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The Impact of Underlying Obstructive Sleep Apnea Treatment on Exercise Capacity in Patients With Pulmonary Hypertension Undergoing a Cardiac Rehabilitation Program

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Abstract

Purpose: Obstructive sleep apnea (OSA)–related pulmonary hypertension (PH) can often be reversed with treatment of OSA via continuous positive airway pressure. We hypothesized that treatment of OSA would be associated with a greater improvement in exercise capacity (EC) with cardiac rehabilitation (CR), especially in patients with PH as compared with those who are untreated.

Methods: We reviewed medical records of 315 consecutive patients who participated in CR. Pulmonary hypertension status was assessed on the basis of peak tricuspid regurgitant velocity (>2.8 m/sec) on pre-CR echocardiograms. The OSA status (no, untreated, or treated OSA) was determined on the basis of results from sleep studies, continuous positive airway pressure device data, and physician notes. Exercise capacity was assessed by measuring metabolic equivalents (METs) using a treadmill stress test before and after CR.

Results: We included 290 patients who participated in CR with available echocardiographic data: 44 (15%) had PH, and 102 (35%) had known OSA (30 treated and 72 untreated). Patients with OSA versus those with no OSA were more likely to have PH ($P = .06$). Patients with PH versus

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no-PH were associated with significantly lower baseline METs in crude and adjusted analyses ($P \leq .004$). The PH and OSA status in isolation were not associated with changes in METs ($P > .2$) with CR. There was a significant interaction between OSA treatment and PH in crude and adjusted analyses ($P \leq .01$): treatment vs no treatment of OSA was associated with a clinically and statistically greater improvement in METs in patients who participated in CR with but not without PH.

Conclusion: Baseline PH was associated with decreased baseline EC but did not attenuate CR-related improvements in METs. However, in the subset of OSA patients with PH, OSA therapy was associated with improved EC after CR.

Keywords

cardiac rehabilitation; exercise capacity; obstructive sleep apnea; outcomes; pulmonary hypertension

Obstructive sleep apnea (OSA) is an important disorder thought to affect up to 1 billion people worldwide.[1] Although it has major neurocognitive and cardiovascular sequelae, it frequently goes undiagnosed and untreated even in high-risk patients.[2–5] One consequence of OSA which is underappreciated is its relationship to and physiological connection with pulmonary hypertension (PH).[6-8]

Although some of the early reports of OSA suggested that right-sided heart failure may be associated, the role of OSA in mediated PH (specifically World Health Organization group 3) has been debated.[9,10] Despite suggestions of a link between OSA and right-sided heart failure, subsequent studies did not show major elevations in pulmonary artery pressure with OSA alone. It was discovered that a daytime abnormality in arterial blood gasses was frequently present in OSA patients with PH. Sajkov and McEvoy[11] showed an important link between OSA and PH with three principal features. First, the elevations in pulmonary artery pressure in patients with OSA were generally mild to moderate. Second, the elevations in pulmonary artery pressure were reversible when OSA was treated with continuous positive airway pressure (CPAP).[7,8] Third, there was marked hypoxic vasoreactivity such that patients experienced major elevations in pulmonary artery pressure with minor hypoxic stimuli. These findings suggest that PH is a treatable sequela of OSA.[12]

One area of tangible outcomes research is cardiac rehabilitation (CR), as the exercise capacity (EC) of a patient is both scientifically measurable and clinically impactful on impactful on the life of the patient.[13,14] With regard to exercise, OSA has been associated with impaired EC in some but not all studies.[15–17] Cardiac rehabilitation is recommended as a class 1 indication for patients with cardiovascular disease.[18–23] However, the impact of OSA on CR outcomes is unclear and untested. Tolle et al[24] showed previously that exercise-induced PH can be a mechanism of exercise limitation in some patients, yet, the impact of OSA in modulating this association is undetermined. Moreover, OSA is known to impair systemic endothelial function although there are minimal data regarding whether systemic endothelial dysfunction is predictive of abnormalities in pulmonary endothelial function or not.[25] Thus, at least in theory, OSA could decrease EC due to the effects on the systemic endothelial function. Based on this conceptual framework, we sought to test the

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hypothesis that treatment of OSA would help optimize improvement in EC with CR therapy. We further assessed the prevalence of diagnosed OSA in a CR cohort, its relationship with PH, and the impact of PH on exercise outcomes in these patients. Given the adverse effects of OSA on the pulmonary circulation, it was our hypothesis that the subset of patients with OSA and PH who were treated with CPAP would receive a greater benefit from CR than patients with OSA and PH not treated with CPAP.

METHODS

The protocol for this study was approved by the institutional review board (UCSD IRB 190538 3/27/2019). We reviewed the charts from 315 consecutive patients who participated in CR from January 1, 2018, to March 15, 2019, at a large academic center. Three of these 315 patients underwent CR twice during this time period, and for these patients we excluded data from the second CR period. Furthermore, since assessment of pulmonary vascular pressure at the start of CR was critical to our hypotheses, we excluded 22 patients who did not have echocardiogram data available to assess tricuspid regurgitant velocity (TRV) at baseline. Thus, data from 290 unique patients were included in the final analysis (164 of these 290 patients also had post-CR echocardiography data on TRV available). Patients were eligible for CR due to at least one of the following indications: acute myocardial infarction within the last 12 mo, stable angina, coronary artery bypass grafting, percutaneous coronary intervention, heart valve repair or replacement, stable chronic systolic heart failure, heart transplant, and peripheral artery disease. Patients were subject to either a standard or an intensive CR program. Although the supervised exercise component training was the same for both CR programs, additional dietary (plant-based diet) and lifestyle modifications such as stress management and social support were included in the intensive CR. Obstructive sleep apnea was defined as an apnea-hypopnea index/respiratory-event index >5/hr on an in-lab or home sleep study, or a physician diagnosis of OSA,[26] and some general OSA characteristics were abstracted from sleep study reports (including obstructive/central apnea index and oxygen desaturation nadir). Patients with OSA were considered “treated” if using CPAP >4 hr/night on >70% of nights during the CR period and verified on the basis of data from CPAP manufacturer cloud-based databases,[27] or if physician notes indicated treatment during the time period the patient participated in CR.

Exercise capacity was assessed by measuring metabolic equivalents (METs) using a treadmill stress test before and after CR. Exercise treadmill testing 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 heart rate or until symptoms (such as dyspnea, fatigue, and chest pain), 1-mm ST depression on electrocardiogram, abnormal blood pressure response, or ventricular ectopy occurred. The Bruce treadmill test estimates maximal oxygen uptake and the maximum METs indirectly using a standard formula and the performance of the person on a treadmill as the workload was increased. This protocol is consistent with those used in standardized measurement methods in other CR studies.[28] The change in METs completed by each patient from baseline to end of CR was obtained. 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”). Echocardiograms for each patient before and after completing

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CR were analyzed and peak TRV was obtained at both time points. Pulmonary hypertension was defined as peak TRV >2.8 m/sec by echocardiogram.[29] Some of our participants were included in other as yet unpublished studies.

STATISTICAL ANALYSES

Categorical data were summarized as n (%) and compared using Fisher exact tests, while continuous data were summarized using the median (IQR) univariably analyzed via Wilcoxon rank sum tests. Multivariable regression was used to (i) assess for interactions between PH (yes/no) and OSA status (no OSA, untreated OSA, treated OSA), and (ii) to adjust for major covariates by employing a backward selection procedure (based on Bayes' information criterion, given the large number of candidate covariates; note, the main effects of PH and OSA status as well as their interaction were forced into the model during the backward selection procedure). Baseline METs were log-transformed for multivariable analyses to increase normality. Candidate covariates for all regression models included the following baseline characteristics: age, sex, body mass index, race (using 3 dummy variables to encode the 4 classes: White, Black, Asian, and Other), Hispanic ethnicity, underlying cardiac condition, smoking, alcohol use, asthma, and chronic obstructive pulmonary disease. For multivariable analyses using the change in METs as the outcome, we further included the type of CR program (intensive cardiac rehabilitation [Ornish] vs standard), CR adherence (% sessions), CR duration (d), and pre-CR METs as candidate covariates. Significant interactions in multivariable analyses were further investigated using Tukey tests. All analyses were performed in R (3.6.1) using a P value of <.05 to denote statistical significance, and variance inflation factors (VIF) of <5 to indicate absence of substantial multicollinearity issues.

RESULTS

We included 290 patients in whom we could determine baseline-PH status (44 PH, 246 non-PH). General characteristics of PH and non-PH subjects were similar (Table 1). The demographics of the participants were consistent with our clinical experience: the median age was 67 yr, and most patients were overweight (average body mass index of 26.9 kg/m^2) with 27% female patients and 27% of the cohort non-White patients. Overall, 102 (35%) patients had OSA (30 treated and 72 untreated; Table 2). The rates of PH were not statistically significantly different in patients with OSA versus those with no OSA (21% vs 12%; P = .06). Results were similar when adjusting for baseline characteristics (OR = 1.7, P = .13). In the subset of 164 patients who had echocardiograms before and after CR, OSA status was not associated with changes in PH status (P = .7) or peak TRV (P = .47).

BASELINE ESTIMATED METS

Compared with no PH, PH at baseline was associated with significantly lower baseline EC as measured in estimated METs (3.8 [3.0, 4.9] vs 3.0 [2.6, 3.8], P_{Wilcoxon}<.001). Results were similar when adjusting for baseline characteristics and/or including OSA status in multiple regression using log-transformed baseline estimated METs as the dependent variable ($P \leq .004$; VIF<3).

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CHANGE IN ESTIMATED METS

Pulmonary hypertension and OSA status in isolation were not associated with changes in estimated METs ($P > .2$); however, there was a significant interaction between OSA treatment and PH both in crude and adjusted analyses (including CR adherence and estimated METs at baseline as covariates): treatment of OSA was associated with a clinically and statistically greater improvement in estimated METs in CR patients with, but not without, PH (Table 3 and Figure).

DISCUSSION

Our novel findings demonstrate that OSA and PH are common in patients participating in CR (n = 30). Patients with PH (vs no PH) have significantly lower baseline EC expressed in estimated METs but still benefit from the CR intervention. In our CR cohort, OSA was highly prevalent and only a minority of patients are actively treated. Importantly, among the patients participating in CR, we observed a significantly greater improvement in EC in CPAP-treated patients with OSA and PH as compared with non–CPAP-treated patients with OSA and PH despite similar degrees of PH.

These data motivate further investigation into this area, particularly given the paucity of literature that currently exists. Beitler et al[17] previously demonstrated impaired EC in patients with OSA whereas Jen et al[16] showed no major impairment. Notably, both studies were small and the types of patients enrolled were different from one another. For example, the average daily activity in various locations may differ on the basis of the weather and the local culture, such that exercise performance in general may vary on the basis of where the studies took place. For example, the Beitler study included participants in Boston primarily from a sleep clinic whereas the Jen study included people in San Diego primarily from a cardiology clinic. Thus, larger more systematic studies are needed.[15] The encouragement of exercise training in patients with OSA is commonly done, given the high prevalence of obesity in these patients.[30,31] Despite this notion, minimal effort has been made to understand the mechanisms underlying the impaired EC in these patients. Furthermore, our findings suggest that OSA should perhaps be treated prior to an exercise program, particularly in patients with PH. Further studies are needed to understand this relationship better.

In general, OSA has been underdiagnosed and undertreated.[32] The reasons for this finding are unclear[33] but may relate to lack of awareness among patients and providers regarding the potential importance of untreated sleep disorders on overall health. In addition, the diagnostic testing has been considered cumbersome, even though home testing has greatly facilitated establishing an OSA diagnosis. In addition, treatment of OSA with CPAP has a poor reputation in some circles, even though recent data suggest that the vast majority of patients are adherent to CPAP using modern technology with adequate education and support.[27,34] Thus, we hope that our new findings help encourage improved awareness regarding the clinical impact of diagnosing and treating OSA.

Despite the strengths of our study, we acknowledge a number of limitations. First, we relied on echocardiography to assess TRV rather than invasive hemodynamic monitoring,

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which would be considered the gold standard.[35] We made this decision based on our study design as we collected real-world data where pulmonary artery catheterization is performed infrequently in such a context. Second, our sample size was modest for the subset of patients with OSA and PH who were using CPAP therapy. However, the overall size of our cohort was quite large and thus the lack of treated OSA reflects the reality of our clinical practice rather than inadequate methodology on our part. We hope that our findings encourage more systematic assessment of sleep and OSA outcomes in the CR setting. Third, based on our study design, we view our findings as correlative rather than proving causation. Randomized studies in this context would be challenging although would certainly help draw more definitive causal inferences. Fourth, our study was a single-center study that limits its generalizability. San Diego has rich ethnic and demographic diversity, but the population may be healthier, in general, than other parts of the world. Thus, further studies would be encouraged. Fifth, we relied on established diagnoses for classification of OSA status, and thus it is possible if not likely that we misclassified some patients with subclinical disease. Thus, we encourage larger more systematic studies involving gold standard assessments but still believe that our new findings are useful in guiding subsequent studies. Despite these limitations, we believe that our findings represent an important addition to the literature and encourage further study and more mechanistic research in the future.

CONCLUSIONS

Cardiac rehabilitation is a beneficial intervention for many patients with cardiovascular disease, and our study supports its use specifically in patients with PH. Although our data suggest that this subset of patients may have EC that is decreased at baseline, they were still able to achieve clinically important improvements in estimated METs. In the subset of patients with both OSA and PH, those who were treated with CPAP therapy before starting CR had an even greater increase in estimated METs than patients with OSA and PH who were not treated with CPAP. This finding could suggest that pretreatment with CPAP therapy may be beneficial in this subset of patients participating in CR. Further prospective studies are required to define strategies to optimize CR outcomes.

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KEY PERSPECTIVE

- What is novel?
  - Obstructive sleep apnea (OSA) is common in patients with pulmonary hypertension (PH) participating in cardiac rehabilitation (CR).
  - Treatment of OSA before starting an exercise training program in this subpopulation of patients may be associated with improvement in CR outcomes, namely, exercise capacity (EC).
- What are the clinical and/or research implications?
  - This research should guide clinicians to screen patients participating in CR and treat those who are found to have OSA in addition to PH with continuous positive airway pressure nightly in order to optimize CR outcomes.
  - Our research provides a target for future systematic study of this promising subgroup to best optimize hemodynamic changes and enhance the CR-related improvement in EC.

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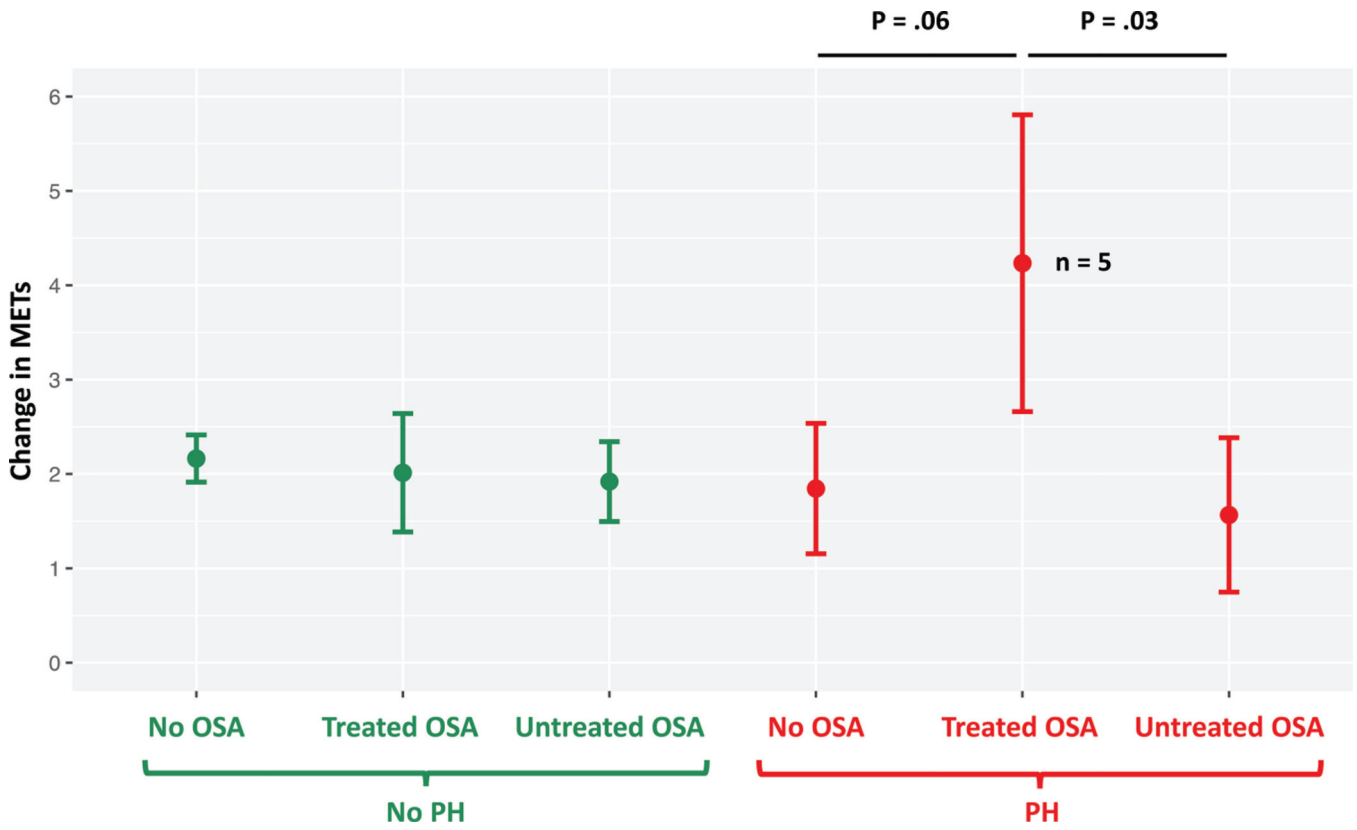

Figure.

Mean predicted change in METs based on PH and OSA treatment status. Results are based on the adjusted model (Table 3) for a subject with average CR adherence (75.5% of all sessions) and average METs at baseline (4.0). METs indicates metabolic equivalents; OSA, obstructive sleep apnea; PH, pulmonary hypertension. This figure is available in color online (www.jcrpjournal.com).

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Table 1

General Characteristics and OSA Status

	Overall, n = 290[a]	PH, n = 44[a]	No PH, n = 246[a]
General characteristics			
Age, yr	67 (59, 73)	69 (61, 75)	66 (59, 73)
Sex, female	79 (27)	14 (32)	65 (26)
Body mass index, kg/m^2	26.9 (24.3, 30.3)	28.1 (23.9, 30.9)	26.8 (24.4, 29.9)
Ornish CR program	88 (30)	11 (25)	77 (31)
Race			
White	213 (73)	32 (73)	181 (74)
Black	13 (4.5)	3 (6.8)	10 (4.1)
Asian	26 (9.0)	4 (9.1)	22 (8.9)
Other	38 (13)	5 (11)	33 (13)
Hispanic ethnicity	27 (9.3)	4 (9.1)	23 (9.3)
Reasons for rehabilitation			
Stable angina pectoris	32 (11)	5 (11)	27 (11)
CABG	41 (14)	4 (9.1)	37 (15)
PCI	94 (32)	8 (18)	86 (35)
Valvular surgery	36 (12)	6 (14)	30 (12)
Heart transplant/LVAD	12 (4)	2 (4)	10 (4)
Acute MI (past 12 mo)	43 (15)	6 (14)	37 (15)
Stable HFrEF	57 (20)	18 (41)	39 (16)
PAD	6 (2)	1 (2)	5 (2)
Duration of CR, d	90 (58, 126)	92 (68, 124)	90 (58, 126)
CR adherence, % sessions	100 (42, 100)	94 (35, 100)	100 (42, 100)
Smoking status			
Current	5 (2)	0 (0)	5 (2)
Former	106 (37)	17 (39)	89 (36)
Never/unclear	179 (62)	27 (61)	152 (62)
Alcohol status			
Current	126 (43)	14 (32)	112 (46)

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	Overall, n = 290[a]	PH, n = 44[a]	No PH, n = 246[a]
Former	24 (8)	3 (7)	21 (8)
Never	140 (48)	27 (61)	113 (46)
Asthma	33 (11)	7 (16)	26 (11)
COPD	36 (12)	6 (14)	30 (12)
β-Blocker use	210 (72)	34 (77)	176 (72)
ACE inhibitor use	90 (31)	14 (32)	76 (31)
MRA use	61 (21)	13 (30)	48 (20)
TRV at baseline, m/sec	2.41 (2.15, 2.65)	3.04 (2.89, 3.23)	2.31 (2.10, 2.50)
METs at baseline	3.7 (2.9, 4.7)	3.0 (2.6, 3.8)	3.8 (3.0, 4.9)
METs at end of CR	5.6 (4.3, 7.0)	4.7 (3.4, 6.3)	5.8 (4.5, 7.3)
OSA status			
No OSA	188 (65)	23 (52)	165 (67)
OSA	102 (35)	21 (48)	81 (33)
Treated OSA	30 (10)	5 (11)	25 (10)
Untreated OSA	72 (25)	16 (36)	56 (23)

Abbreviations: ACE, angiotensin converting enzyme; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; CR, cardiac rehabilitation; HFrEF, heart failure with reduced ejection fraction; LVAD, left ventricular assist device; METs, metabolic equivalents; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; OSA, obstructive sleep apnea; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; PH, pulmonary hypertension; TRV, tricuspid regurgitation velocity.

[a]Data are presented as n (%) or median (IQR).

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Table 2

Sleep Apnea Characteristics

	OSA, n = 102[a]		No OSA, n = 188[a]	
Pulmonary hypertension	21 (21)		23 (12)	
TRV at baseline, m/sec	2.44 (2.20, 2.76)	90	2.40 (2.11, 2.61)	148
Sleep apnea severity				
OSA status based on physician notes only	21 (21)		175 (93)	
REI, hr^{-1}	22 (14, 44)	81	2 (1, 4)	13
OAI, hr^{-1}	2 (1, 7)	74	0 (0, 2)	13
CAI, hr^{-1}	1 (0, 5)	73	0 (0, 0)	13
Spo_2 nadir, %	82 (75, 85)	78	86 (82, 90)	13
Time with Spo_2< 88%, %MT	2 (0, 8)	72	0 (0, 0)	13
Treated OSA[b]	30 (29)			
Mean CPAP usage to min	408 (342, 435)	12		
Residual REI on CPAP	1.4 (1.1, 3.1)	12		
Untreated OSA[c]	72 (71)			
Mean CPAP usage to min	218 (181, 240)	10		
Residual REI on CPAP	3.8 (2.8, 8.7)	10		

Abbreviations: CAI, central apnea index; CPAP, continuous positive airway pressure; MT, monitoring time; OAI, obstructive apnea index; OSA, obstructive sleep apnea; REI, respiratory event index; Spo_2, saturation of oxygen from pulse oximeter; TRV, tricuspid regurgitation velocity.

[a]Data are presented as n (%) or median (IQR), or n.

[b]Thirty OSA patients were considered treated based on objective data (12 patients) or physician notes (18 patients).

[c]Seventy-two OSA patients were considered untreated based on objective data (10 patients), or because there was no evidence of treatment based on physician notes (62 patients).

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Table 3

Associations Between Pulmonary Hypertension, Obstructive Sleep Apnea Treatment Status, and the Change in Estimated Metabolic Equivalents

	Crude Model[a,b]			Adjusted Model[a-c]		
	β	**SE**	***P* Value**	**β**	**SE**	***P* Value**
Pulmonary hypertension	−.61	0.40	.13	−.32	0.37	.40
Treated OSA	−.13	0.37	.73	−.15	0.34	.66
Untreated OSA	−.33	0.27	.22	−.24	0.25	.33
PH × Treated OSA[d]	2.55	1.00	.01[e]	2.54	0.93	.007[e]
PH × Untreated OSA	.18	0.64	.78	.04	0.59	.95

Abbreviations: OSA, obstructive apnea index; PH, pulmonary hypertension.

[a] Variance inflation factors were <3 indicating that there was no substantial multicollinearity.

[b] The R^2 was 0.04 for the crude model and 0.17 for the adjusted model, respectively.

[c] Covariates in the final adjusted model were CR adherence and estimated METs at baseline.

[d] Here the reference level is "no OSA." When using "untreated OSA" as the reference level, then **β** = 2.37 (***P*** = .02) and **β** = 2.57 (***P*** = .009) in the crude and adjusted models, respectively.

[e] ***P*** < .05