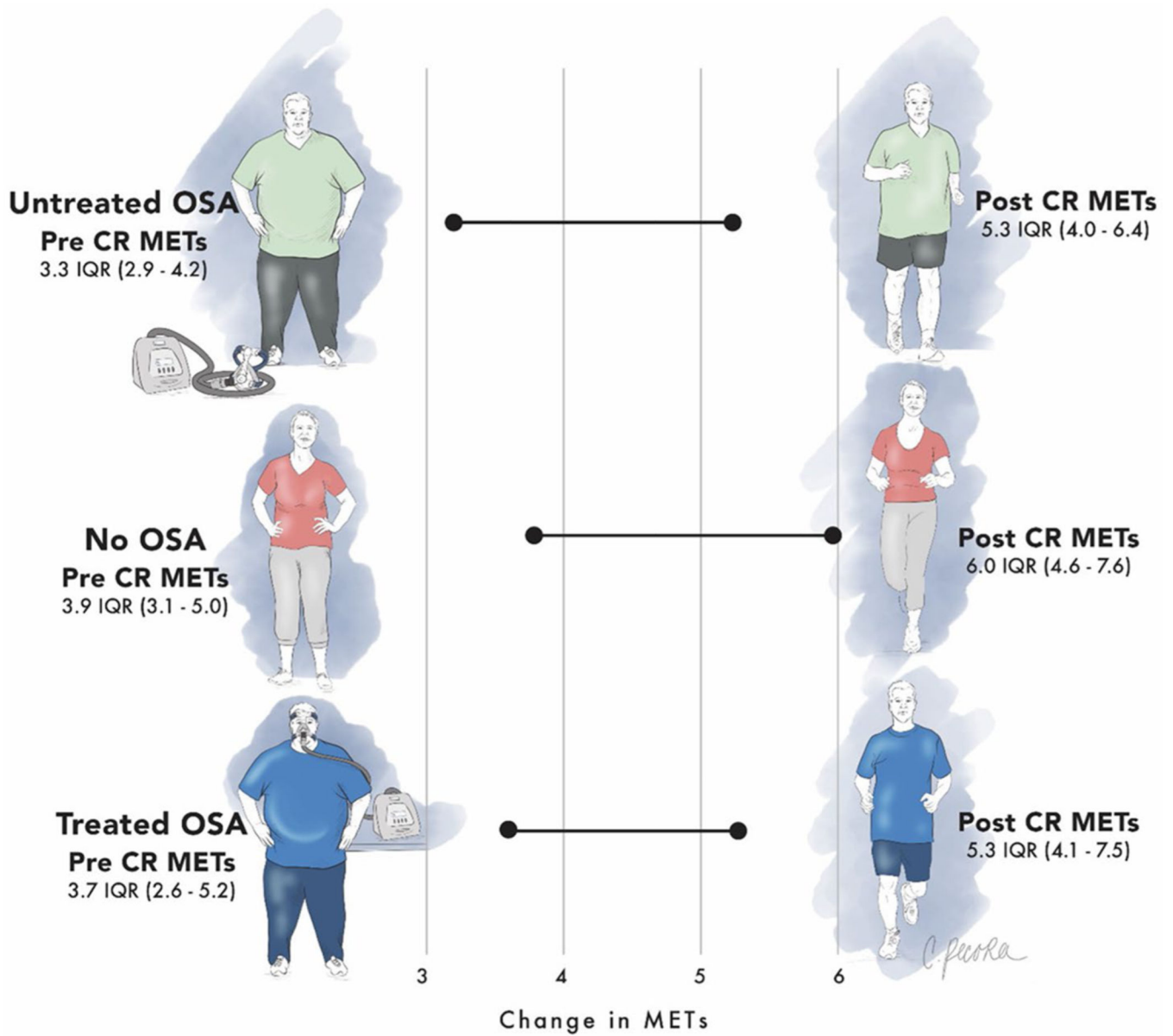
Fig. 2.
Illustration of key results. Patients with treated OSA tended to have similar exercise capacity at baseline and follow-up as patients without any OSA

Table 1

General characteristics

	OSA (N = 103)		n	No OSA (N = 209)		n	P
	Median %	[IQR] (n)		Median %	[IQR] (n)		
General characteristics Age, years	68	[61 to 75]		66	[57 to 73]		.03
Female sex	17%	(17)		34%	(71)		**.001**
Body mass index, kg/m^2	28.5	[26 to 35]		26.1	[24 to 29]		**<.001**
Ornish program, yes	31%	(32)		33%	(68)		.9
Race							.5
White	78%	(80)		71%	(148)		
Black	6%	(6)		5%	(10)		
Asian	7%	(7)		10%	(21)		
Other	10%	(10)		14%	(30)		
Hispanic	10%	(3)		10%	(21)		.4
Reason for rehab							
Stable angina pectoris	18%	(19)		8%	(16)		**0.007**
CABG	14%	(14)		14%	(30)		> .9
PCI	24%	(25)		39%	(81)		**.01**
Valvular surgery	10%	(10)		13%	(27)		.5
Heart transplant/LVAD	5%	(5)		3%	(7)		.5
Acute MI (past 12 months)	14%	(14)		14%	(30)		> .9
Stable HFrEF	25%	(26)		16%	(34)		.07
PAD	3%	(3)		1%	(3)		.4
Days of CR	84	[58 to 119]		91	[58 to 126]		.6
CR adherence, % sessions	100	[50 to 100]		100	[42 to 100]		.8
Smoking status							.3
Current	2%	(2)		1%	(3)		
Former	43%	(44)		35%	(73)		
Never/unclear	55%	(57)		64%	(133)		
Alcohol status							.5
Current	47%	(48)		41%	(86)		

	OSA (N = 103)		n	No OSA (N = 209)		n	P
	Median %	**[IQR] (n)**		**Median %**	**[IQR] (n)**		
Former	9%	(9)		8%	(16)		
Never/unclear	45%	(46)		51%	(107)		
Asthma	14%	(14)		10%	(21)		.3
COPD	17%	(17)		10%	(21)		.14
Beta-blocker use	75%	(77)		70%	(147)		.5
ACE-inhibitor use	35%	(36)		27%	(57)		.2
MRA use	25%	(26)		21%	(44)		.5
Sleep apnea severity REI, h^{-1}	22	[14 to 44]	82	2.2	[1 to 3.9]	14	**<.001**
OAI, h^{-1}	2	[1 to 7]	75	0.2	[0 to 1.5]	14	**<.001**
CAI, h^{-1}	1	[0 to 5]	74	0	[0 to 0.3]	14	**<.001**
SpO$_2$ nadir, %	82	[75 to 85]	79	87	[83 to 91]	14	**<.001**
Time with SpO$_2$ < 88%, %MT	2	[0 to 7]	73	0	[0 to 0]	15	**<.001**
Mean CPAP usage, min	328	(223 to 414)	22	na			
Residual REI on CPAP	2.8	[1.4 to 4.6]	22	na			

ACE, angiotensin-converting enzyme; *REI*, respiratory event index; *CABG*, coronary artery bypass graft; *CAI/OAI*, central/obstructive apnea index; *HFrEF*, heart failure with reduced ejection fraction; *IQR*, interquartile range; *LVAD*, left ventricular assist device; *MI*, myocardial infarction; *MRA*, mineralocorticoid receptor antagonist; *%MT*, percent of monitoring time; *PAD*, peripheral artery disease; *PCI*, percutaneous coronary intervention; *SD*, standard deviation. Bolded entries are values meeting statistical significance

Table 2

Differences in exercise performance based on OSA diagnosis

| | Univariable analyses | | | | | | | Multivariable analyses | | | | |
| | OSA (N = 103) | | No OSA (N = 209) | | (OSA vs. no OSA) | | | (OSA vs. no OSA) | | | | |
	Median Mean	[IQR] (SD)	Median Mean	[IQR] (SD)	Medians	Mean	P_{crude} A	beta	SE	$P_{adjusted}$	Interpretation B	(95% CI)
Pre-CR METs	**3.3**	**[2.9 to 4.5]**	**3.9**	**[3.1 to 5]**	**– 0.6**		**.01**					
Pre-CR METs	**3.8**	**(1.32)**	**4.2**	**(1.52)**	**– 0.4**		**.02**					
log(Pre-CR METs)	**1.27**	**(0.33)**	**1.37**	**(0.33)**	**– 0.1**		**.01**	**– 0.12**	**0.04**	**.003**	**– 11.3%**	**(– 18 to – 3.9)** C
Post-CR METs	**5.3**	**[4 to 7]**	**6**	**[4.6 to 7.6]**	**– 0.7**		**.04**					
Pre-CR METs	5.7	(2.37)	6.3	(2.46)	– 0.6		.05					
log(Post-CR METs)	**1.66**	**(0.41)**	**1.76**	**(0.39)**	**– 0.1**		**.04**	– 0.09	0.05	.06	– 8.7%	(– 17.1 to 0.4) D
Change in METs	1.8	[0.6 to 2.6]	2	[0.9 to 3]	– 0.2		.22					
Change in METs	2.0	(1.71)	2.2	(1.74)	– 0.2		.38	– 0.13	0.2	.51	– 0.13	(– 0.52 to 0.26) E

METs, metabolic equivalents; *CR*, cardiac rehabilitation; *OSA*, obstructive sleep apnea; *IQR*, interquartile range; *CI*, confidence interval; *SD*, standard deviation

A Based on Wilcoxon rank-sum test or *t*-test

B To promote normality, pre/post-CR METs were log-transformed for multivariable analyses; thus, the beta can be interpreted as a percentage difference based on the formula: [1-exp(beta)]*100; the change in METs did not require transformation; thus, the beta reflects the absolute difference between both groups after adjusting for covariates

C Adjusted for sex

D Adjusted for sex, body mass index, CR adherence (%sessions), Ornish program (yes/no)

E Adjusted for baseline METs, CR adherence (%sessions) Bolded entries are values meeting statistical significance

Table 3

Differences in exercise performance based on OSA treatment status

	Univariable analyses							Multivariable analyses				
	Median	[IQR]	Median	[IQR]	Medians	P crude	P global	beta	SE	P adjusted	Interpretation[A]	(95% CI)
Pre-CR METs												
OSA treatment status							.03					
Untreated vs. no OSA	**3.3**	**[2.9 to 4.2]**	**3.9**	**[3.1 to 5]**	**−0.6**	**.03**		**−0.13**	**0.05**	**.007**	**−11.7%**	**(−19.3 to −3.5)** [B]
Treated vs. no OSA	3.7	[2.6 to 5.2]	3.9	[3.1 to 5]	−0.2	.52		−0.11	0.07	.10	−10.1%	(−20.9 to 2.1)[B]
Post-CR METs												
OSA treatment status							0.065					
Untreated vs. no OSA	5.3	[4 to 6.4]	6	[4.6 to 7.6]	−0.7	.052		**−0.13**	**0.05**	**.02**	**−11.9%**	**(−20.5 to − 2.4)** [C]
Treated vs. no OSA	5.3	[4.1 to 7.5]	6	[4.6 to 7.6]	−0.7	.71		0.02	0.08	.78	2.3%	(−12.6 to −2.4)[C]
Change in METs												
OSA treatment status							0.18					
Untreated vs. no OSA	1.7	[0.5 to 2.6]	2	[0.9 to 3.0]	−0.3	.24		−0.27	0.23	.24	−0.27	(−0.71 to 0.18)[D]
Treated vs. no OSA	2	[1.2 to 2.9]	2	[0.9 to 3.0]	0	.74		−0.20	0.32	.53	−0.20	(−0.43 to 0.83)[D]

For abbreviations, see Table 2 footnote

[A] To promote normality, pre/post-CR METs were log-transformed for multivariable analyses; thus, the beta can be interpreted as a percentage difference based on the formula: [1−exp(beta)]*100; the change in METs did not require transformation; thus, the beta reflects the absolute difference between both groups after adjusting for covariates

[B] Adjusted for sex

[C] Adjusted for sex, body mass index, CR adherence (%sessions), Ornish program (yes/no)

[D] Adjusted for baseline METs, CR adherence (%sessions)

Bolded entries are values meeting statistical significance