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Altered ventilatory responses to exercise testing in young adult men with obstructive sleep apnea

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Summary
Background: Obstructive sleep apnea (OSA) is a disorder characterized by repetitive obstructions of the upper airway. Individuals with OSA experience intermittent hypoxia, hypercapnia, and arousals during sleep, resulting in increased sympathetic activation. Chemoreflex activation, arising from the resultant oscillatory disturbances in blood gases from OSA, exerts control over ventilation, and may induce increases in sympathetic vasoconstriction, contributing to increased long-term risks for hypertension (HTN) and cardiovascular disease (CVD).
Methods: To evaluate whether OSA elicits exaggerated ventilatory responses to exercise in young men, 14 overweight men with OSA and 16 overweight men without OSA performed maximal ramping cycle ergometer exercise tests. Oxygen consumption (VO_2), ventilation, (V_E), ventilatory equivalents for oxygen (V_E/VO_2) and carbon dioxide (V_E/VCO_2), and V_E/VCO_2 slope were measured.
Results: The VO_2 response to exercise did not differ between groups. The V_E, V_E/VCO_2, V_E/VO_2 were higher ($p < 0.05$, 0.002, and $p < 0.02$, respectively) in the OSA group across all workloads. The V_E/VCO_2 slope was greater in the OSA group ($p < 0.05$). The V_E/VCO_2 slope and AHI were significantly correlated ($r = 0.56$, $p < 0.03$). Thus, young, overweight men with

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OSA exhibit increased ventilatory responses to exercise when compared to overweight controls. This may reflect alterations in chemoreflex sensitivity, and contribute to increased sympathetic drive and HTN risk.

Introduction

Obstructive sleep apnea (OSA) is a sleep disorder prevalent in approximately 2–4% of the middle-aged adult population.[1] Recent estimates, however suggest that over 85% of those with significant OSA, who would benefit from treatment, go undiagnosed.[2,3] This disorder has been associated with increased risk for the development of several adverse health conditions,[4] and it has recently been reported that OSA may also independently increase the risk for cardiovascular morbidity and mortality.[5–7] The strongest relationship, however, appears to be that between OSA and the occurrence of hypertension (HTN), which demonstrates an independent, dose–response relationship between OSA severity and HTN risk.[8,9]

The mechanisms linking OSA to HTN are unclear, but several proposed mechanisms suggest a complex interaction of several factors. Heightened sympathetic nervous system activation has been demonstrated in OSA, which persists during waking hours, and is above that which is seen in obesity alone.[10,11] Treatment of OSA with nasal continuous positive airway pressure (CPAP) has been shown to decrease sympathetic activity.[10,12]

Chemoreflexes exert powerful control over ventilation and contribute directly to sympathetic activation.[13] Tonic activation of the chemoreflexes, and a significantly greater ventilatory response to acute hypoxic breathing has been documented in OSA patients at rest[14,15] above that which has been previously noted in obesity alone.[16] Exercise is another instance when chemoreflex sensitivity augments,[17] and recent studies examining individuals with central sleep apnea (CSA) and congestive heart failure (CHF) demonstrated an exaggerated ventilatory response to exercise in CSA subjects, suggesting an enhanced chemosensitivity above CHF alone.[18,19] Significant correlations between CSA severity and the V_E/VCO_2 slope, a marker of chemosensitivity and predictor of poor prognosis with CHF, were also reported.[18,19]

Limited data is available on the responses to graded exercise testing in OSA, and no published studies have examined the ventilatory responses at submaximal and maximal exercise intensities. Therefore, the purpose of this study is to evaluate the ventilatory responses to graded exercise testing in young men with undiagnosed OSA, to examine whether a possible alteration in chemoreflex sensitivity may be an early clinical sign in the progression of OSA.

Methods

Study subjects

Sedentary overweight males with untreated OSA ($n = 14$), and control subjects matched for age, body mass index (BMI), and central adiposity, but without OSA ($n = 16$) were recruited from the local university community through campus notices as well as newspaper advertisements. Subjects were between 18 and 26 years of age and were classified as overweight according to BMI criteria.[20] All subjects underwent pre-screening which included an initial qualification questionnaire to identify any potential exclusion criteria, as well as a detailed health history questionnaire. All subjects were non-smokers, who were free from acute respiratory infection during the previous 6 weeks, including tonsillitis and adenoiditis. Subjects were free from significant cardiovascular, pulmonary, metabolic, or musculoskeletal disorders that would preclude maximal aerobic exercise testing. Subjects were not taking any prescribed vasoactive medications, hypnotics, sedatives, analgesics, psychotropics, steroids, or sympathomimetics. Individuals who had participated in regular physical activity (>3 days per week, >30 min per day) for the previous 6 months were considered physically active and excluded.[21] All methods and procedures, approved by the Institutional Review Board of Virginia Polytechnic Institute and State University (Virginia Tech), Blacksburg, VA, were explained to the subjects, who then read and gave written informed consent.

Home sleep evaluation

Subjects underwent an unattended, limited home sleep evaluation consisting of: (1) nasal flow detection via nasal cannula; (2) finger pulse oximetry; (3) respiratory effort detection via belts positioned on the upper and lower torso; and (4) body position detection, to screen for the presence of OSA, utilizing the Embletta portable device (Embla, Broomfield, CO). The Embletta device and other portable systems similar to the Embletta have previously been validated vs. nighttime polysomnography (PSG).[22–24] Embletta data were interpreted by a sleep technician and transposed into an apnea hypopnea index (AHI), with the results verified by the physician investigator who is a sleep specialist. Apnea is defined as a cessation of airflow for 10 s or greater. Hypopnea is defined a 50% or greater reduction in airflow for at least 10 s coupled with a decrease in oxygen saturation (≥4%).[4] Subjects were then classified into either the OSA group (OSA) (AHI > 5 events h^{-1}), or the no-OSA group (No-OSA) (AHI < 5 events h^{-1}).

Body composition measurement

Subjects completed total body dual-energy X-ray absorptiometry (DXA) scans (version 8.26a:3*, QDR4500A, Hologic Inc., Bedford, MA) for measurement of fat mass (FM) and body fat percentage (BF%). Central abdominal fat was measured from total body DXA scans by examining the region of interest defined by the top edge of the second to bottom edge of the fourth lumbar vertebra.[25] All DXA

measures were conducted and analyzed by one investigator. Weekly scans of an external soft tissue bar (Hologic Inc.) were completed to ensure quality control for soft tissue mass measurements. Test–retest reliability data for this DXA have been reported elsewhere.[26,27]

Ramp exercise testing

Subjects completed a maximal cycle ergometer exercise test. Anthropometric measures of height, weight, neck circumference (NC), waist circumference (WC), and hip circumference (HC) were measured prior to the exercise test. Resting heart rate (HR) and blood pressure were obtained in the seated position, after a minimum of 5 min of rest. An electronically braked cycle ergometer (SensorMedics®, Yorba Linda, CA) was utilized for each exercise test. A standardized protocol for each subject was utilized, which has been previously described.[28] Respiratory gas exchange measurements were obtained during the exercise test using a computer controlled, breath-by-breath system (SensorMedics Vmax 229®, Yorba Linda, CA). Values were calculated to 10 s averages. Measurements included oxygen consumption (VO_2), minute ventilation (V_E), carbon dioxide production (VCO_2), respiratory exchange ratio (RER) and peak VO_2 (VO_{2pk}). The two highest 10 s VO_2 values achieved during the last minute of exercise were averaged to obtain the VO_{2pk} value. The V_E/VO_2 and V_E/VCO_2 ratios were calculated at several submaximal workloads and at peak exercise. The V_E/VCO_2 slope was calculated from exercise onset to peak as previously described.[29,30]

Statistical analysis

All statistical analyses were performed using SPSS version 15.0 (SPSS Inc., Chicago, IL). Independent *t*-tests were used to evaluate differences in baseline descriptive characteristics between groups. Effects of group, exercise intensity (watts), and interactions on ventilatory measures were evaluated using two-way repeated measures ANOVA. Pearson *r* correlations were calculated to explore potential relationships between select ventilatory measures and AHI. A value of $p < 0.05$ was considered statistically significant.

Results

Subject characteristics

Demographic and descriptive characteristics for the study participants are presented in Table 1. No differences were noted between groups for age, BMI, NC, WC, HC, BF%, and central abdominal fat. Central abdominal fat was positively correlated with AHI ($r = 0.42$, $p = 0.02$) across all study subjects.

Exercise test measures

Heart rate and blood pressure responses did not differ between the groups at rest or during exercise and these findings are summarized elsewhere.[31] The VO_2 responses between groups did not differ at any submaximal exercise intensity or at maximum effort ($p = 1.0$), nor did peak work rate (Watts) achieved ($p = 0.30$). As shown in Fig. 1, VE, V_E/VCO_2, and V_E/VO_2 responses were higher in the OSA group at all workloads ($p < 0.05$, $p < 0.002$ and $p = 0.02$, respectively). The V_E/VCO_2 slope was greater in the OSA compared to the control group ($p = 0.045$) (Fig. 2), and was positively correlated with AHI ($r = 0.56$, $p = 0.001$) (Fig. 3). No difference in the RER between groups was noted at any submaximal workload or at peak ($p = 0.30$). Peak exercise responses for all subjects are presented in Table 2. Maximal test endpoints were achieved in both groups (peak RER > 1.1; peak RPE > 16).

Table 1 Subject characteristics.

	OSA ($n = 14$)	No-OSA ($n = 16$)
Age (years)	22.4 (2.8)	21.4 (2.6)
AHI (events $h^{-}1$)	22.7 (18.5)*	2.5 (1.3)
Height (cm)	171.6 (18.6)	178.2 (6.1)
Weight (kg)	99.6 (13.4)	99.4 (12.4)
BMI (kg $m^{-}2$)	32.0 (3.7)	31.4 (3.7)
NC (cm)	40.8 (2.1)	40.6 (2.6)
WC (cm)	100.5 (8.1)	95.4 (9.7)
HC (cm)	115.4 (8.1)	110.1 (8.4)
FM (kg)	29.1 (7.6)	26.0 (7.2)
% body fat	28.5 (4.7)	25.9 (4.5)
CAF (kg)	8.7 (2.4)	7.0 (1.9)

Values are means with SD in parentheses. AHI, apnea/hypopnea index; BMI, body mass index; NC, neck circumference; WC, waist circumference; CAF, central abdominal fat.
* $p < 0.0001$.

Discussion

This study is the first to evaluate ventilatory responses to exercise in young, overweight men with untreated OSA. The major finding is that OSA, and not obesity, results in increased ventilatory responses to graded exercise testing in young men, reflected by significantly greater V_E, V_E/VCO_2, and V_E/VO_2 measures across all submaximal exercise intensities and peak exercise (Fig. 1). In subjects matched for age, BMI, BF%, central abdominal fat, and VO_2, those with OSA demonstrated an exaggerated ventilatory response relative to carbon dioxide output and oxygen consumption. This finding is in contrast to that findings of Lin et al.,[32] which reported no difference between the OSA and control group in either peak V_E/VO_2 or V_E/VCO_2.

Exaggerated V_E/VCO_2 slope, a marker of chemoreflex sensitivity, has previously been found to be a potent predictor of poor prognosis in patients with CHF[29,33–35], a condition frequently seen in patients with central sleep apnea (CSA) as well as OSA. Artz et al.[19] found, in middle-age individuals with CHF and CSA, the V_E/VCO_2 slope, with exercise, was greater than those without CSA. They also reported a significant correlation between the V_E/VCO_2 slope and AHI ($r = 0.613$; $p < 0.001$).[19] More recently, Meguro et al.[18] also reported a greater V_E/VCO_2 slope in middle-aged CHF patients with CSA compared to CHF subjects without CSA ($p < 0.01$). To our knowledge, no studies have examined the response to exercise in OSA subjects. Results from the current study indicate that this

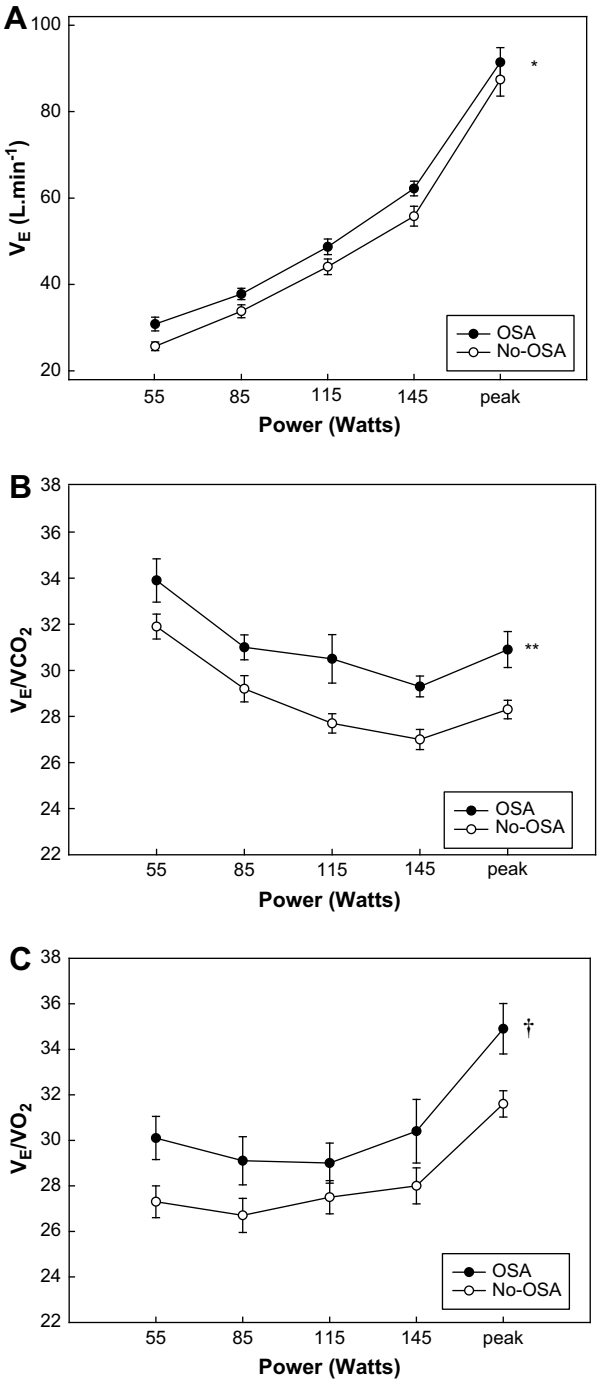

Figure 1 Submaximal and maximal ventilatory responses during cycle ergometer exercise in young, sedentary men: (A) V_E was greater across all workloads in the OSA ($n = 14$) vs. No-OSA ($n = 16$) group (*$p < 0.05$); (B) V_E/VCO_2 was greater across all workloads in the OSA vs. No-OSA group (**$p < 0.002$); (C) V_E/VO_2 was greater across all workloads in the OSA vs. No-OSA group (†$p < 0.02$).

measure of chemoreflex sensitivity is increased in young overweight men with OSA. We report a correlation between the V_E/VCO_2 slope and AHI similar to that of Artz et al. ($r = 0.56$ vs. 0.61).[19] Further examination of this relationship with OSA is required.

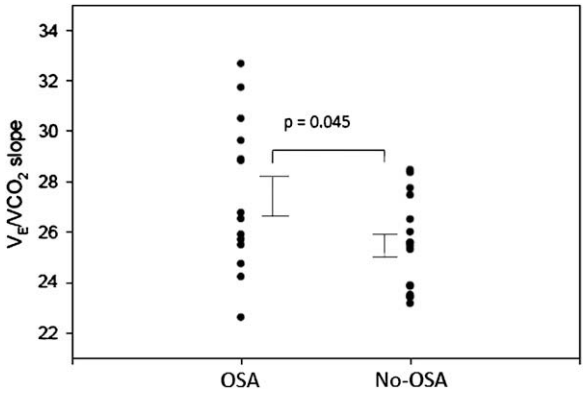

Figure 2 The individual and mean values of the V_E/VCO_2 slope of patients with OSA ($n = 14$) vs. No-OSA ($n = 16$).

The possible mechanisms underlying the exaggerated ventilatory responses may be multifaceted. The repetitive nocturnal bouts of hypoxia and hypercapnia operant in OSA have been implicated to induce alterations in the central and peripheral chemoreceptors.[36] Narkiewicz et al. previously demonstrated a tonic activation of the chemoreceptors in OSA patients,[15] and further demonstrated exaggerated chemoreflex sensitivity in OSA patients through breathing a hypoxic mixture that resulted in a greater V_E and muscle sympathetic nerve activation in the OSA group vs. non-OSA controls at rest.[14] Results of the current study agree with, and extend those of Narkiewicz et al.[14,15] suggesting that the intermittent nighttime hypoxia of OSA potentiates increased peripheral chemoreceptor sensitivity that persists during waking hours, and manifests during graded exercise testing. The underlying mechanisms that contribute to the alterations in chemoreceptor function are not well understood. Recent evidence suggests that multiple adaptive mechanisms may play a role, including alterations in vascular endothelial function, increased angiotensin II activity, as well increased generation of reactive oxygen species.[37,38]

Studies utilizing animal and human models support an increased peripheral chemoreceptor gain in response to

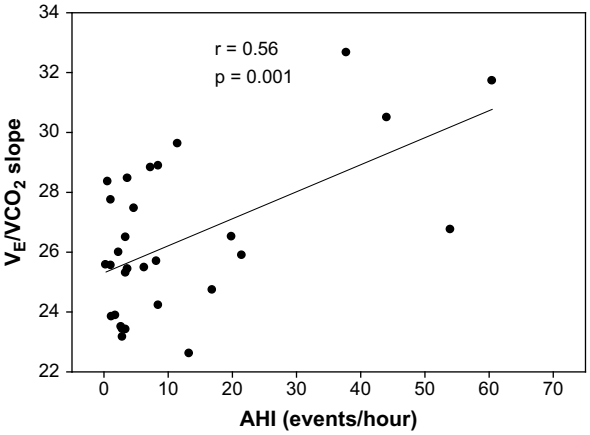

Figure 3 Relation between V_E/VCO_2 slope and the apnea–hypopnea index (AHI) in 30 overweight young men. The AHI is a measure of obstructive sleep apnea and its severity, as assessed by overnight somnography.

Table 2 Cardiopulmonary and perceptual responses to exercise.

	VO_2 peak ($mL.kg^{-1}.min^{-1}$)	V_E/VCO_2 slope	RER peak	RPE peak
OSA (n = 14)				
1	29.6	24.2	1.22	N/A
2	23.5	25.7	1.10	17
3	35.3	25.5	1.10	15
4	26.8	25.9	1.04	19
5	31.3	32.7	1.18	17
6	35.3	22.6	1.04	18
7	21.2	30.5	1.13	17
8	23.6	28.8	1.15	20
9	26.1	26.8	1.11	17
10	27.0	29.6	1.15	16
11	22.1	26.5	1.09	19
12	24.5	31.7	1.22	19
13	29.3	24.7	1.23	19
14	24.0	28.9	1.15	20
Mean (SD)	27.1 (4.5)	27.4 (3.0)	1.14 (0.06)	17.5 (1.6)
No-OSA (n = 16)				
1	24.5	23.4	1.16	16
2	28.9	25.4	1.09	17
3	25.9	27.7	1.16	18
4	25.8	26.0	1.1	18
5	22.7	28.5	1.11	17
6	26.3	23.4	1.11	18
7	19.6	23.9	1.12	17
8	24.9	25.3	1.12	15
9	26.0	23.8	1.15	17
10	25.2	26.5	1.13	20
11	26.5	25.6	1.07	19
12	34.3	27.5	1.19	18
13	31.4	23.2	1.21	16
14	35.1	23.5	1.04	16
15	26.7	28.4	1.14	19
16	44.2	25.6	1.12	18
Mean (SD)	28.0 (5.8)	25.5 (1.8)	1.13 (0.04)	17.4 (1.3)

RER, respiratory exchange ratio; RPE, rating of perceived exertion.

chronic intermittent hypoxia.[39–46] Data from these studies suggest that increased endothelin-1, a potent modulator of the peripheral chemoreceptors that is produced in the vascular endothelium, increases chemoreflex sensitivity. Rey et al. further showed an increased ventilatory response in animals exposed to hypoxic breathing.[46] Human studies in OSA subjects have also reported increases in endothelin-1 or its precursors, and the potential for CPAP to improve these factors.[43–45]. Our finding of an exaggerated ventilatory response to ramping exercise in young men with OSA is consistent with this hypothesized mechanism of increased chemoreceptor gain due to chronic intermittent hypoxia, possibly involving related alterations in vascular endothelial function. Further study is needed to clarify these adaptive mechanisms, particularly with respect to effects in exercise.

Another potential mechanism has been suggested by recent investigations that have reported alterations in the skeletal muscle function as a result of OSA.[47,48] Data from these studies indicated that OSA patients have a reduced peak blood lactate response during maximal exercise, as well as a diminished rate of blood lactate clearance. Taken together, these findings suggest a defect in muscle oxidative metabolism in OSA subjects.[47,48] While we did not measure lactate or catecholamine levels in the current study, we observed no differences in the VO_2 or RER responses in the two study groups. This suggests similar oxygen cost at the same power output, as well as a similar metabolic fuel mix. Taken together, it is unlikely that possible OSA-related differences in muscle oxidative metabolism would be an explanation for exaggerated ventilatory responses observed here.

One potential limitation is that nighttime PSG testing was not utilized for OSA diagnosis. Nighttime PSG is the standard and accepted tool for OSA diagnosis. The Embletta has been validated relative to PSG results,[22] but is dependent upon the subject's ability to properly set up the device independently. Subjects were provided verbal and visual instruction by study personnel, written instructions for device setup, and contact information for study personnel in case further instruction was needed. Another limitation was that cycle ergometry was utilized for the ramp exercise test rather than treadmill walking. Cycle ergometry can result in lower peak VO_2 values. In the current study, however, peak RER values for each group were greater than maximal criteria (RER $>$ 1.1), suggesting maximal efforts in all subjects.

In conclusion, the results of the current study indicate that exercise testing results in exaggerated ventilatory responses in young, overweight men with untreated OSA. These responses are suggestive of alterations in chemoreflex sensitivity and breathing efficiency in these individuals, beyond that seen with obesity alone. These findings also suggest the potential for clinical exercise testing in improving risk stratification and clinical decision making leading to patient selection for OSA diagnostic testing with PSG.

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Conflict of interest statement

Trent A. Hargens, Stephen G. Guill, Adrian Aron, Donald Zedalis, John M. Gregg, Sharon M. Nickols-Richardson, and William G. Herbert have no conflicts to disclose.

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