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Authors

Beitler, Jeremy R
Awad, Karim M
Bakker, Jessie P
et al.

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Obstructive Sleep Apnea Is Associated with Impaired Exercise Capacity: A Cross-Sectional Study

Jeremy R. Beitler, M.D.[1]; Karim M. Awad, M.D.[4]; Jessie P. Bakker, Ph.D.[2]; Bradley A. Edwards, Ph.D.[2]; Pam DeYoung, B.A.[5]; Ina Djonlagic, M.D.[2]; Daniel E. Forman, M.D.[3]; Stuart F. Quan, M.D.[2,6]; Atul Malhotra, M.D.[5]

[1]Division of Pulmonary and Critical Care Medicine, [2]Division of Sleep Medicine, and [3]Division of Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA; [4]Department of Neurology, Beth Israel Deaconess Medical Center, Boston, MA; [5]Division of Pulmonary and Critical Care Medicine, University of California, San Diego, San Diego, CA; [6]Arizona Respiratory Center, University of Arizona College of Medicine, Tucson, AZ

SCIENTIFIC INVESTIGATIONS

Objective: Obstructive sleep apnea (OSA) is associated with increased risk of adverse cardiovascular events. Because cardiopulmonary exercise testing (CPET) aids in prognostic assessment of heart disease, there is rising interest in its utility for cardiovascular risk stratification of patients with OSA. However, the relationship between OSA and exercise capacity is unclear. This study was conducted to test the hypothesis that OSA is associated with impaired exercise capacity.

Methods: Fifteen subjects with moderate-to-severe OSA (apnea-hypopnea index [AHI] ≥ 15 events/h) and 19 controls with mild or no OSA (AHI < 15 events/h) were enrolled. Subjects underwent standard polysomnography to determine AHI and exclude other sleep disorders. Resting metabolic rate was measured via indirect calorimetry, followed by maximum, symptom-limited CPET. Subjects completed a sleep diary and physical activity questionnaire characterizing behaviors in the week prior to testing.

Results: Percent predicted peak oxygen uptake ($\dot{V}O_2$) was significantly lower in OSA subjects than controls (70.1% ± 17.5% vs 83.8% ± 13.9%; p = 0.02). Each 1-unit increase in log-transformed AHI was associated with a decrease in percent predicted peak $\dot{V}O_2$ of 3.20 (95% CI 0.53-5.88; p = 0.02). After adjusting for baseline differences, this association remained significant (p < 0.01). AHI alone explained 16.1% of the variability observed in percent predicted peak $\dot{V}O_2$ (p = 0.02).

Conclusions: OSA is associated with impaired exercise capacity. Further study is needed to evaluate the utility of CPET for prognostic assessment of patients with OSA.

Keywords: obstructive sleep apnea, exercise test, cardiopulmonary exercise test, exercise tolerance, risk assessment

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Obstructive sleep apnea (OSA) has numerous adverse cardiovascular effects.[1] Increased systemic hypertension, nocturnal arrhythmia, and both nonfatal and fatal cardiovascular events have been associated with OSA.[2-4] Because cardiopulmonary exercise testing (CPET) aids in prognostic assessment of patients with heart disease,[5-7] there is rising interest in the potential utility of CPET for cardiovascular risk stratification in patients with OSA.[8-10]

The impact of obstructive sleep apnea (OSA) on exercise capacity remains unclear. Prior studies examining exercise capacity in OSA patients have yielded conflicting results, with some demonstrating reduced exercise capacity[11-16] and others suggesting exercise capacity is not impaired.[8-10,17,18] These studies have several methodological limitations that make reconciling their findings challenging. In some studies, peak oxygen uptake ($\dot{V}O_2$) was calculated from estimating equations rather than direct gas exchange measurements,[11,16] diminishing reliability of the assessment.[19] Others relied only on a thermister to detect respiratory events during polysomnography (PSG),[8,16] which underestimates such events compared to nasal pressure sensors[20] and likely led to enrollment of OSA subjects in the control group. In one study, controls did not undergo PSG testing at all.[17]

BRIEF SUMMARY

Current Knowledge/Study Rationale: Obstructive sleep apnea (OSA) is associated with increased risk of cardiovascular events. Cardiopulmonary exercise testing aids in prognostic assessment of heart disease, raising interest in its utility for cardiovascular risk stratification in patients with OSA; however, the relationship between OSA and exercise capacity is unclear.

Study Impact: This study demonstrated that OSA is associated with impaired exercise capacity. Further study is needed to evaluate the potential role for cardiopulmonary exercise testing in cardiovascular risk assessment of patients with OSA.

Other potential confounding factors limiting interpretation of prior studies include absent reporting of duration[10,12-16] and severity[13,15,16] of hypoxemia during sleep, sleep behavior in the days prior to testing,[8-18] and use of β-blocking medications.[8,9,11,12,14-17] Furthermore, differences in age, gender, body mass index, and apnea-hypopnea index (AHI) make definitive comparison across studies challenging.

The present study was designed to address these limitations in evaluating the association between OSA and exercise capacity. We tested the hypothesis that subjects with moderate-to-severe

OSA have lower peak $\dot{V}O_2$ during CPET evaluation than control subjects with mild or no OSA. We also tested whether a dose-response relationship exists between AHI and peak $\dot{V}O_2$ after adjusting for differences in baseline covariates.

METHODS

Study Subjects

Two groups of subjects were studied: subjects with newly diagnosed untreated moderate-to-severe OSA (AHI ≥ 15 events/h) and controls with mild or no OSA (AHI < 15 events/h). Subjects with OSA were recruited from the sleep clinic at Brigham and Women's Hospital, and controls were recruited from the community. All subjects underwent PSG testing to confirm the diagnosis of OSA (in the OSA group), evaluate for previously undiagnosed moderate-to-severe OSA (control group), and exclude other sleep disorders. Subjects were eligible for participation if between 18 and 65 years old, capable of performing exercise testing, and in good physical and mental health without other comorbidities or therapies that could influence excessive daytime sleepiness. Subjects were excluded if receiving continuous positive airway pressure (CPAP) treatment, as well as for sleep disorders other than OSA, including central sleep apnea, circadian rhythm disorder, REM sleep without atonia, periodic leg movements of sleep index > 15 events/h, insomnia, and narcolepsy. Subjects were also excluded for known heart disease, heart failure, chronic obstructive pulmonary disease, alcohol or other drug abuse, and pregnancy. The Brigham and Women's Hospital Institutional Review Board approved the protocol, and written informed consent was obtained from all participants.

Study Protocol

Standard in-laboratory PSG testing was performed on all subjects and consisted of an electroencephalogram, bilateral electrooculogram, submental electromyogram, bilateral leg electromyogram, standard electrocardiogram (ECG), measurements of airflow via thermister and nasal pressure, monitoring of respiratory effort with chest and abdominal bands, and pulse oximetry. The PSG was performed and scored in accordance with American Academy of Sleep Medicine standards[21] by a registered PSG technologist blinded to the CPET results. Sleep behavior in the prior 7 days was recorded using a self-report sleep diary.

To account for potential differences in routine physical activity that might lead to improved physical conditioning and higher exercise capacity, physical activity was measured using the International Physical Activity Questionnaire. This well-validated self-report survey evaluates physical activity over the preceding 7 days.[22] Results are reported as estimated metabolic equivalents of task (METs) × minutes per week.

Resting metabolic rate and respiratory quotient were measured with indirect calorimetry (Vmax Encore 29N Metabolic Cart, CareFusion, Yorba Linda, CA), using the ventilated hood technique. All measurements were performed between 08:00 and 12:00, with subjects fasting overnight prior to testing. Subjects were positioned lying supine at 45 degrees in bed in a quiet room and were instructed to limit movement while watching a non-stimulating video. This position was maintained ≥ 20 min and until steady-state measurements were achieved.

Immediately following indirect calorimetry, subjects underwent maximum, symptom-limited CPET on a cycle ergometer (Lode Corival, Groningen, Netherlands) under supervision of a trained physiotherapist and cardiologist. Breath-by-breath respiratory gas exchange measurements were obtained with a metabolic cart (Medgraphics Ultima, St. Paul, MN). After a 2-min resting interval and 1 min of active cycling without resistance, a ramp protocol of 10-15 W/min was used. All subjects were encouraged to exercise until exhaustion.[23] During testing, heart rate, ECG, and pulse oximetry were recorded continuously. Blood pressure was recorded in 2-min intervals. Peak $\dot{V}O_2$ was calculated as the maximum oxygen uptake in the final 20 sec of exercise. The ventilatory threshold was defined by the V-slope method as the exercise level at which exhaled CO_2 increased exponentially relative to $\dot{V}O_2$.

Results for peak $\dot{V}O_2$, the primary outcome, were reported relative to age- and weight-predicted norms using the Wasserman formula[24,25] to allow comparison across subjects with different baseline characteristics.[23] Maximum predicted heart rate was calculated using the Astrand formula.[19] Ventilatory efficiency, the $\dot{V}_E/\dot{V}CO_2$ slope, was calculated as the slope of the linear regression line relating $\dot{V}_E$ and $\dot{V}CO_2$.[26] Peak oxygen pulse was calculated by dividing peak $\dot{V}O_2$ by peak heart rate. Good effort was assessed using a threshold peak respiratory exchange ratio of ≥ 1.10.

Statistical Analysis

Data from OSA and control subjects were compared using Fisher exact test for categorical variables and t-test or Wilcoxon rank sum test for continuous variables as appropriate. Multivariable linear regression was used to determine the association between percent predicted peak $\dot{V}O_2$ (primary outcome measure) and AHI (*a priori* predictor of interest), adjusting for differences in baseline covariates that reached statistical significance. Analysis of variance (ANOVA) was performed to determine the proportion of total variability in percent predicted peak $\dot{V}O_2$ explained by the PSG predictor variables before and after adjusting for baseline differences. To approximate better a normal distribution, AHI was log-transformed for all regression and ANOVA analyses. In an exploratory secondary analysis, multivariable linear regression was also performed to determine the association between percent predicted peak $\dot{V}O_2$ and other PSG indices that differed significantly between OSA and control subjects in univariate analysis.

Data for continuous variables are expressed as mean ± SD for normally distributed variables and median [interquartile range] for non-normally distributed variables. A two-sided α level of 0.05 was considered statistically significant. Statistical analysis was performed using SAS 9.3 (SAS Institute, Cary, NC).

RESULTS

Baseline Characteristics

Fifteen subjects with moderate-to-severe OSA (AHI ≥ 15 events/h) and 19 control subjects with mild or no OSA (AHI < 15 events/h) were enrolled. Baseline characteristics are presented in **Table 1**. OSA subjects were significantly older than control subjects (age 47.9 ± 11.5 years versus 34.3 ± 12.0 years,

Table 1—Baseline characteristics.

	Moderate-Severe OSA AHI ≥ 15 (n = 15)	Control AHI < 15 (n = 19)	p value
Age (years)	47.9 ± 11.5	34.3 ± 12.0	< 0.01
Male sex, no. (%)	12 (80.0%)	10 (52.6%)	0.15
Race or ethnicity, no. (%)			
White	11 (73.3%)	10 (52.6%)	
Black	3 (20.0%)	6 (31.6%)	0.53
Other	1 (6.7%)	3 (15.8%)	
Comorbidities, no (%)			
Diabetes	2 (13.3%)	0	0.19
Hypertension	3 (20.0%)	4 (21.1%)	1.00
Depression	2 (13.3%)	0	0.19
Body mass index (kg/m^2)	32.2 ± 7.8	28.8 ± 6.5	0.17
Resting metabolic rate (kcal/day)	1650 ± 262	1604 ± 302	0.67
Resting metabolic rate (% predicted)	89.9 ± 9.3	88.5 ± 7.9	0.68
Typical physical activity (MET-minutes/week)	2341 [1386, 4164]	3936 [1260, 6492]	0.37

Data are presented as number (%), mean ± SD, or median [IQR]. MET refers to metabolic equivalent of task, estimated using the International Physical Activity Questionnaire.

Table 2—Polysomnography and clinical sleep data.

	Moderate-Severe OSA AHI ≥ 15 (n = 15)	Control AHI < 15 (n = 19)	p value
Apnea-hypopnea index (events/h)	37.6 [26.8, 55.3]	1.5 [0.7, 5.4]	< 0.01
Total sleep time (min)	356.9 ± 79.1	388.2 ± 106.8	0.38
Sleep efficiency	75.8 ± 15.1	78.3 ± 15.8	0.66
Arousal index	37.2 ± 18.8	14.7 ± 5.0	< 0.01
Minimum SpO_2 (%)	81 [75, 82]	92 [87, 93]	< 0.01
Mean SpO_2 (%)	94 [93, 95]	97 [95, 98]	< 0.01
Sleep time with SpO_2 < 90% (min)	21.9 [16.3, 81.0]	0 [0, 0.9]	< 0.01
Total sleep time in prior 24 hours (h)	7.3 ± 1.8	6.6 ± 1.6	0.30
Mean daily sleep time in prior 7 days (h)	7.7 ± 1.2	7.9 ± 0.7	0.53

Data are presented as mean ± SD or median [IQR].

$p < 0.01$) but did not differ significantly by body mass index or resting metabolic rate. Two OSA subjects were taking atenolol. No other subjects were receiving treatment with a β-blocker at the time of study.

Polysomnography and Sleep Behavior

AHI was significantly higher among OSA subjects than control subjects (37.6 [26.8, 55.3] versus 1.5 [0.7, 5.4] events/h, $p < 0.01$; **Table 2**). OSA subjects had more severe hypoxemia during sleep as measured by minimum oxygen saturation (81 [75, 82] vs 92 [87, 93] %, $p < 0.01$), mean oxygen saturation (94 [93, 95] vs 97 [95, 98] %, $p < 0.01$), and sleep time with oxygen saturation < 90% (21.9 [16.3, 81.0] vs 0 [0, 0.9] min, $p < 0.01$). Total sleep time during PSG and subjective report of sleep time in both the 24 h and 7 days immediately prior to exercise testing did not differ significantly between groups.

Cardiopulmonary Exercise Testing

All control subjects and all but one OSA subjects demonstrated maximal effort (peak respiratory exchange ratio 1.06 for remaining subject). Peak $\dot{V}O_2$ expressed as a percent of the predicted maximum was significantly lower among OSA subjects than controls (70.1% ± 17.5% vs 83.8% ± 13.9%; $p = 0.02$; **Table 3**, **Figure 1**). This significant difference remained when peak $\dot{V}O_2$ was expressed per kg body weight (19.1 ± 6.4 vs 25.2 ± 9.5 mL/kg/min; $p = 0.04$). Differences between OSA subjects and controls in other key exercise parameters, including ventilatory efficiency ($\dot{V}_E/\dot{V}CO_2$ slope), ventilatory threshold, maximum voluntary ventilation, and peak oxygen pulse did not reach statistical significance.

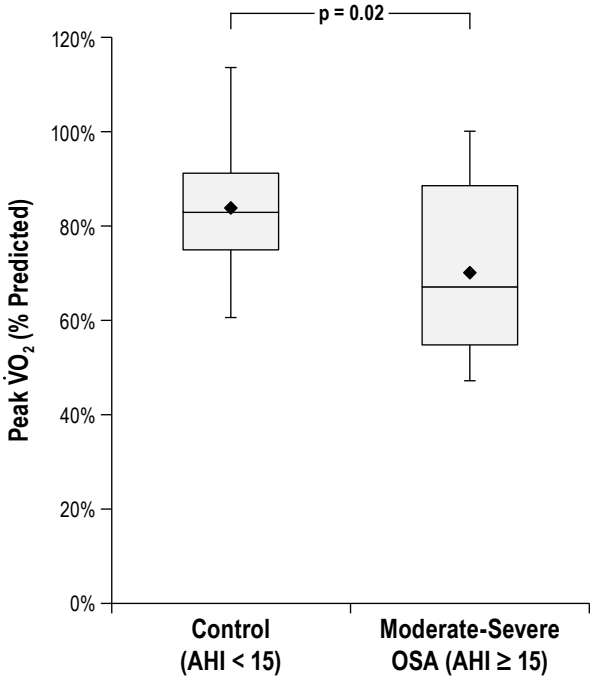
In a sensitivity analysis, data were reanalyzed, grouping subjects according to an AHI threshold of 5 events/h. Peak $\dot{V}O_2$ again was significantly lower among high-AHI subjects (AHI ≥ 5 events/h) compared to low-AHI subjects (AHI < 5 events/h), both when expressed as a percent of the predicted maximum (71.5% ± 15.5% vs 87.9% ± 14.3%; $p < 0.01$) and per kg body weight (19.0 ± 5.7 vs 28.2 ± 9.9 mL/kg/min; $p < 0.01$). Peak diastolic blood pressure also was significantly higher among subjects with AHI ≥ 5 events/h (81 ± 7 vs. 74 ± 10; $p = 0.05$), while the proportion of subjects with hypertension did not differ significantly.

Table 3—Cardiopulmonary exercise data.

	Moderate-Severe OSA AHI ≥ 15 (n = 15)	Control AHI < 15 (n = 19)	p value
Peak $\dot{V}O_2$ (% predicted)	70.1 ± 17.5	83.8 ± 13.9	0.02
Peak $\dot{V}O_2$ (mL/kg/min)	19.1 ± 6.4	25.2 ± 9.5	0.04
Ventilatory threshold (% predicted peak $\dot{V}O_2$)	41.2 ± 12.6	48.0 ± 16.1	0.19
Maximal $\dot{V}_E$ (L/min)	62.5 ± 24.1	68.1 ± 16.6	0.43
Ventilatory efficiency ($\dot{V}_E/\dot{V}CO_2$ slope)	25.7 ± 4.0	25.0 ± 3.1	0.61
Peak respiratory exchange ratio	1.21 [1.18, 1.28]	1.20 [1.17, 1.34]	0.86
Peak systolic blood pressure (mm Hg)	179 ± 31	173 ± 24	0.47
Peak diastolic blood pressure (mm Hg)	81 ± 9	76 ± 9	0.18
Peak heart rate (% predicted)	85.0 ± 20.8	90.5 ± 7.7	0.35
Peak oxygen pulse (mL O_2/beat)	12.5 ± 3.2	12.2 ± 4.2	0.81

Data are presented as mean ± SD or median [IQR].

Figure 1—OSA is associated with impaired exercise capacity.



Box plots illustrate the median and interquartile range (boxes), mean (diamond), and maximum and minimum observed values (whiskers) of percent predicted peak $\dot{V}O_2$ for moderate-severe OSA (AHI ≥ 15 events/h; n = 15) and control (AHI < 15 events/h; n = 19) subjects.

The association between percent predicted peak $\dot{V}O_2$ and AHI was assessed using linear regression and ANOVA with and without adjusting for age, the only baseline characteristic to differ significantly between groups. In the unadjusted analysis, each 1-unit increase in $\log_e$(AHI) was associated with a decrease in percent predicted peak $\dot{V}O_2$ of 3.20 (95% CI 0.53 to 5.88; p = 0.02). After adjusting for differences in age, the association between log-transformed AHI and percent predicted peak $\dot{V}O_2$ remained significant (β = -4.78; 95% CI -1.30 to -8.26; p < 0.01). Log-transformed AHI alone explained 16.1% of the variability observed in percent predicted peak $\dot{V}O_2$ (p = 0.02). When age was added to the model, log-transformed AHI and age together explained 21.4% of the variability observed (p = 0.03). The association between percent predicted peak $\dot{V}O_2$ and AHI remained significant in post hoc univariate and multivariate analyses excluding the 2 OSA subjects on β-blocker therapy. In an exploratory secondary analysis, other PSG indices that were significantly different between OSA and control subjects were not significantly associated with percent predicted peak $\dot{V}O_2$ after adjusting for age.

DISCUSSION

The central finding of this study is that OSA is associated with decreased exercise capacity, measured by percent predicted peak $\dot{V}O_2$. Increasing OSA severity, as reflected by higher AHI, predicts impaired exercise capacity in a dose-response fashion both before and after adjustment for significant baseline differences.

Several potential mechanisms exist by which OSA may both impair exercise capacity and increase cardiovascular risk. Decreased maximal lactate concentration and delayed lactate elimination have been observed in OSA subjects during exercise compared to age- and BMI-matched controls, suggesting impaired glycolytic and oxidative metabolism, respectively.[14] Muscle biopsy studies have demonstrated structural and bioenergetic changes in skeletal muscle fiber in OSA subjects,[27] as well as increased microvascularization in skeletal muscle,[11] similar to changes observed in other states of chronic hypoxia. Several studies have demonstrated an abnormal cardiovascular response during exercise or recovery in OSA patients, including increased diastolic blood pressure, decreased stroke volume, attenuated heart rate during peak exercise and recovery, and global ventricular dysfunction.[8-10,13,17,28,29] OSA may contribute directly to left ventricular dysfunction via hypoxia and intermittent increase in afterload during apneic and hypopneic events.[30,31]

There are several key differences between this study and prior reports, which had yielded conflicting results on the association between OSA and impaired exercise capacity. The present study rigorously evaluated for OSA and other sleep-related breathing disorders by requiring that all subjects undergo

standard in-laboratory PSG using current gold standard techniques. Electroencephalogram, electrooculogram, and submental electromyogram were used for reliable determination of sleep-wake and sleep staging. Nasal pressure was used in addition to a thermistor to measure airflow more accurately. Respiratory effort was evaluated directly with chest and abdominal bands. Moreover, assessment of sleep behavior over the 7 days prior to CPET ensured differences could not be attributable to variability in short-term sleep deficit. Finally, usual physical activity and resting metabolic rate were measured to exclude their potential contribution to residual confounding.

Despite this study's strength in rigor, there are a number of important limitations. First, age was significantly different between OSA subjects and controls. Age is unlikely to have led to substantial bias because percent predicted peak $\dot{V}O_2$ accounts for age in its calculation.[24,25] Moreover, adjusted analysis including age as a covariate did not alter the findings. Second, emphasis on extensive characterization of the study population resulted in a small sample size, which makes the effect estimate less precise, as reflected in the wide confidence intervals. Third, two OSA subjects were taking β-blockers at the time of evaluation, which may limit exercise capacity independent of other factors.[32] Excluding these patients from the analysis did not change the findings. Fourth, subjects were grouped according to an AHI threshold of 15 events/h rather than by diagnosis of OSA; this approach was chosen *a priori* and is supported by the dose-response relationship observed between AHI and percent predicted peak $\dot{V}O_2$. Re-analysis using a lower AHI threshold of 5 events/h did not change the study findings. Finally, because the data are cross-sectional, the possibility of reverse causation exists, whereby limited exercise capacity contributes to OSA rather than vice versa.[33] Future studies would benefit from longitudinal follow-up including assessment of exercise capacity following initiation of CPAP for OSA.

The present study demonstrates an important relationship between increasing AHI and impaired exercise capacity. Probable mechanisms for this association overlap considerably with that between OSA and adverse cardiovascular events, leading to the possibility that CPET may provide an early window into cardiovascular risk stratification of patients with OSA. Future studies are needed to determine whether CPET offers prognostic significance in OSA, and importantly whether treatment of OSA effectively modifies this risk.

ABBREVIATIONS

AHI, apnea-hypopnea index
CPAP, continuous positive airway pressure
CPET, cardiopulmonary exercise testing
ECG, electrocardiogram
Events/h, events per hour
OSA, obstructive sleep apnea
PSG, polysomnography
$\dot{V}O_2$, oxygen uptake
95% CI, 95% confidence interval

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SUBMISSION & CORRESPONDENCE INFORMATION

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Address correspondence to: Jeremy R. Beitler, M.D., Division of Pulmonary and Critical Care Medicine, Brigham and Women's Hospital, 221 Longwood Avenue, BLI 036, Boston, MA 02115; Tel: (617) 732-5619; Fax: (617) 732-7337; E-mail: jbeitler@partners.org

DISCLOSURE STATEMENT

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