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REVIEW ARTICLES

OSA and cardiorespiratory fitness: a review

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The effects of untreated obstructive sleep apnea (OSA) on cardiopulmonary function remain unclear. Cardiorespiratory fitness (CRF), commonly reflected by VO_2 max measured during cardiopulmonary exercise testing, has gained popularity in evaluating numerous cardiopulmonary conditions and may provide a novel means of identifying OSA patients with the most clinically significant disease. This emerging testing modality provides simultaneous assessment of respiratory and cardiovascular function with results helping uncover evidence of evolving pathology in either organ system. In this review, we highlight the current state of the literature in regard to OSA and CRF with a specific focus on changes in cardiovascular function that have been previously noted. While OSA does not appear to limit respiratory function during exercise, studies seem to suggest an abnormal cardiovascular exercise response in this population including decreased cardiac output, a blunted heart rate response (ie, chronotropic incompetence), and exaggerated blood pressure response. Surprisingly, despite these observed changes in the cardiovascular response to exercise, results involving VO_2 max in OSA remain inconclusive. This is reflected by VO_2 max studies involving middle-aged OSA patients showing both normal and reduced CRF. As prior studies have not extensively characterized oxygen desaturation burden, we propose that reductions in VO_2 max may exist in OSA patients with only the most significant disease (as reflected by nocturnal hypoxia). Further characterizing this relationship remains important as some research suggests that positive airway pressure therapy or aerobic exercise may improve CRF in patients with OSA. In conclusion, while it likely that severe OSA, via an abnormal cardiovascular response to exercise, is associated with decreased CRF, further study is clearly warranted to include determining if OSA with decreased CRF is associated with increased morbidity or mortality.

Keywords: obstructive sleep apnea, cardiopulmonary exercise testing, cardiorespiratory fitness, VO_2 max

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INTRODUCTION

Cardiorespiratory fitness (CRF), typically defined by the efficiency by which the cardiovascular and respiratory systems supply oxygen to skeletal muscle during exercise, is an emerging topic in preventive medicine. In a joint statement in 2016 by the European Association for Cardiovascular Prevention and Rehabilitation and the American Heart Association, cardiopulmonary exercise testing (CPET) to assess CRF was emphasized as a valuable tool in the management of numerous cardiopulmonary conditions (eg, chronic obstructive pulmonary disease, congestive heart failure, obesity).[1] CRF, most commonly reflected by measurement of the maximum oxygen uptake (VO_2 max) during CPET, is a reliable predictor of cardiovascular disease and mortality (perhaps even more so than traditional risk factors) and has shown promise in helping determine optimal timing for transplantation in heart failure.[2–7] Given this rising interest in CRF as a prognostic tool, including in healthy patients, novel methods for determining VO_2 max as well as demographic-specific normative values are being developed to aid interpretation.[8–11] With these advances, routine assessment of CRF may become a reality, allowing for early recognition of heightened cardiovascular risk and implementation of preventive measures to reduce long-term morbidity and mortality. One condition where this may be particularly useful is obstructive sleep apnea (OSA), where CRF assessment may help identify patients at elevated cardiovascular risk whom positive airway pressure (PAP) or alternative OSA therapies may benefit most.

OSA, characterized by repetitive partial or complete obstruction of the upper airway during sleep, impacts between 9% and 38% of the population and may elevate cardiovascular risk.[12,13] Repetitive hypoxia-reoxygenation events and nocturnal arousals associated with OSA elevate serum inflammatory biomarkers, sympathetic nervous system activity, and endothelial dysfunction that together may contribute to atherogenesis.[14–23] Literature evaluating the relationship between OSA and the development of various cardiovascular conditions is robust, with studies demonstrating an association between OSA and hypertension, atrial fibrillation, sudden cardiac death, and myocardial infarction.[24–30] The extent to which this relationship is affected by OSA severity (defined by variables such as daytime sleepiness, apnea-hypopnea index [AHI], and degree of oxygen desaturation) remains debated, though it is likely that more severe disease portends greater cardiovascular risk.[31,32] This association between OSA and clinical cardiovascular disease has stimulated interest in the effects of OSA on CRF as a potential prognostic and therapeutic tool. In the course of this review, we seek to present the current state of the literature in regard to OSA and CRF as defined by physiologic performance during CPET. While this discussion will primarily focus on VO_2 max as a direct reflection of CRF, we will briefly explore prior findings involving indirect measures of CRF including heart rate and blood pressure response to peak exercise and respiratory efficiency parameters also collected during CPET. To aid in comparison, we will describe prior OSA study groups by both AHI and SpO_2 nadir, two of the commonly used variables to describe OSA severity in prior research on this topic.

RESULTS

Exercise and OSA

During CPET, graded exercise is performed with the use of a treadmill or cycle ergometer while respiratory gas exchange is measured via a nonrebreathing valve and metabolic cart.[33] This setup allows for measurement of airflow volume as well as concentration of oxygen and carbon dioxide in expired gas which can be utilized to determine minute ventilation (VE), consumption of oxygen (VO_2) and production of carbon dioxide (VCO_2), respiratory exchange ratio (VCO_2/VO_2), and ventilation/carbon dioxide production ratio (VE/VCO_2). These variables, along with continuous pulse oximetry monitoring (SpO_2), provide information about exercise performance. Of these variables, VO_2 provides the most comprehensive measure of cardiopulmonary performance during exercise and is represented by the following formula in which arterial and venous oxygen content are represented by C_aO_2 and C_vO_2:

$$VO_2 = (HR \times SV) \times (C_aO_2 - C_vO_2).$$

During exercise, predictable increases in cardiac stroke volume, heart rate, tissue blood oxygen extraction, and VE occur until the maximum consumption of oxygen or VO_2 max is achieved. Age, sex, and race all influence normative values for VO_2 max, which may not be achieved by certain individuals due to cardiovascular, pulmonary, and metabolic disorders or due to physical deconditioning or submaximal patient effort.[34] Suggested algorithms for CPET interpretation begin with an assessment of VO_2 max, which if reduced (< 85% predicted) should be followed by a determination of the etiology of limitation. A gas exchange or pulmonary limitation is indicated when there is a decrease in SpO_2 of greater than 4% (or to an absolute value less than 90%) at peak exercise or there is an elevation in peak VE to greater than 80% of maximum ventilatory volume, while a VE/VCO_2 > 40 at peak exercise may suggest cardiovascular limitation. Nonlinear trends in exercise heart rate and blood pressure may also suggest cardiovascular limitation, while a peak heart rate less than 85% predicted maximum or a respiratory exchange ratio < 1.0 likely reflects submaximal exercise effort.[1]

The mechanism by which OSA may limit exercise performance remains unclear. Interestingly, despite being a primarily pulmonary condition, OSA does not appear to limit the respiratory response to exercise. Studies of ventilatory response and gas exchange during peak exercise in patients with OSA have been predominantly normal, including those involving patients with the most severe disease (as represented by AHI and degree of oxygen desaturation). In a recent study by Han et al comparing patients with obesity hypoventilation syndrome (AHI 40.4 events/h, SpO_2 nadir 71.9%) to those with eucapnic OSA (AHI 45.6 events/h, SpO_2 nadir 72.4%) and obesity without OSA (AHI 3.9 events/h, SpO_2 nadir 85.0%), the respiratory response to exercise was noted to be similar between groups as represented by peak VE/maximum ventilatory volume (57.2% vs 54.3% vs 49.6%, $P > .05$) and SpO_2 at peak exercise (98.8% vs 98.5% vs 98.0%).[35] Similarly, in a study by Bernhardt et al comparing 8 obese patients with OSA (AHI 25.4 events/h, SpO_2 nadir not reported [NR]) to 8 age- and weight-matched controls (AHI 1.3 events/h, SpO_2 nadir NR), peak VE (31.8 vs 26.2 L/min; $P = .129$) and tidal volume (1,277 vs 1,421; $P = .947$) were similar between groups.[36]

Abnormal muscle metabolism has been postulated as a contributor to reduced exercise performance in OSA, though the research to support this hypothesis is limited. In a study involving needle biopsy of the quadriceps femoris of 12 consecutive patients with severe OSA (AHI 70 events/h, SpO_2 nadir NR) and six healthy controls, the diameter of type II skeletal muscle fibers was smaller and activity of muscle metabolic enzymes comparatively less in patients with OSA.[37] Likewise, in a study of 11 patients with moderate OSA (AHI 25.6 events/h, SpO_2 nadir 85%), blood lactate concentration and rate of lactate elimination during exercise were significantly decreased in patients with OSA compared to controls, a finding which may suggest impaired glycolytic and oxidative metabolism in the skeletal muscle of patients with OSA.[38] Studies involving normal patients without OSA exposed to hypoxic environmental conditions have also shown abnormalities in skeletal muscle function. In a study of high-altitude climbers with prolonged exposure to hypoxic conditions, muscle biopsies revealed a reduction in skeletal muscle fiber size and density as well as muscle oxidative capacity, changes that may occur with the intermittent hypoxia characteristic of moderate to severe OSA.[39] These studies suggest that muscle structure and function may be altered in OSA; however, the potential of this mechanism to affect CRF in OSA remains unknown.

The most convincing evidence to date supports a potential cardiovascular limitation to exercise in OSA. In a comprehensive study by Alonso-Fernández et al involving CPET with cardiac output measurement (by the CO_2 rebreathing equilibrium method), it was found that nonhypertensive patients with untreated severe OSA (AHI 43.6 events/h, SpO_2 nadir 72%) and normal resting left ventricular function had significant reductions in cardiac output at peak exercise compared to healthy controls.[40] Interestingly, after the patients with OSA received 3 months of treatment with PAP, their left ventricular systolic performance during exercise significantly improved. Other studies have suggested subclinical abnormalities in resting left and right ventricular mass and systolic function in OSA, although these results have been inconsistent.[41,42] In one study by Shivalkar et al, subclinical differences in stroke volume, intraventricular septum thickness, and right ventricular free wall motion were noted in patients with severe OSA (AHI 42 events/h, SpO_2 nadir 76%) compared to controls, and these abnormalities improved with continuous PAP (CPAP) therapy.[43] Decrements in left ventricular diastolic filling have also been previously noted in patients with moderate to severe OSA, with one study showing grade 1 diastolic dysfunction in more than 20% of these patients.[44,45] In addition to these potential abnormalities in ventricular size and function, subclinical abnormalities in the pulmonary vasculature may also be present in untreated OSA, with one study showing a correlation between pulmonary arterial stiffness and OSA severity.[46]

Multiple studies also suggest a blunted heart rate response, or chronotropic incompetence, to peak exercise in OSA, which may also be an indicator of cardiovascular limitation in this population. This finding is thought to be due to functional downregulation of cardiac β1-receptor activity from chronic sympathetic hyperactivity.[47,48] In a study of middle-aged women with and without OSA undergoing exercise testing, peak heart rate was significantly lower in those with mild and moderate-to-severe OSA (148 and 144 beats per minute [bpm], respectively) compared to controls (158 bpm).[49] Similarly, in a study comparing 21 patients with moderate-to-severe OSA (AHI 55 events/h, SpO_2 nadir NR) to 10 healthy controls, chronotropic reserve (a marker of heart rate response to exercise) was significantly lower in patients with OSA (79.0% vs 99.0%; $P=.01$).[50] Most convincingly, in a meta-analysis by Mendelson et al that evaluated patients with OSA with mild, moderate, and severe disease, it was found that patients with OSA, regardless of severity, had a significantly lower peak heart rate compared to controls with a mean difference of approximately 8 bpm ($P=.02$).[51] This postulated downregulation of cardiac β1-receptor activity may not only limit peak exercise performance but also delay heart rate recovery (HRR) postexercise.[52] Cholidou et al identified that patients with mild/moderate and severe OSA had progressively less HRR at 1, 2, and 3 minutes after peak exercise compared to controls without OSA (HRR at 1 minute: 29 [control] vs 24 [mild/moderate OSA] vs 20 [severe OSA] bpm; HRR at 2 minutes: 40 vs 34 vs 28 bpm; HRR at 3 minutes: 46 vs 39 vs 33 bpm; $P<.05$).[53]

Studies showing an exaggerated blood pressure response to exercise in OSA may also support this hypothesis. Kasiakogias et al studied 57 patients with hypertension and moderate-to-severe OSA (AHI 30 events/h, SpO_2 nadir 80.4%) and 57 hypertensive controls. They found peak systolic blood pressure during exercise was higher in patients with OSA (197.6 vs 187.8 mm Hg; $P=.03$), with significantly more patients with OSA having a hypertensive response to exercise, defined as peak systolic blood pressure ≥ 210 mm Hg (44% vs 19%; $P=.009$).[54] Multivariate analysis in this study revealed that a hypertensive response to exercise independently correlated with AHI and SpO_2 nadir. Similar results were noted in a CPET study by Przybyłowski et al involving 111 patients with OSA (AHI 47.2 events/h, SpO_2 nadir 68.5%) in which a hypertensive response to peak exercise was noted in 35%.[55] An abnormal diastolic blood pressure response in patients with OSA has similarly been noted. In a study of 17 normotensive patients with OSA (AHI 33.3 events/h, SpO_2 nadir 89.6%) and 10 blood pressure-matched controls, a higher diastolic blood pressure at peak exercise was noted in patients with OSA (115 vs 101 mm Hg; $P<.01$), with patients with OSA reaching a diastolic blood pressure of 110 mm Hg at a lower VO_2.[56] This exaggerated diastolic blood pressure response to exercise was also noted in other studies by Vanhecke et al and Barros de Carvalho et al, though in the latter this was partially attributed to higher resting diastolic blood pressure.[49,57]

VO_2 max and OSA

Despite the aforementioned evidence linking untreated OSA with potential cardiovascular and muscular dysfunction during exercise (variables expected to limit VO_2 max), studies involving VO_2 max in patients with OSA have had variable results. An explanation for this variability remains unclear, though it may reflect differences in study demographics, OSA severity as reflected by degree of oxygen desaturation, and OSA phenotypic subtypes as previously suggested by Zinchuk and Yaggi.[58] From a demographic standpoint, body weight, age, and sex have all been postulated to influence the cardiovascular effects of OSA, though the degree to which these variables influence the relationship between untreated OSA and VO_2 max is not clearly defined. For body weight, this is made evident by the discordant results in prior studies comparing both lean and obese patients with OSA. Regarding age and sex, studies involving middle-aged male patients have predominantly shown a reduction in VO_2 max, while more age- and sex-diverse studies have mostly not shown a reduction. Perhaps it is those patients with the more traditional definition of OSA (middle-aged obese males) who have the most significant effect on VO_2 max.

In regard to OSA severity, prior research on this topic has focused predominantly on AHI, which may limit comparability between studies. It is becoming apparent that OSA severity is more nuanced than previously believed, with continued evidence supporting that it is likely the degree of nocturnal hypoxia expressed by oxygen desaturation depth and duration, rather than the frequency of OSA events (as reflected by the AHI), that most significantly affects the cardiovascular system.[59] Measures of hypoxia during polysomnography including SpO_2 nadir, time spent with oxygen saturation < 90%, and oxygen desaturation index have all shown better predictability of cardiovascular outcomes in prior research compared to AHI, though thresholds of significance remain unclear.[60] More recently, the "hypoxic burden" (a measure to quantify the depth and duration of nocturnal oxygen desaturation) has garnered attention as a reliable prognosticator of cardiovascular risk in OSA.[61] Unfortunately, prior studies evaluating VO_2 max in OSA have not extensively evaluated these hypoxia measures and have at best only included SpO_2 nadir, an imperfect reflection of nocturnal hypoxia. Ultimately it may be the degree of hypoxia in OSA, rather than AHI, which has the greatest influence on VO_2 max. It seems likely that if untreated OSA affects VO_2 max it will be most apparent in those with significant oxygen desaturation (expressed by time with SpO_2 nadir < 80%).

As noted previously, significant variability in demographics including age and sex as well as limited data on degree of oxygen desaturation make it difficult to establish trends between those studies which have shown a reduction in VO_2 max and those which have not. Despite this, we note that prior studies showing a reduction in VO_2 max in patients with OSA have predominantly involved middle-aged male patients with moderate to severe OSA. In these studies, degree of hypoxia is expressed predominantly by SpO_2 nadir and VO_2 max reduction has ranged from 3 to 9 $mL \cdot kg^{-1} \cdot min^{-1}$ (**Table 1**). In one of the earliest studies, Vanuxem et al found VO_2 max to be reduced by a

Table 1—Studies showing reduced VO_2 max in untreated OSA.

Study	Methods	Patient Characteristics	Key Findings and Results
Vanuxem et al, 1997[38]	• Case-control • Type 1 PSG • Cycle ergometer CPET to exhaustion with respiratory gas exchange measurements by a metabolic cart • AHI >10 events/h vs AHI ≤ 10 events/h	• Setting: community • 20 patients • Age: 47.8 y (OSA) vs 41.9 y (controls); $P > .05$ • BMI: 26.6 (OSA) vs 26.4; $P > .01$ • All male	• AHI: 25.6 events/h (OSA) • Minimum SpO_2: 85.4% (OSA) • VO_2 max, $mL \cdot kg^{-1} \cdot min^{-1}$: 26.2 (OSA) vs 33.2; $P < .005$ • Peak HR: 160 bpm (OSA) vs 166 bpm; $P > .05$ • Peak systolic BP: 206 (OSA) vs 194; $P > .05$ • Peak diastolic BP: 104 (OSA) vs 92; $P < .05$
Lin et al, 2006[63]	• Case-control • Type 1 PSG • Cycle ergometer CPET to exhaustion with respiratory gas exchange measurements by a metabolic cart • AHI > 30 events/h vs AHI < 10 events/h	• Setting: sleep clinic • 40 patients • Age: 47 y (OSA) vs 44 y (controls); $P > .05$ • BMI: 28.3 (OSA) vs 27.6; $P > .05$ • Male: 90% (OSA) vs 90%; $P > .05$	• AHI: 44 events/h (OSA) vs 5 events/h; $P < .05$ • Minimum SpO_2: 65.5% (OSA) vs 91.9%; $P < .05$ • VO_2 max, $mL \cdot kg^{-1} \cdot min^{-1}$: 21.6 (OSA) vs 30.1; $P < .05$ • Peak HR: 156 bpm (OSA) vs 161 bpm; $P > .05$
Beitler et al, 2014[62]	• Case-control • Type 1 PSG • Cycle ergometer CPET to exhaustion with respiratory gas exchange measurements by a metabolic cart • AHI ≥ 15 events/h vs AHI < 15 events/h	• Setting: hospital sleep clinic • 34 patients • Age: 47.9 y (OSA) vs 34.3 y (controls); $P < .01$ • BMI: 32.2 (OSA) vs 28.8; $P = .17$ • Male: 80% (OSA) vs 53%; $P = .15$	• AHI: 37.6 events/h (OSA) vs 1.5 events/h; $P < .01$ • Minimum SpO_2: 81% (OSA) vs 92%; $P < .01$ • TST SpO_2 < 90%: 21.9 (OSA) vs 0 min; $P < .01$ • VO_2 max (% predicted): 70.1% (OSA) vs 83.8%; $P = .02$ • VO_2 max, $mL \cdot kg^{-1} \cdot min^{-1}$: 19.1 (OSA) vs 25.2; $P = .04$ • Peak HR (% predicted): 85 (OSA) vs 90; $P = .35$ • Peak systolic BP: 179 (OSA) vs 173; $P = .47$ • Peak diastolic BP: 81 (OSA) vs 76; $P = .18$
Nanas et al, 2010[50]	• Case-control • Type 1 PSG • Treadmill CPET to exhaustion with respiratory gas exchange measurements by a metabolic cart • AHI ≥ 25 events/h vs AHI < 5 events/h	• Setting: sleep clinic • 31 patients • Age: 48 y (OSA) vs 46 y (controls); $P > .05$ • BMI: 29.3 vs 28.1; $P > .05$ • All male	• AHI: 55 events/h (OSA) • Minimum SpO_2: not reported • VO_2 max (% predicted): 88% (OSA) vs 98%; $P < .05$ • VO_2 max, $mL \cdot kg^{-1} \cdot min^{-1}$: 28.7 (OSA) vs 34.7; $P < .01$ • Peak HR (% predicted): 96 (OSA) vs 103; $P > .05$ • Peak HR: 155 bpm (OSA) vs 172 bpm; $P > .05$
Chien et al, 2012[64]	• Case-control • Type 1 PSG • Cycle ergometer CPET to exhaustion with respiratory gas exchange measurements by a metabolic cart • AHI ≥ 30 events/h vs AHI < 5 events/h	• Setting: sleep clinic • 60 patients • Age: 50 y (OSA) vs 50 y (controls); $P = .74$ • BMI: 26.5 vs 25.8; $P = .30$ • All male	• AHI: 48.4 events/h (OSA) vs 2.7 events/h; $P < .001$ • Minimum SpO_2: 70% (OSA) vs 86%; $P < .001$ • %TST SpO_2 < 90%: 20.6 (OSA) vs 0.1; $P < .001$ • VO_2 max, $mL \cdot kg^{-1} \cdot min^{-1}$: 25.0 (OSA) vs 27.7; $P = .003$ • Peak HR: 153 bpm (OSA) vs 165 bpm; $P = .001$
Vanhecke et al, 2008[57]	• Prospective observational • Type 1 PSG • Treadmill CPET to exhaustion with respiratory gas exchange measurements by a metabolic cart	• Setting: bariatric clinic • 92 patients • Age: 46 y (OSA) vs 45 y (controls); $P = .59$ • BMI: 50 (OSA) vs 47; $P = .15$ • Male: 32% (OSA) vs 30%; $P = .83$	• AHI: 32.5 events/h (OSA) vs 2.5 events/h; $P < .001$ • Minimum SpO_2: not reported • VO_2 max, $mL \cdot kg^{-1} \cdot min^{-1}$: 17.6 (OSA) vs 21.1; $P < .001$ • % rise HR: 79 (OSA) vs 99; $P = .02$ • % rise systolic BP: 44 (OSA) vs 41; $P = .77$

(continued on following page)

Table 1—Studies showing reduced VO2 max in untreated OSA. (*Continued*)

Study	Methods	Patient Characteristics	Key Findings and Results
	• AHI > 15 events/h vs AHI < 5 events/h		• % rise diastolic BP: 10 (OSA) vs 2; *P* = .005
Evans et al, 2014[71]	• Prospective observational • Type 1 PSG • Cycle ergometer CPET to exhaustion with respiratory gas exchange measurements by a metabolic cart • AHI ≥ 1 event/h vs AHI < 1 event/h	• Setting: pediatric hospital sleep clinic • 71 patients • Age: 10 y (OSA) vs 10 y (controls); *P* = .85 • Male: 68% (OSA) vs 35%; *P* = .81	• AHI: 8.9 events/h (OSA) vs 0.4 events/h; *P* < .001 • Minimum SpO_2: 85% (OSA) vs 90%; *P* = .002 • VO_2 max, $mL{\cdot}kg^{-1}{\cdot}min^{-1}$: 20.8 (OSA) vs 29.6; *P* < .001 • Peak HR: 159 bpm (OSA) vs 173 bpm; *P* = .006

AHI = apnea-hypopnea index, BMI = body mass index, BP = blood pressure, bpm = beats per minute, CPET = cardiopulmonary exercise testing, HR = heart rate, OSA = obstructive sleep apnea, PSG = polysomnography, SpO_2 = oxygen saturation, TST = total sleep time, VO_2 = maximum oxygen uptake.

mean of 6.8 $mL{\cdot}kg^{-1}{\cdot}min^{-1}$ in middle-aged males with moderate OSA (AHI 25 events/h, SpO_2 nadir 85%) compared to controls (26.4 vs 33.2 $mL{\cdot}kg^{-1}{\cdot}min^{-1}$; $P < .005$).[38] In similarly matched populations, Beitler et al and Lin et al found comparable results in patients with severe OSA. Beitler at al noted a 6.1 $mL{\cdot}kg^{-1}{\cdot}min^{-1}$ reduction in VO_2 max in patients with OSA (AHI 37 events/h, SpO_2 nadir 81%), while Lin et al found a 8.5 $mL{\cdot}kg^{-1}{\cdot}min^{-1}$ reduction in patients with severe OSA with more substantial oxygen desaturation (AHI 44 events/h, SpO_2 nadir 65%).[62,63] Furthering this trend, Nanas et al found a reduction in VO_2 max of 6 $mL{\cdot}kg^{-1}{\cdot}min^{-1}$ (28.7 vs 34.7 $mL{\cdot}kg^{-1}{\cdot}min^{-1}$; $P < .01$) in a study of middle-aged males with moderate to severe OSA (AHI 55 events/h, SpO_2 nadir NR), though degree of hypoxia was not reported.[50] Studies by Chien et al and Vanhecke found slightly lower reductions of 3.6 $mL{\cdot}kg^{-1}{\cdot}min^{-1}$ and 3.5 $mL{\cdot}kg^{-1}{\cdot}min^{-1}$, respectively, in patients with severe OSA, though degree of hypoxia was again not mentioned in these studies.[57,64]

Comparatively, studies which have not shown a reduction in VO_2 max have involved more diverse OSA populations from age and sex composition but have been similarly limited in their evaluation of nocturnal hypoxia (**Table 2**). Several of these studies have involved younger adults and geriatric populations as well as a significantly larger representation of female patients. In a study by Rizzi et al evaluating middle-aged lean and obese patients with and without OSA, it was noted that VO_2 max negatively correlated with the presence of obesity, but not OSA (32.1 [lean OSA] vs 30.5 [lean controls]; 21.7 [obese OSA] vs 24.7 [obese controls]; $P < .01$). In this study the lean OSA group had moderate disease (AHI 22.5 events/h, SpO_2 nadir 86.5%), while the obese OSA group had severe disease (AHI 33 events/h, SpO_2 nadir 78.3%).[65] Similar results were noted by Cepeda et al in a study comparing 30 patients with metabolic syndrome with and without OSA (AHI 42 events/h, SpO_2 nadir 77%) to 16 healthy controls in which VO_2 max was significantly decreased in those with metabolic syndrome but was not affected by the presence of OSA (22.6 vs 23.6 vs 28.7 $mL{\cdot}kg^{-1}{\cdot}min^{-1}$; $P < .05$).[66] These two studies highlight the potential for common comorbidities (with high cardiovascular risk) to confound assessment of the independent clinical cardiovascular effects of OSA in prior research.

In a younger population of military personnel, our group found similar normal results regarding VO_2 max (34.9 vs 35.5 $mL{\cdot}kg^{-1}{\cdot}min^{-1}$; $P = .65$) in those with moderate-to-severe OSA (AHI 32.7 events/h, SpO_2 nadir 84.2%) compared to those with mild disease (5.8 events/h, SpO_2 88.3%).[67] Hargens et al, in evaluating an even younger population (mean age 22 years) with and without OSA, found no significant difference in VO_2 max between groups (27.1 vs 28.0 $mL{\cdot}kg^{-1}{\cdot}min^{-1}$).[68] In this study, the patients with OSA had moderate disease (AHI 22.7 events/h), but their SpO_2 nadir was only 86%. In addition to a relatively low hypoxic burden, the normal VO_2 max results in these prior two studies may be explained by a shorter duration of sleep-disordered breathing. As the patients were younger, the negative cardiovascular sequelae of OSA may not have developed. However, studies in older populations have not always supported this explanation. In a study comparing nonobese, hypertensive older adult patients with and without OSA, Barbosa et al noted an age-related reduction in VO_2 max that was not influenced by the presence of OSA (17.2 vs 16.9 $mL{\cdot}kg^{-1}{\cdot}min^{-1}$; $P < .05$).[69] While SpO_2 nadir was not reported in this study, the 4% oxygen desaturation index was only 14.1 events/h with a mean oxygen saturation of 94%. These negative findings may again be related to a low hypoxic burden, though they may also be explained by survival bias which has been noted in prior studies of older adult patients with OSA.[70]

From a pediatric perspective there is one study evaluating this association between OSA and VO_2 max. Evans et al reported a reduction in VO_2 max of 8.8 $mL{\cdot}kg^{-1}{\cdot}min^{-1}$ in 40 children with moderate OSA (AHI 8.9 events/h, SpO_2 nadir 85%) compared to 31 controls (20.8 vs 29.6 $mL{\cdot}kg^{-1}{\cdot}min^{-1}$; $P < .001$).[71] Of note, mean age in this study was 10 years. Pediatric OSA manifests in different ways from adult OSA to include typically less severe oxygen desaturations; a larger percentage of patients with upper airway obstruction due to enlarged tonsils and adenoids, which is amenable to surgical treatment; and a shorter duration of disease. While residual

Table 2—Studies showing no reduction in VO_2 max in untreated OSA.

Study	Methods	Patient Characteristics	Key Findings and Results
Rizzi et al, 2013[65]	• Case-control • Type 1 PSG • Treadmill CPET to exhaustion with respiratory gas exchange measurements by a metabolic cart • AHI ≥ 10 events/h vs AHI < 5 events/h	• Setting: sleep clinic • 115 patients • Age: 53.7 y (lean OSA) vs 50.8 y (lean controls) vs 50.7 y (obese OSA) vs 49.1 y (obese controls); $P = .1$ • BMI: 22.1 (lean OSA) vs 22.8 vs 33.6 (obese OSA) vs 33.4; $P < .01$ • 31% male	• AHI: 22.4 events/h (lean OSA) vs 2.8 events/h (lean controls) vs 33.3 events/h (obese OSA) vs 2.9 events/h (obese controls); $P < .01$ • Minimum SpO_2: 86.5% (lean OSA) vs 91.2% (lean controls) vs 78.3% (obese OSA) vs 88.9% (obese controls); $P < .01$ • %TST $SpO_2 < 90\%$: 10.5% (lean OSA) vs 0% vs 32.9% (obese OSA) vs 0.2%; $P < .01$ • VO_2 max, $mL \cdot kg^{-1} \cdot min^{-1}$: 32.1 (lean OSA) vs 30.5 vs 21.7 (obese OSA) vs 24.7; $P < .01$ (for obesity only, not OSA) • Peak HR: 158 bpm (lean OSA) vs 161 bpm vs 151 bpm (obese OSA) vs 159; $P = .1$ • Peak systolic BP: 174 (lean OSA) vs 173 vs 184 (obese OSA) vs 192; $P = .07$ • Peak diastolic BP: 81 (lean OSA) vs 83 vs 92 (obese OSA) vs 89; $P = .02$ (obese OSA only)
Powell et al, 2019[67]	• Case-control • Type 1 PSG • Treadmill CPET to exhaustion with respiratory gas exchange measurements by a metabolic cart • AHI ≥ 15 events/h vs AHI < 15 events/h	• Setting: military treatment facility (active-duty personnel with dyspnea) • 98 patients • Age: 40.7 y (OSA) vs 39.4 y (controls); $P = .45$ • BMI: 30.4 (OSA) vs 29.9; $P = .46$ • Male: 97.5% (OSA) vs 93.1%; $P = .64$	• AHI: 32.7 events/h (OSA) vs 5.8 events/h; $P < .0001$ • Minimum SpO_2: 84.2% (OSA) vs 88.3%; $P = .0008$ • VO_2 max, $mL \cdot kg^{-1} \cdot min^{-1}$: 34.9 (OSA) vs 35.5; $P = .65$ • VO_2 max (% predicted): 101% (OSA) vs 102%; $P = .60$ • Peak HR: 166 bpm (OSA) vs 171 bpm; $P = .09$ • Peak systolic BP: 178 (OSA) vs 180; $P = .77$ • Peak diastolic BP: 78 (OSA) vs 74; $P = .28$
Hargens et al, 2008[68]	• Case-control • Type 3 OCST • Cycle ergometer CPET to exhaustion with respiratory gas exchange measurements by a metabolic cart • AHI ≥ 5 events/h vs AHI < 5 events/h	• Setting: community • 44 patients • Age: 22.4 y (OSA) vs 21.4 y (no OSA) vs 21.4 y (controls); $P > .05$ • BMI: 32.0 (OSA) vs 31.4 (no OSA) vs 22.0; $P < .05$ • All male	• AHI: 22.7 events/h (OSA) vs 2.5 events/h (no OSA) vs 2.0; $P < .05$ • Minimum SpO_2: 86.2 (OSA) vs 88.3 (no OSA) vs 90.0; $P > .05$ • VO_2 max, $mL \cdot kg^{-1} \cdot min^{-1}$: 27.1 (OSA) vs 28.0 (no OSA) vs 33.2; $P < .05$ (only for normal BMI controls) • Peak HR: 179 bpm (OSA) vs 180 bpm (no OSA) vs 181 bpm; $P > .05$ • Peak systolic BP: 196 (OSA) vs 202 (no OSA) vs 193; $P > .05$ • Peak diastolic BP: 90 (OSA) vs 91 (no OSA) vs 89; $P > .05$
Barbosa et al, 2018[69]	• Case-control • Type 1 PSG • Treadmill CPET to exhaustion with respiratory gas exchange measurements by a metabolic cart • AHI ≥ 15 events/h vs AHI < 5 events/h	• Setting: community older adult patients • 28 patients • Age: 70.6 y (OSA) vs 69.3 y (controls); $P > .05$ • BMI: 26.2 (OSA) vs 27.0; $P > .05$ • Male: 23% (OSA) vs 13%; $P > .05$	• AHI: 24.4 events/h (OSA) vs 2.3 events/h; $P < .01$ • Minimum SpO_2: not reported • ODI: 14.1 events/h (OSA) vs 2.5 events/h; $P < .01$ • VO_2 max, $mL \cdot kg^{-1} \cdot min^{-1}$: 17.2 (OSA) vs 16.9; $P > .05$ • Peak HR: 144 bpm (OSA) vs 150 bpm; $P > .05$ • Peak systolic BP: 201 (OSA) vs 197;

(continued on following page)

Table 2—Studies showing no reduction in VO2 max in untreated OSA. (*Continued*)

Study	Methods	Patient Characteristics	Key Findings and Results
			$P > .05$ • Peak diastolic BP: not reported
Cepeda et al, 2015[66]	• Case-control • Type 1 PSG and cycle ergometer CPET to exhaustion with respiratory gas exchange measurements by a metabolic cart • AHI ≥ 15 events/h vs AHI < 15 events/h	• Setting: outpatient cardiac clinic; patients with metabolic syndrome • 76 patients • Age: 49 y (MetS + OSA) vs 46 y (MetS, no OSA) vs 46 y (controls); $P > .05$ • BMI: 32 (MetS + OSA) vs 32 (MetS, no OSA) vs 25; $P < .05$ • Male: 60% (MetS + OSA) vs 46% (MetS, no OSA) vs 44%; $P > .05$	• AHI: 42 events/h (MetS + OSA) vs 7 events/h (MetS, no OSA) vs 4 events/h; $P < .05$ • Minimum SpO_2: 77% (MetS + OSA) vs 88% (MetS, no OSA) vs 91%; $P < .05$ • VO_2 max, $mL \cdot kg^{-1} \cdot min^{-1}$: 22.6 (MetS + OSA) vs 23.6 (MetS, no OSA) vs 28.7; $P < .05$ for controls; no difference between MetS groups • Peak HR: 156 bpm (MetS + OSA) vs 164 bpm (MetS, no OSA) vs 166 bpm; $P > .05$

AHI = apnea-hypopnea index, BMI = body mass index, BP = blood pressure, bpm = beats per minute, CPET = cardiopulmonary exercise testing, HR = heart rate, MetS = metabolic syndrome, OCST = out of center sleep testing, ODI = oxygen desaturation index, OSA = obstructive sleep apnea, SpO_2 = oxygen saturation, PSG = polysomnography, TST = total sleep time, VO_2 = maximum oxygen uptake.

OSA in older children postadenotonsillectomy may more closely resemble OSA seen in adults, data regarding surgical history were not available for this study, making a comparison difficult. Future pediatric research would benefit from further delineation of these pediatric phenotypes.

In comparison to these previously noted observational cohort studies, a 2018 meta-analysis by Mendelson et al may provide the most impactful assessment of the relationship between untreated OSA and VO_2 max. In this study evaluating 29 studies and 1,493 patients, a mean reduction in VO_2 max of $2.66\,mL \cdot kg^{-1} \cdot min^{-1}$ was noted in patients with varying degrees of untreated OSA ($P < .001$).[51] Somewhat surprisingly, this reduction in peak VO_2 was similar irrespective of OSA severity, with patients with severe OSA having a mean reduction of $2.5\,mL \cdot kg^{-1} \cdot min^{-1}$ compared to $1.9\,mL \cdot kg^{-1} \cdot min^{-1}$ in those with mild to moderate disease ($P = .15$). Mean reductions in VO_2 max were similar when comparing younger (age < 50 years) and older (age > 50 years) patients with OSA. Interestingly, a larger relative reduction in VO_2 max was found in nonobese compared to obese OSA patients (-4.1 vs $-1.2\,mL \cdot kg^{-1} \cdot min^{-1}$; $P < .001$). This study, which is the most comprehensive to date, used body mass index, AHI, and age in the sensitivity analyses and did not determine the effects of hypoxia on VO_2 max.

Submaximal exercise and OSA

There is similar uncertainty in regard to the effect of untreated OSA on submaximal exercise, most notably the 6-minute walk test (6MWT). The 6MWT is easy to perform and has prognostic value in various cardiopulmonary conditions to include heart failure and chronic obstructive pulmonary disease (COPD). Furthermore, distance walked on the 6MWT may be predictive of cardiovascular mortality and risk of cardiovascular disease in the general population.[72] Pływaczewski et al noted a prevalence of 18% for reduced exercise capacity on the 6MWT (less than 400 m walked) in a study of 151 middle-aged patients with severe OSA (AHI 42.4 events/h, SpO_2 nadir 71%), though body mass index appeared to influence this result.[73] In a study of slightly older patients with moderate to severe OSA (AHI 51.5 events/h, SpO_2 nadir NR) by Naghan et al, it was found that the duration of oxygen desaturation during polysomnography (time with SpO_2 < 90%) was predictive of distance walked as well as degree of SpO_2 reduction during the 6MWT. Those with severe OSA had a significantly lower percent-predicted distance on the 6MWT compared to those with moderate disease (75.9% vs 92.4%; $P = .020$), though total distance did not reach significance (477 m vs 555 m; $P = .173$). While SpO_2 nadir was not mentioned in this study, oxygen desaturation appeared substantial with patients averaging greater than 2 hours with SpO_2 < 90%.[74] The same result was noted in a study by Saad et al involving similarly aged patients (49 years) with severe OSA (AHI 62 events/h, SpO_2 nadir NR). In this study, percent-predicted distance on the 6MWT (83% vs 100%; $P < .05$) and total distance walked (512 m vs 585 m; $P < .05$) were reduced in those with OSA compared to controls. SpO_2 nadir was not mentioned in this study, though average SpO_2 during sleep in the OSA group was reduced at 90%.[75] Finally, in a cluster analysis of older patients (66 years) with severe OSA (AHI 38.3 events/h, SpO_2 nadir NR) by Vitacca et al, there was a high incidence of exercise limitation on the 6MWT. In this study, 29.2% had mild exercise limitation (6MWT < 85% predicted and ≥ lower limit of normal) and 31.9% had severe exercise limitation (6MWT < lower limit of normal) with mean distance walked being only 356 m. There was substantial nocturnal oxygen desaturation in this population with an average of 34% of time spent with SpO_2 < 90%, though other comorbidities including COPD appeared to influence this relationship as well.[76]

There are also studies that do not support a reduction in 6MWT performance in untreated OSA. Despite showing reduced cardiac output and cardiac index in older patients with moderate OSA, Hargens et al found that 6MWT distance was not different compared to controls.[77] In a younger study population (36 years), Alameri et al found a similar distance walked on the 6MWT in 55 obese patients with severe OSA (AHI 66.6 events/h, SpO_2 nadir NR) compared to obese controls (389 m vs 408 m; $P > .05$).[78] As with studies involving VO_2 max, these results may suggest it is the degree of nocturnal hypoxia, rather than AHI, which influences submaximal exercise performance. Better defining this relationship will be important as impaired functional capacity in patients with OSA may be associated with increased mortality.[79]

CPAP and exercise

Better understanding this relationship between untreated OSA and exercise performance may aid future determination of patients most likely to benefit from intervention. Unfortunately, research evaluating the effect of OSA therapies such as PAP on exercise performance is limited. In an early study involving 6 male patients with severe OSA (AHI 62.5 events/h, SpO_2 nadir 43.2%), it was noted that 1 week of nasal CPAP usage resulted in a 3.8 $mL \cdot kg^{-1} \cdot min^{-1}$ improvement in VO_2 max.[80] Similarly, Shifflett et al noted a 7.6% reduction in VO_2 at 60% peak estimated power after 4 weeks of nasal CPAP in patients with severe OSA (AHI 48 events/h, SpO_2 nadir NR), indicating improved overall CRF, though results did not reach statistical significance.[81] Conversely, in a study by Guillermo et al, VO_2 max was unchanged by PAP therapy in patients with moderate/severe OSA (AHI > 20 events/h, SpO_2 nadir NR) despite a noted reduction in VO_2 max prior to therapy.[82] We suspect that improvement in CRF with PAP therapy likely depends on patient population as well as PAP compliance. It may be the combination of strict compliance to PAP therapy in OSA patients with the most significant burden of nocturnal hypoxia which is associated with an improvement in exercise performance.

Determining those patients with OSA with reduced CRF may also allow for introduction of exercise regimens to improve fitness. While a few prior studies have suggested that aerobic exercise may improve OSA severity, regular exercise may be less common in this population.[83–85] Unfortunately, there is limited research specifically evaluating the effect of regular exercise on CRF in patients with OSA. In a meta-analysis by Iftikhar et al involving 129 patients with moderate to severe OSA, a mean improvement in VO_2 max of 3.9 $mL \cdot kg^{-1} \cdot min^{-1}$ was noted after engagement in an aerobic exercise regimen lasting from 12 to 24 weeks. Aerobic exercise in the included studies typically consisted of 30-minute sessions occurring three to five times per week and targeting achievement of the anaerobic threshold.[86] Of note, there was an improvement in OSA severity (as reflected by AHI) after completion of the exercise regimen that was independent of body mass index, which may explain this improvement in VO_2 max. Future research would benefit from evaluating the effects of aerobic exercise on VO_2 max in patients with OSA independent of a reduction in OSA severity. Additionally, to our knowledge there are no studies which have evaluated CPET in predicting morbidity and mortality, whereas there have been many studies evaluating this in other clinical populations.[87–89]

CONCLUSIONS

The effects of OSA on exercise capacity remain unresolved. Given the extensive research showing a link between OSA and adverse cardiovascular effects, it remains plausible that untreated OSA, especially when associated with a substantial hypoxic burden, may adversely impact exercise tolerance. How OSA effects CRF, especially VO_2 max, is likely influenced by several variables including OSA severity and patient demographics. Future research should standardize reported polysomnographic variables, especially regarding hypoxic burden, and explore the impact of these variables on CRF in order to provide better insight into prognosis and treatment of patients with OSA.

ABBREVIATIONS

6MWT, 6-minute walk test
AHI, apnea-hypopnea index
bpm, beats per minute
CPAP, continuous positive airway pressure
CPET, cardiopulmonary exercise testing
CRF, cardiorespiratory fitness
HRR, heart rate recovery
NR, not reported
OSA, obstructive sleep apnea
PAP, positive airway pressure
VE, minute ventilation

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DISCLOSURE STATEMENT

All authors have seen and approved this manuscript. Dr. Mysliwiec is Vice President, Medical Affairs for NOCTEM. He has served as a consultant for CPAP Medical, Bluegrass Oxygen, and Sleep Care Inc. He has previously consulted for Ebb Therapeutics and Nightware and received honoraria from Springer Healthcare LLC and Jazz Pharmaceuticals. Dr. Morris is a paid speaker for Janssen Pharmaceuticals and Vyaire Medical. The other authors report no conflicts of interest, and there is no other funding to disclose for this study. The views expressed herein are those of the authors and do not reflect the official policy or position of Brooke Army Medical Center, the U.S. Army Medical Department, the U.S. Army Office of the Surgeon General, the Department of the Army, the Department of the Air Force, and the Department of Defense or the U.S. government.