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Short-Term Modulation of the Ventilatory Response to Exercise is Preserved in Obstructive Sleep Apnea

Vipa Bernhardt[1,2], **Gordon S. Mitchell**[3], **Won Y. Lee**[4], and **Tony G. Babb**[1]

[1]Institute for Exercise and Environmental Medicine, Texas Health Presbyterian Hospital Dallas and UT Southwestern Medical Center, Dallas, TX, USA

[2]Texas A&M University-Commerce, Department of Health and Human Performance, Commerce, TX, USA

[3]University of Florida, Department of Physical Therapy, Gainesville, FL, USA

[4]Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX, USA

Abstract

Background—The ventilatory response to exercise can be transiently adjusted in response to environmentally (e.g., breathing apparatus) or physiologically altered conditions (e.g., respiratory disease), maintaining constant relative arterial P_{CO2} regulation from rest to exercise (Mitchell and Babb, 2006); this augmentation is called short-term modulation (STM) of the exercise ventilatory response. Obesity and/or obstructive sleep apnea could affect the exercise ventilatory response and the capacity for STM due to chronically increased mechanical and/or ventilatory loads on the respiratory system, and/or recurrent (chronic) intermittent hypoxia experienced during sleep. We hypothesized that: 1) the exercise ventilatory response is augmented in obese OSA patients compared with obese non-OSA adults, and 2) the capacity for STM with added dead space is diminished in obese OSA patients.

Methods—Nine obese adults with OSA (age: 39 ± 6 yr, BMI: 40 ± 5 kg/m^2, AHI: 25 ± 24 events/hr [range 6–73], mean ± SD) and 8 obese adults without OSA (age: 38 ± 10 yr, BMI: 37 ± 6 kg/m^2, AHI: 1 ± 2) completed three, 20-min bouts of constant-load submaximal cycling exercise (8 min rest, 6 min at 10 and 30 W) with or without added external dead space (200 or 400 ml; 20 min rest between bouts). Steady-state measurements were made of ventilation ($\dot{V}_E$), oxygen consumption ($\dot{V}_{O2}$), carbon dioxide production ($\dot{V}_{CO2}$), and end-tidal P_{CO2} ($P_{ET_{CO2}}$). The exercise ventilatory response was defined as the slope of the $\dot{V}_E$-$\dot{V}_{CO2}$ relationship ($\Delta \dot{V}_E/\Delta \dot{V}_{CO2}$).

Results—In control (i.e. no added dead space), the exercise ventilatory response was not significantly different between non-OSA and OSA groups ($\Delta \dot{V}_E/\Delta \dot{V}_{CO2}$ slope: 30.5 ± 4.2 vs 30.5 ± 3.8, $p > 0.05$); $P_{ET_{CO2}}$ regulation from rest to exercise did not differ between groups ($p > 0.05$). In trials with added external dead space, $\Delta \dot{V}_E/\Delta \dot{V}_{CO2}$ increased with increased dead space ($p <$

Corresponding author: T.G. Babb, Ph.D., Institute for Exercise and Environmental Medicine, 7232 Greenville Ave, Ste 435, Dallas, TX 75231, TonyBabb@TexasHealth.org.

0.05) and the $P_{ET_{CO2}}$ change from rest to exercise remained small (<2 mmHg) in both groups, demonstrating STM. There were no significant differences between groups.

Conclusions—Contrary to our hypotheses: 1) the exercise ventilatory response is not increased in obese OSA patients compared with obese non-OSA adults, and 2) the capacity for STM with added dead space is preserved in obese OSA and non-OSA adults.

Keywords

Obesity; Sleep apnea; P_{CO2}; Obesity hypoventilation syndrome

INTRODUCTION

Healthy, younger and older non-obese women and men exhibit an augmented exercise ventilatory response when challenged with added external dead space; this effect is termed short-term modulation (STM) of the exercise ventilatory response (Wood et al., 2008a, 2010, 2011). STM is a mechanism which modulates and adjusts the exercise ventilatory response in response to environmentally or physiologically increased respiratory dead space to maintain an appropriate ventilatory response and to preserve a constant relative arterial P_{CO2} (Pa_{CO2}) with respect to its resting level (Mitchell and Babb, 2006; Mitchell et al., 2008).

Adding dead space to the respiratory system increases resting neural respiratory drive, ventilation, and Pa_{CO2} due to classical negative feedback from CO_2 chemoreceptors; and subsequent ventilatory responses to exercise are increased independent from changes in chemoreceptor feedback from rest to exercise, demonstrating altered feed-forward contributions to breathing in exercise (Mitchell, 1990). Mitchell and colleagues (Bach et al., 1993; Henderson and Mitchell, 2000; Mitchell et al., 2008) demonstrated that STM requires the activation of spinal serotonin receptors in goats; the relevant serotonin receptors have been postulated to be located on respiratory motor neurons (Mitchell et al., 2001). Serotonin receptor activation may render respiratory motor neurons more excitable, enhancing respiratory muscle activation and ventilation for the same descending neural respiratory drive during exercise (Mitchell and Johnson, 2003). Obesity places a unique challenge on the respiratory system due to increased chest wall and abdominal fat compressing the lungs, leading to low lung volume breathing (Babb et al., 2008) and an increase in the work of breathing, especially during exercise (Bernhardt and Babb, 2014; Bhammar et al., 2016; Gibson, 2000; Kress et al., 1999). Despite these challenges, the ventilatory response to exercise is usually preserved in obese adults when corrected for the increased metabolic cost of a given work rate (Wasserman and Whipp, 1975).

Obesity is one of the strongest risk factors for developing obstructive sleep apnea (OSA) (Young et al., 1993); up to 77% of obese individuals are diagnosed with OSA (Frey and Pilcher, 2003; Lopez et al., 2008; O'Keeffe and Patterson, 2004). Conversely, OSA may contribute to weight gain and obesity (Carter and Watenpaugh, 2008; Shah and Roux, 2009). OSA is characterized by repetitive episodes of upper airway obstruction during sleep (i.e., developing increased respiratory pressures, sleep fractionation and chronic intermittent hypoxia (CIH). Thus, obese OSA patients are often burdened by multiple factors, including obesity and OSA-related respiratory challenges.

CIH elicits plasticity in the central neural control of breathing via serotonin-dependent mechanisms (Ling et al., 2001). Repetitive activation of serotonin receptors during CIH elicits long lasting enhancement of synaptic inputs to respiratory motor neurons and, potentially, their responses to increased neural respiratory drive associated with exercise (Ling et al., 2001) (i.e., increased neural output from motor neurons to respiratory muscles, thereby increasing the exercise ventilatory response). Obesity and CIH associated with OSA may impact STM in multiple ways. First, since CIH preconditioning enhances the ability to express serotonin-dependent respiratory motor plasticity (Gerst et al., 2011; Ling et al., 2001), including CIH accompanied by other attributes of OSA (Lee et al., 2009), serotonin-dependent STM may be enhanced in OSA patients. On the other hand, the capacity for STM is limited in both animal models (Mitchell, 1990) and normal humans (Wood et al., 2008a, 2010, 2011), suggesting that mechanical impairment associated with obesity and increased upper airway resistance may overload the system, diminishing the ability to express further STM with the addition of respiratory dead space.

STM (or lack thereof) has never been studied in obese humans, either with or without OSA. Thus, we tested the hypotheses that: 1) otherwise healthy obese human subjects (without OSA) retain the capacity for STM with increased respiratory dead space, at least through a limited range; 2) the exercise ventilatory response in obese OSA patients is unchanged versus otherwise healthy obese adults; and 3) the capacity for STM with added respiratory dead space is enhanced in obese OSA patients.

METHODS

Subjects

Nineteen obese adults diagnosed with (n=9) or without OSA (n=8) were recruited via flyers and word-of-mouth from the UT Southwestern Clinical Center for Sleep and Breathing Disorders. The presence or absence of OSA was determined as part of their clinical evaluation via polysomnography using nasal air flow via nasal cannula, finger pulse oximetry, and thoracic respiratory effort at a minimum to score apnea/hypopnea events. An apnea-hypopnea index (AHI) was generated. Apnea is defined as a cessation of airflow for ≥10 s. Hypopnea is defined as a ≥50% reduction in airflow for ≥10 s coupled with a reduction in oxygen saturation (≥4%). OSA was defined as an AHI of greater than five events per hour during sleep (Epstein et al., 2009). Exclusion criteria included current smoker or recent history of smoking, cardiovascular disease, asthma, anxiety or depression, and prior use of sleep apnea treatment (such as continuous positive airway pressure). The study was approved by the UT Southwestern Medical Center and all subjects gave their written informed consent to participate.

Subjects visited the exercise physiology laboratory on two occasions and were asked not to eat or consume caffeine for at least 2 h before each visit. On visit 1, standard measurements of height, weight, and body circumferences (neck, chest, waist, hips). A resting ECG was performed to exclude any significant cardiovascular abnormalities. Spirometry, lung volumes, and diffusing capacity measurements were performed via whole body plethysmography (model V62W body plethysmograph, SensorMedics), according to ATS/ERS guidelines (1995; Pellegrino et al., 2005).

STM protocol

On visit 2, subjects performed the STM protocol used the same equipment as previously described (Wood et al., 2008a, 2010, 2011). Subjects were instrumented with forehead pulse oximeter and 3-lead ECG. All subjects performed submaximal exercise on an electromagnetically braked cycle ergometer. Subjects performed three 18-min trials, consisting of a 6-min rest period followed by 6 min at 10 W and 6 min at 30 W. One trial was a control with no added dead space; for the other two trials an external dead space with a volume of 200 or 400 mL was added to the breathing circuit. The order of the three trials was randomized. A rest period of 20 min was given in between trials. Expired gas was collected in 200 L expiratory bags at rest (last 3 min) and during each level of exercise (last 2 min) for determination of gas exchange ($\dot{V}_{O2}$, $\dot{V}_{CO2}$) and minute ventilation ($\dot{V}_E$). End-tidal P_{CO2} ($P_{ET_{CO2}}$) and breathing frequency (R_f) was manually recorded from a capnograph every 15 s. Tidal volume (V_T) was calculated as $\dot{V}_E/R_f$.

Data analysis

Anthropometric measures and pulmonary function variables were assessed using independent t-test. The exercise ventilatory response was defined as the slope of the $\dot{V}_E$-$\dot{V}_{CO2}$ relationship ($\Delta \dot{V}_E/\Delta \dot{V}_{CO2}$) as previously described (Wood et al., 2008a). STM was assessed using a two-way ANOVA with repeated measures on exercise (three levels: rest, 10W, 30W) and dead space (three levels: control, 200, 400 mL); Tukey's posthoc test was used in individual comparisons to make statistical inferences. Ventilatory response to exercise (i.e., without added dead space) was assessed by comparing the resting, 10W, and 30W variables from the control trial (i.e., no dead space); one-way ANOVA with repeated measures (group and exercise level) was used. The effect of added dead space on ventilation at rest was assessed by comparing resting variables from the control trial (i.e. no dead space) with the resting variables from the 200 and 400 mL dead space trials; one-way ANOVA with repeated measures was used. Hypercapnic ventilatory response was determined by calculating the individual slopes of the $\Delta \dot{V}_E/\Delta P_{ET_{CO2}}$ linear regression. All statistical analyses were performed with IBM SPSS Statistics Version 22. Data are presented as mean ± SD.

RESULTS

Two subjects (ID 508 and 520) were excluded from the main analyses due to suspected obesity hypoventilation syndrome, which is defined as the combined presence of obesity (i.e BMI > 30kg/m^2) daytime hypoventilation/hypercapnia (i.e. Pa_{CO2} >45 mmHg), and sleep-disordered breathing in the absence of alternative neuromuscular, mechanical or metabolic explanation for hypoventilation (for a review, see (Mokhlesi, 2010)). Data from these two subjects will be presented separately at the end.

Subject characteristics and pulmonary function

Subject characteristics were not different between the Non-OSA and OSA groups (Table 1). Body mass indexes ranged from 29.4 – 47.9 kg/m^2. One subject was classified as overweight, five as obesity class I, two as obesity class II, and seven as obesity class III. In the OSA group, the AHI ranged from 6–73 events/hr. Three subjects were classified as

having mild OSA (i.e., AHI ≥ 5 < 15), two had moderate OSA (i.e., AHI ≥ 15 < 30), and two had severe OSA (i.e., AHI ≥ 30). Neck circumference was significantly greater in the OSA group. Figure 2 shows the relationship between AHI and BMI.

All subjects had normal spirometry and diffusing capacities; and normal or slightly reduced lung volumes (Table 1). There were no significant differences between groups in pulmonary function. No subject had significant changes in lung function following bronchodilator inhalation (data not shown).

Ventilation, breathing pattern, and gas exchange at rest and during exercise

Table 2 shows the ventilatory, breathing pattern, and gas exchange responses at rest and during 10W and 30W of exercise without added dead space (i.e., control condition). No statistically significant differences between groups were observed in the measurements at rest (individual p-values given in table). However, $\dot{V}_E$ tended to be higher in the OSA compared with the Non-OSA group ($p = 0.129$) (Figure 3). $\dot{V}_E$ ($p < 0.05$), $\dot{V}_{CO2}$ ($p < 0.05$), and $\dot{V}_{O2}$ ($p < 0.05$) increased with exercise intensity (i.e., from rest to 10W to 30W). P_{ETCO2} did not significantly differ from rest to exercise ($p > 0.05$). There was no association between the individual subject's AHI and their slope of $\dot{V}_E/\dot{V}_{CO2}$ (Figure 4).

Resting ventilatory response to added dead space

No statistically significant differences were observed between groups in the resting ventilatory response to added dead space (p-values in Table 3 and Figure 5). However, $\dot{V}_E$ and $\dot{V}_{CO2}$ tended to be higher in the OSA compared with the Non-OSA group ($p = 0.118$ and $p = 0.144$, respectively). At rest, P_{ETCO2} ($p < 0.05$) and $\dot{V}_E$ ($p < 0.05$) were higher with added dead space than without in both groups, indicating that resting ventilatory response was augmented with dead space. The elevated $\dot{V}_E$ was due to increases in V_T ($p < 0.05$) only, not R_f ($p > 0.05$).

The hypercapnic ventilatory response was within normal limits (mean ± SD of individual slopes 2.8 ± 2.3 L/min/Torr) (Figure 6).

Short-term modulation of the exercise ventilatory response

Table 4 shows the changes in ventilation, breathing pattern, and gas exchange variables in response to increasing exercise intensity and added dead space between the groups (three-way ANOVA). A main effect of dead space on the slope of the exercise ventilatory response ($\Delta\dot{V}_E/\Delta\dot{V}_{CO2}$) was observed (Figure 7), the slope increased with increasing dead space; but there was no main effect of group ($p > 0.05$). The slope tended to decrease with increasing exercise intensity ($p = 0.051$). $\Delta\dot{V}_E$ showed main effects of dead space and exercise intensity ($p < 0.05$), but no differences between groups; $\dot{V}_E$ increased with increasing dead space and exercise intensity. The increased $\Delta\dot{V}_E$ in the OSA groups was due to both increased breathing frequency and tidal volume (ΔR_f and ΔV_T). There was a main effect of exercise intensity on $\Delta\dot{V}_{CO2}$, CO_2 production was higher at higher exercise intensity.

No significant differences were found in ΔP_{ETCO2}. For both groups, ΔP_{ETCO2} from rest to each exercise level with added dead space was lower or very close to that without added dead space (mean change <2 mmHg), indicating that CO_2 was not retained.

Obesity Hypoventilation Syndrome

The two subjects with suspected OHS had two of the highest body mass indexes of the subjects in this study (Figure 2) and had lower than predicted lung function (Table 5). In line with the definition of OHS, they exhibited elevated resting P_{ETCO2} values (44 and 46 mmHg, respectively). When challenged with increasing dead space and with increasing exercise intensity, ΔP_{ETCO2} was increased (Figure 8) as P_{ETCO2} increased up to 55 and 52 mmHg, respectively. The $\Delta \dot{V}_E/\Delta \dot{V}_{CO2}$ slope increased with increasing dead space (i.e., control to 400 ml DS) (Figure 8) but it cannot be determined whether this increase was due to STM or the retention of CO2. Nevertheless, ventilation was not adjusted to meet the demand of the increased dead space.

DISCUSSION

The main findings of this study are: 1) the exercise ventilatory response is similar between obese OSA patients and obese adults without OSA, and 2) both groups had equal capacity for STM with added respiratory dead space, in contrast to our hypotheses. Additionally, two subjects with suspected OHS demonstrated a reduced ventilatory response to exercise and CO_2 retention, which made determination of STM impossible; thus, careful evaluation of OSA patients who may also have OHS is clinically important.

This study demonstrates that STM of the exercise ventilatory response is preserved despite increased mechanical loads imposed by obesity or OSA. On the other hand, ventilatory responses to exercise or chemoreflex activation are diminished in OHS patients. These findings support the view that the respiratory control system exhibits considerable capacity for modulation and/or plasticity to increase neural respiratory muscle drive and ventilatory output in order to maintain a constant relative PCO_2 in response to physiological (e.g. obesity, OSA) and imposed (e.g. external added dead space) conditions (Mitchell and Babb, 2006; Poon et al., 2007). However, the capacity seems to reach a limit in OHS, where the ventilatory output fails to compensate for the increasing PCO_2 both at rest and during exercise. Although limited by the number of subjects, especially in the more severe OSA range, our results demonstrate that STM can be expressed in obesity and OSA. Interesting findings in a limited group of OHS subjects establish the need for more intensive research in this area.

Ventilatory response to exercise

The increase in ventilation during submaximal exercise occurs in direct proportion to the increased metabolic CO_2 production, such that partial pressure of CO_2 in the arterial blood is maintained constant (i.e., CO_2 is not retained, but isocapnic). An increased slope of this $\dot{V}_E/\dot{V}_{CO2}$ relationship is associated with poorer mortality prognosis in chronic heart failure (Arena et al., 2007; Chua et al., 1997; Kleber et al., 2000; Ponikowski et al., 2001). In patients with OSA, Hargens et al (Hargens et al., 2009) found an increased ventilatory

response. The results of the present study were different in that we did not observe an augmented ventilatory response in OSA patients (Figure 31 and Table 2). This discrepancy could be due to differences in patient selection (our subjects were older and more obese) or exercise assessments (our submaximal exercise levels were lower). Hargens et al suggested that chemoreflex sensitivity was altered; however, they did not report P_{CO2} to substantiate this assertion (Hargens et al., 2009). If P_{CO2} was maintained constant during exercise, chemoreflex is not a likely explanation. Lin et al (Lin et al., 2006) found no differences in the ventilatory response to maximal exercise, including $\dot{V}_E/\dot{V}_{CO2}$ and $P_{ET_{CO2}}$ between OSA and healthy subjects, these results are in line with our observations.

Short-term modulation of the exercise ventilatory response

Exercise with added respiratory dead space adjusts the ventilatory response to exercise in order to maintain arterial P_{CO2} regulation with respect to its new, elevated resting level (Babb et al., 2010; Mitchell, 1990). STM is an experimental within-trial augmentation of the exercise ventilatory response; when the respiratory dead space is removed, the exercise ventilatory response reverts to normal. Thus, STM represents the ability of the respiratory control system to adjust breathing during exercise to accommodate other respiratory stimuli or imposed challenges (such as changes in dead space). First demonstrated in goats (Mitchell, 1990), STM is also present and robust in healthy, younger and older women and men (Wood et al., 2010, 2011; Wood et al., 2008b). Results of the current study extend those prior results to include healthy obese individuals as well as obese patients with OSA demonstrating functioning STM; $P_{ET_{CO2}}$ is maintained within 2 mmHg. In the case of OSA patients, a notable difference is an increased $\dot{V}_{CO2}$ as well as increased $\dot{V}_E$, which results in an unchanged $\dot{V}_E/\dot{V}_{CO2}$ relationship.

Obesity Hypoventilation Syndrome

The two suspected OHS subjects were classified as obesity class III and exhibited decreased lung function, which is in agreement with previous studies (Basoglu and Tasbakan, 2014; Javaheri and Simbartl, 2014; Kessler et al., 2001). The $\Delta\dot{V}_E/\Delta\dot{V}_{CO2}$ slope was increased with added dead space; however, ventilation was not increased enough to maintain a constant $P_{ET_{CO2}}$ (Figure 8). Thus, it is not clear whether the increased $\Delta\dot{V}_E/\Delta\dot{V}_{CO2}$ slope is due to chemoreceptor feedback or the feedforward short-term modulation but neither increased ventilation enough to prevent CO_2 retention (Figure 1). The finding that $P_{ET_{CO2}}$ was not maintained suggests that the respiratory control has reached its limit for increasing ventilatory output in response to hypercapnia. Eucapnic obesity is characterized by chronic systemic low grade inflammation and associated inflammatory changes in adipose tissue (Hotamisligil, 2006; Schenk et al., 2008), and OHS is associated with increased inflammatory and decreased antiinflammatory cytokines when compared with eucapnic obese patients (Borel et al., 2009). Thus, it is possible that the limitation of the respiratory controller to respond appropriately to hypercapnia may be due to chronic inflammation associated with obesity that undermines the serotonin-dependent STM and/or that OHS developed because of a deficiency in serotonergic function in the first place.

Resting hypercapnic ventilatory response

Respiratory dead space increases resting ventilatory drive due to hypercapnia and CO_2-chemoreceptor feedback caused by the dead space and reduced alveolar ventilation (for a given tidal volume) (Mitchell, 1990). The slope of the hypercapnic ventilatory response ranges from approximately 0.3 to 3.0 L/min/Torr in Bascom et al (Bascom et al., 1990) and similar values in Clement et al's study (Clement et al., 1992), with the exception of one subject who failed to increase ventilation (the authors did not provide an explanation for the negative slope observed in this subject). The present findings are in agreement since most subjects showed a positive correlation between increased P_{ETCO2} and increased $\dot{V}_E$ (average slope 2.8 ± 2.3 L/min/Torr). Two subjects in the present study stood out as ventilation did not increase with increased P_{ETCO2}. Subject 528 presented with severe OSA (AHI=73 events/hr) and subject 508 with suspected OHS (due to elevated resting P_{ETCO2} of 44 Torr). Based on this limited data, we cautiously suggest that a negative hypercapnic ventilatory response represents the inability of the respiratory system to detect and/or sufficiently correct for the increased CO_2 and this may be due to advanced stages of OSA/OHS.

Limitations

Subject recruitment for this study was challenging due to the limited number of subjects meeting the inclusion criteria. For example, many patients also exhibited uncontrolled hypertension or other comorbidities of sleep apnea. Some were on selective serotonin re-uptake inhibitor medication for diagnosed depression, which we excluded due to complicating responses of the serotonin-dependent STM. The limited sample size, especially of OHS patients, may reduce the generalization of the results. Additionally, there was a wide range of OSA severity (i.e., number of AHI events) and a generally larger variability in the OSA patients compared with non-OSA. This high variability in the individual responses contributed to the lower statistical power. It is possible that with a more narrow range of OSA severity and with a greater number of subjects a statistically difference between groups could have been detected. Also, it is unknown for how long the patients had experienced OSA or OHS symptoms, or if the duration of symptoms can alter STM.

Conclusions

Here we establish that STM of the ventilatory response to exercise is preserved despite obesity and/or OSA, although it may be reduced in patients with obesity hypoventilation syndrome. This is an important development in our understanding of plasticity in the respiratory control system during exercise. STM represents the capacity to preserve homeostatic PCO_2 regulation despite (patho-)physiological and environmental challenges. The limited findings from the OHS patients open up exiting avenues for future research.

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REFERENCES

Standardization of Spirometry, 1994 Update. American Thoracic Society. Am J Respir Crit Care Med. 1995; 152:1107–1136. [PubMed: 7663792]

Arena R, Myers J, Hsu L, Peberdy MA, Pinkstaff S, Bensimhon D, Chase P, Vicenzi M, Guazzi M. The minute ventilation/carbon dioxide production slope is prognostically superior to the oxygen uptake efficiency slope. J Card Fail. 2007; 13:462–469. [PubMed: 17675060]

Babb TG, Wood HE, Mitchell GS. Short- and long-term modulation of the exercise ventilatory response. Med Sci Sports Exerc. 2010; 42:1681–1687. [PubMed: 20164813]

Babb TG, Wyrick BL, DeLorey DS, Chase PJ, Feng MY. Fat distribution and end-expiratory lung volume in lean and obese men and women. Chest. 2008; 134:704–711. [PubMed: 18641101]

Bach KB, Lutcavage ME, Mitchell GS. Serotonin is necessary for short-term modulation of the exercise ventilatory response. Respir Physiol. 1993; 91:57–70. [PubMed: 8441871]

Bascom DA, Clement ID, Cunningham DA, Painter R, Robbins PA. Changes in peripheral chemoreflex sensitivity during sustained, isocapnic hypoxia. Respir Physiol. 1990; 82:161–176. [PubMed: 2127465]

Basoglu OK, Tasbakan MS. Comparison of clinical characteristics in patients with obesity hypoventilation syndrome and obese obstructive sleep apnea syndrome: a case-control study. Clin Respir J. 2014; 8:167–174. [PubMed: 24028180]

Bernhardt V, Babb TG. Weight loss reduces dyspnea on exertion in obese women. Respir Physiol Neurobiol. 2014; 204:86–92. [PubMed: 25220695]

Bhammar DM, Stickford JL, Bernhardt V, Babb TG. Effect of weight loss on operational lung volumes and oxygen cost of breathing in obese women. Int J Obes (Lond). 2016; 40:998–1004. [PubMed: 26869243]

Borel JC, Roux-Lombard P, Tamisier R, Arnaud C, Monneret D, Arnol N, Baguet JP, Levy P, Pepin JL. Endothelial dysfunction and specific inflammation in obesity hypoventilation syndrome. PloS one. 2009; 4:e6733. [PubMed: 19701463]

Carter R, Watenpaugh DE 3rd. Obesity and obstructive sleep apnea: Or is it OSA and obesity? Pathophysiology. 2008; 15:71–77. [PubMed: 18573643]

Chua TP, Ponikowski P, Harrington D, Anker SD, Webb-Peploe K, Clark AL, Poole-Wilson PA, Coats AJ. Clinical correlates and prognostic significance of the ventilatory response to exercise in chronic heart failure. J Am Coll Cardiol. 1997; 29:1585–1590. [PubMed: 9180123]

Clement ID, Bascom DA, Conway J, Dorrington KL, O'Connor DF, Painter R, Paterson DJ, Robbins PA. An assessment of central-peripheral ventilatory chemoreflex interaction in humans. Respir Physiol. 1992; 88:87–100. [PubMed: 1626148]

Epstein LJ, Kristo D, Strollo PJ Jr, Friedman N, Malhotra A, Patil SP, Ramar K, Rogers R, Schwab RJ, Weaver EM, Weinstein MD. Adult Obstructive Sleep Apnea Task Force of the American Academy of Sleep, M. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. J Clin Sleep Med. 2009; 5:263–276. [PubMed: 19960649]

Frey WC, Pilcher J. Obstructive sleep-related breathing disorders in patients evaluated for bariatric surgery. Obes Surg. 2003; 13:676–683. [PubMed: 14627460]

Gerst DG 3rd, Yokhana SS, Carney LM, Lee DS, Badr MS, Qureshi T, Anthouard MN, Mateika JH. The hypoxic ventilatory response and ventilatory long-term facilitation are altered by time of day and repeated daily exposure to intermittent hypoxia. J Appl Physiol. 2011; 110:15–28. (1985). [PubMed: 20724571]

Gibson GJ. Obesity, respiratory function and breathlessness. Thorax 55 Suppl. 2000; 1:S41–S44.

Hargens TA, Guill SG, Aron A, Zedalis D, Gregg JM, Nickols-Richardson SM, Herbert WG. Altered ventilatory responses to exercise testing in young adult men with obstructive sleep apnea. Respir Med. 2009; 103:1063–1069. [PubMed: 19217270]

Henderson DR, Mitchell GS. Short-term modulation of the exercise ventilatory response in goats: effects of 8-OH-DPAT and MPPI. Am J Physiol Regul Integr Comp Physiol. 2000; 279:R1880–R1888. [PubMed: 11049874]

Hotamisligil GS. Inflammation and metabolic disorders. Nature. 2006; 444:860–867. [PubMed: 17167474]

Javaheri S, Simbartl LA. Respiratory determinants of diurnal hypercapnia in obesity hypoventilation syndrome. What does weight have to do with it? Ann Am Thorac Soc. 2014; 11:945–950. [PubMed: 24828690]

Kessler R, Chaouat A, Schinkewitch P, Faller M, Casel S, Krieger J, Weitzenblum E. The obesity-hypoventilation syndrome revisited: a prospective study of 34 consecutive cases. Chest. 2001; 120:369–376. [PubMed: 11502631]

Kleber FX, Vietzke G, Wernecke KD, Bauer U, Opitz C, Wensel R, Sperfeld A, Glaser S. Impairment of ventilatory efficiency in heart failure: prognostic impact. Circulation. 2000; 101:2803–2809. [PubMed: 10859285]

Kress JP, Pohlman AS, Alverdy J, Hall JB. The impact of morbid obesity on oxygen cost of breathing (VO(2RESP)) at rest. Am J Respir Crit Care Med. 1999; 160:883–886. [PubMed: 10471613]

Lee DS, Badr MS, Mateika JH. Progressive augmentation and ventilatory long-term facilitation are enhanced in sleep apnoea patients and are mitigated by antioxidant administration. J Physiol. 2009; 587:5451–5467. [PubMed: 19805747]

Lin CC, Hsieh WY, Chou CS, Liaw SF. Cardiopulmonary exercise testing in obstructive sleep apnea syndrome. Respir Physiol Neurobiol. 2006; 150:27–34. [PubMed: 16448931]

Ling L, Fuller DD, Bach KB, Kinkead R, Olson EB Jr, Mitchell GS. Chronic intermittent hypoxia elicits serotonin-dependent plasticity in the central neural control of breathing. J Neurosci. 2001; 21:5381–5388. [PubMed: 11438615]

Lopez PP, Stefan B, Schulman CI, Byers PM. Prevalence of sleep apnea in morbidly obese patients who presented for weight loss surgery evaluation: more evidence for routine screening for obstructive sleep apnea before weight loss surgery. Am Surg. 2008; 74:834–838. [PubMed: 18807673]

Mitchell GS. Ventilatory control during exercise with increased respiratory dead space in goats. J Appl Physiol. 1990; 69:718–727. [PubMed: 2228882]

Mitchell GS, Babb TG. Layers of exercise hyperpnea: modulation and plasticity. Respir Physiol Neurobiol. 2006; 151:251–266. [PubMed: 16530024]

Mitchell GS, Baker TL, Nanda SA, Fuller DD, Zabka AG, Hodgeman BA, Bavis RW, Mack KJ, Olson EB Jr. Invited review: Intermittent hypoxia and respiratory plasticity. J Appl Physiol. 2001; 90:2466–2475. [PubMed: 11356815]

Mitchell GS, Johnson SM. Neuroplasticity in respiratory motor control. J Appl Physiol. 2003; 94:358–374. (1985). [PubMed: 12486024]

Mitchell GS, Turner DL, Henderson DR, Foley KT. Spinal serotonin receptor activation modulates the exercise ventilatory response with increased dead space in goats. Respir Physiol Neurobiol. 2008; 161:230–238. [PubMed: 18396470]

Mokhlesi B. Obesity hypoventilation syndrome: a state-of-the-art review. Respir Care. 2010; 55:1347–1362. discussion 1363-1345. [PubMed: 20875161]

O'Keeffe T, Patterson EJ. Evidence supporting routine polysomnography before bariatric surgery. Obes Surg. 2004; 14:23–26. [PubMed: 14980029]

Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, Coates A, van der Grinten CP, Gustafsson P, Hankinson J, Jensen R, Johnson DC, MacIntyre N, McKay R, Miller MR, Navajas D, Pedersen OF, Wanger J. Interpretative strategies for lung function tests. Eur Respir J. 2005; 26:948–968. [PubMed: 16264058]

Ponikowski P, Francis DP, Piepoli MF, Davies LC, Chua TP, Davos CH, Florea V, Banasiak W, Poole-Wilson PA, Coats AJ, Anker SD. Enhanced ventilatory response to exercise in patients with chronic heart failure and preserved exercise tolerance: marker of abnormal cardiorespiratory reflex control and predictor of poor prognosis. Circulation. 2001; 103:967–972. [PubMed: 11181471]

Poon CS, Tin C, Yu Y. Homeostasis of exercise hyperpnea and optimal sensorimotor integration: the internal model paradigm. Respir Physiol Neurobiol. 2007; 159:1–13. discussion 14–20. [PubMed: 17416554]

Schenk S, Saberi M, Olefsky JM. Insulin sensitivity: modulation by nutrients and inflammation. J Clin Invest. 2008; 118:2992–3002. [PubMed: 18769626]

Shah N, Roux F. The relationship of obesity and obstructive sleep apnea. Clin Chest Med. 2009; 30:455–465. vii. [PubMed: 19700044]

Wasserman K, Whipp BJ. Excercise physiology in health and disease. Am Rev Respir Dis. 1975; 112:219–249. [PubMed: 239617]

Wood HE, Mitchell GS, Babb TG. Short-term modulation of the exercise ventilatory response in young men. J Appl Physiol. 2008a; 104:244–252. [PubMed: 17991790]

Wood HE, Mitchell GS, Babb TG. Short-term modulation of the exercise ventilatory response in older men. Respir Physiol Neurobiol. 2010; 173:37–46. [PubMed: 20601211]

Wood HE, Mitchell GS, Babb TG. Short-term modulation of the exercise ventilatory response in younger and older women. Respir Physiol Neurobiol. 2011

Wood HE, Semon TL, Comeau LA, Schwartz B, MacDougall RM, Klocko MN, Babb TG. The ventilatory response to exercise does not differ between obese women with and without dyspnea on exertion. Adv Exp Med Biol. 2008b; 605:514–518. [PubMed: 18085327]

Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med. 1993; 328:1230–1235. [PubMed: 8464434]

Highlights

- The ventilatory response to exercise is of fundamental importance to every-day activity.
- Short-term modulation alters the exercise ventilatory response to maintain P_aCO_2.
- Obesity and/or obstructive sleep apnea could affect this neural mechanism.
- The findings suggest that STM seems to be preserved in obesity and OSA.
- However, it may be diminished in obesity hypoventilation syndrome patients.

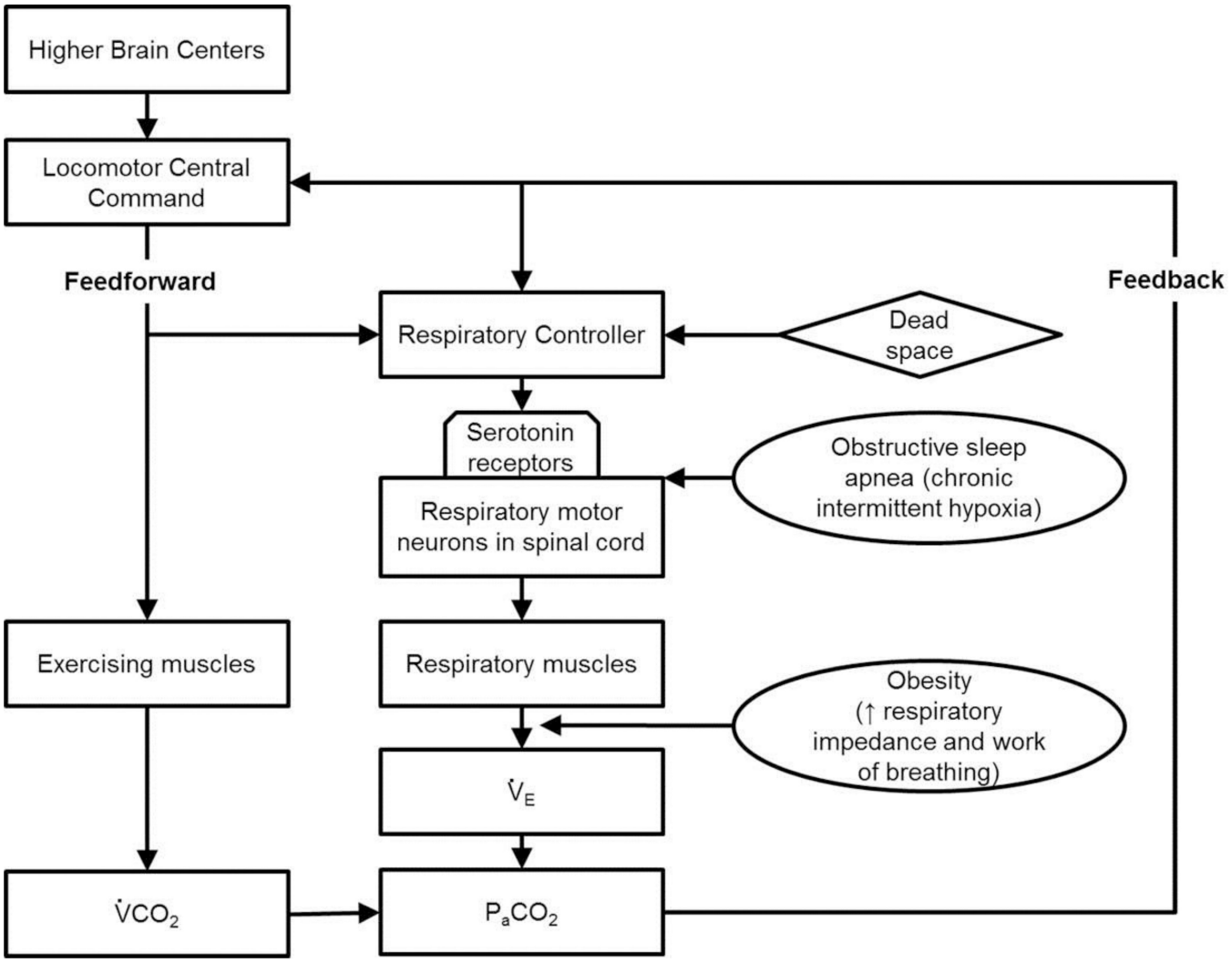

Figure 1.

Model of the interactions between the feedforward and feedback mechanisms when challenged with added ventilatory dead space, obesity, and obstructive sleep apnea.

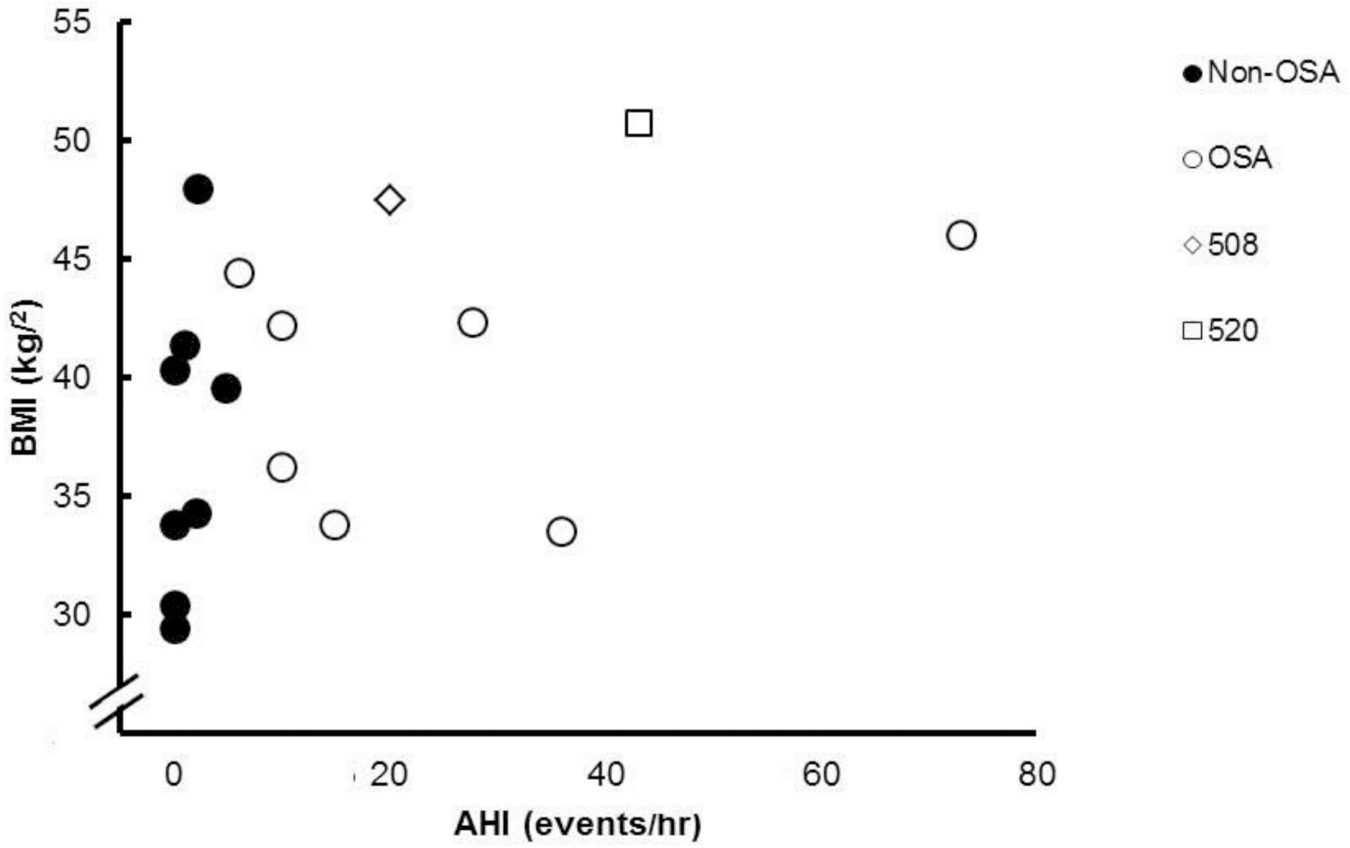

Figure 2.

Relationship between apnea-hypopnea index (AHI) and body mass index (BMI) for non-OSA (filled circles), OSA (open circles), and special cases 508 (open diamond) and 520 (open square).

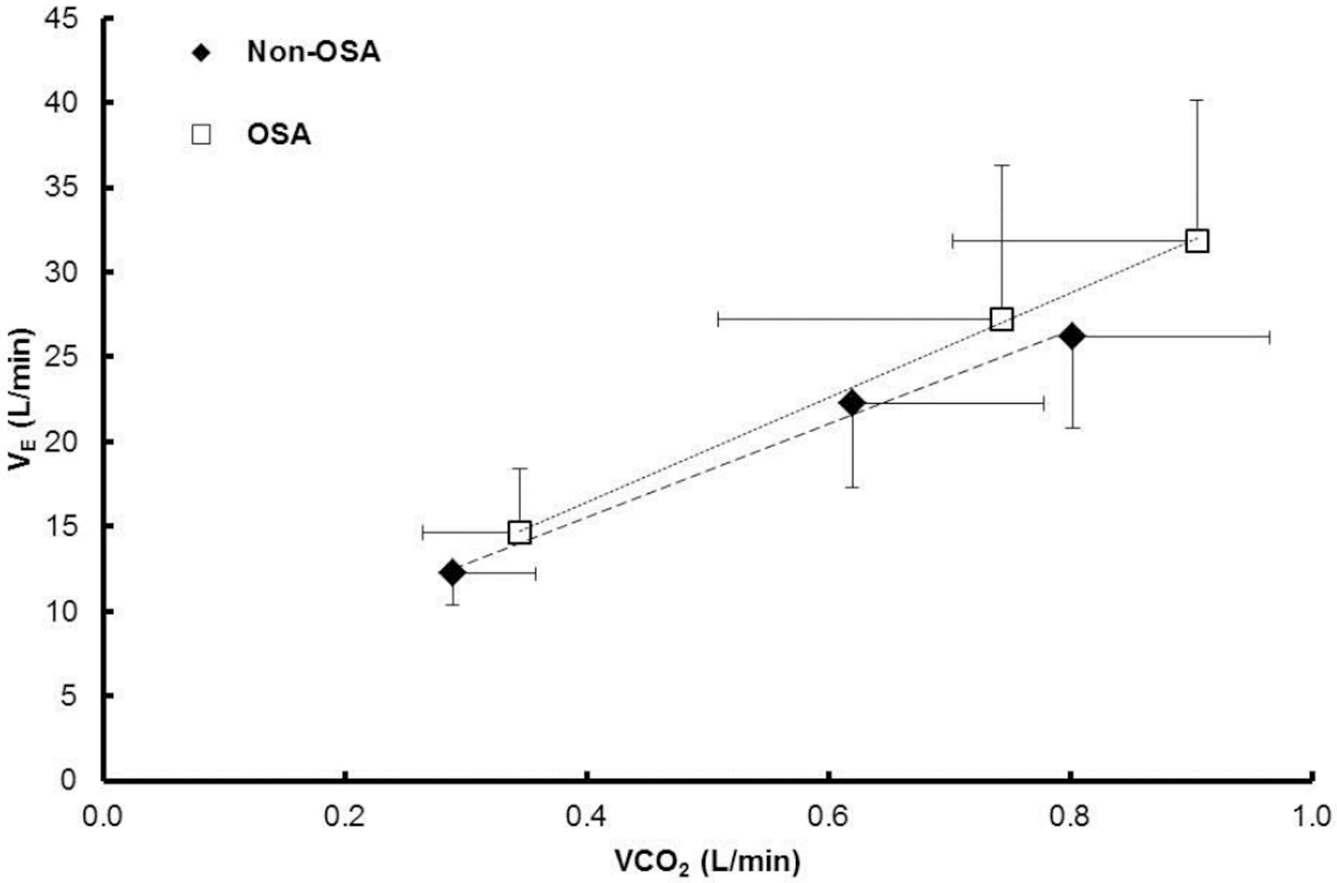

Figure 3.

Ventilatory response at rest and at 10W and 30W cycling exercise. Mean ± SD. The slope of $\Delta \dot{V}_E/\Delta \dot{V}_{CO2}$ was calculated from each individual subject's linear regressions.

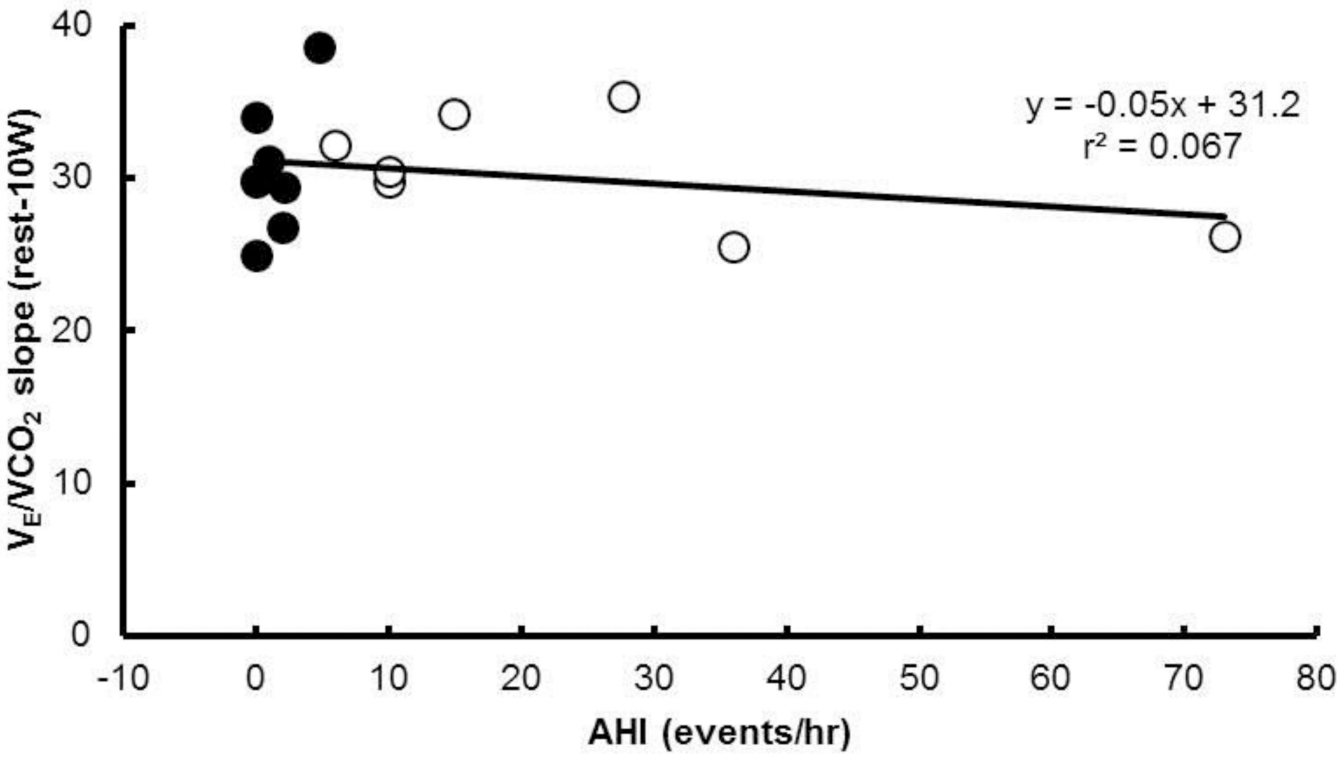

Figure 4.

Individual responses to submaximal 30W exercise. No association between the severity of sleep apnea (i.e., AHI) and the ventilatory response to exercise (i.e., slope of $\Delta \dot{V}_E/\Delta \dot{V}_{CO2}$).

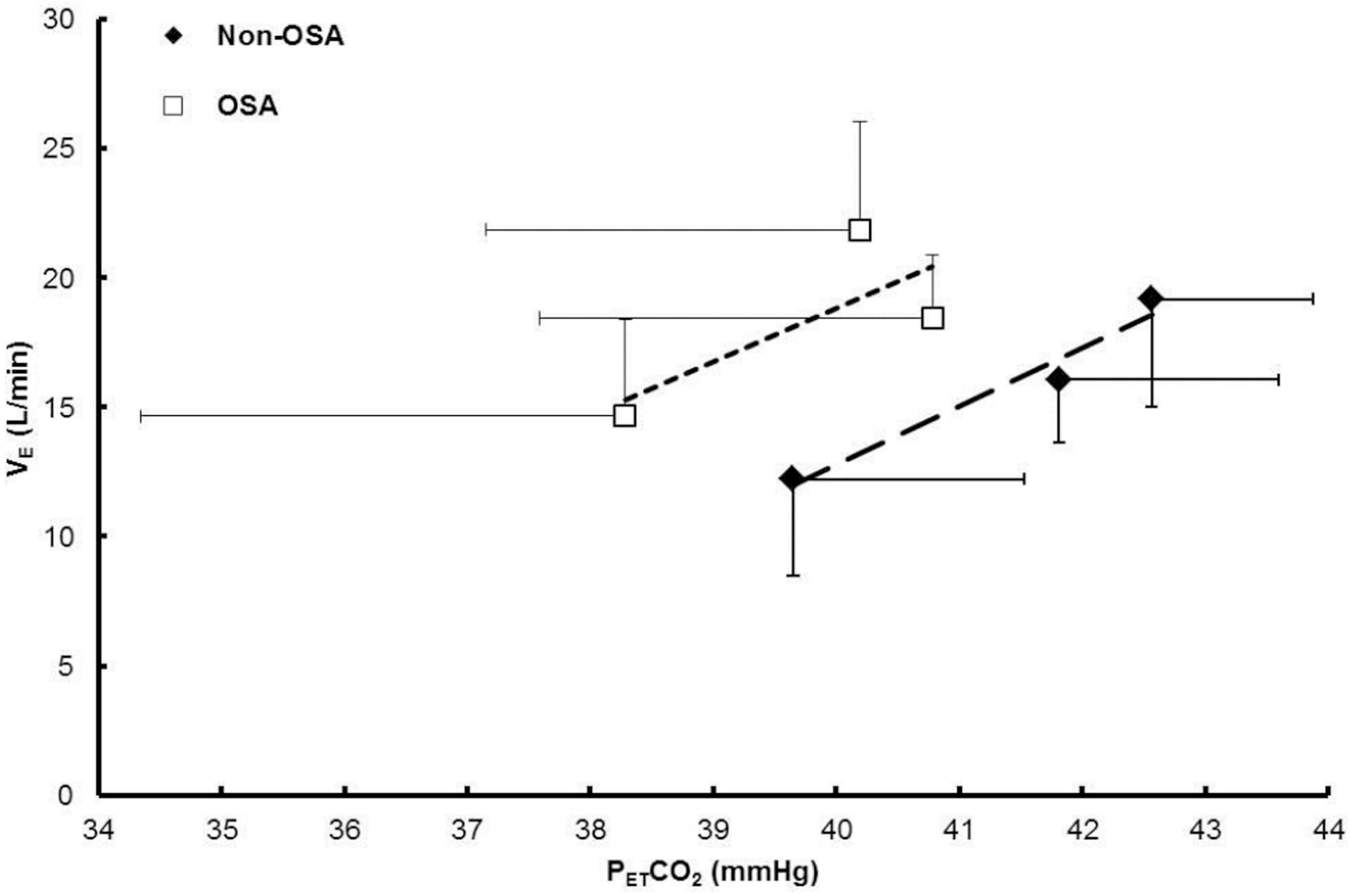

Figure 5.
Resting ventilatory response without (i.e., control) and with added dead space (i.e., 200 mL and 400 mL).

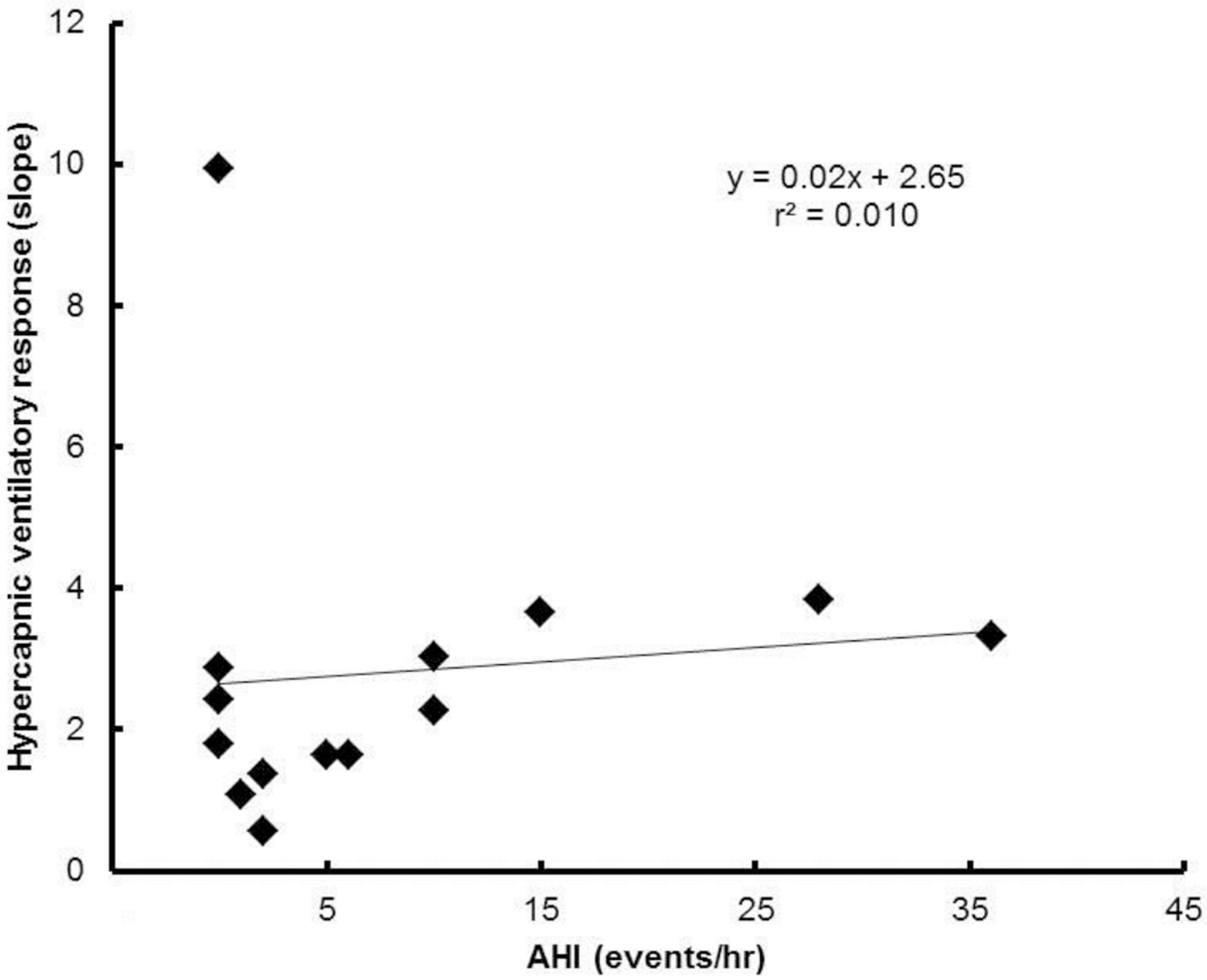

Figure 6.
Hypercapnic ventilatory response at rest for each subject.

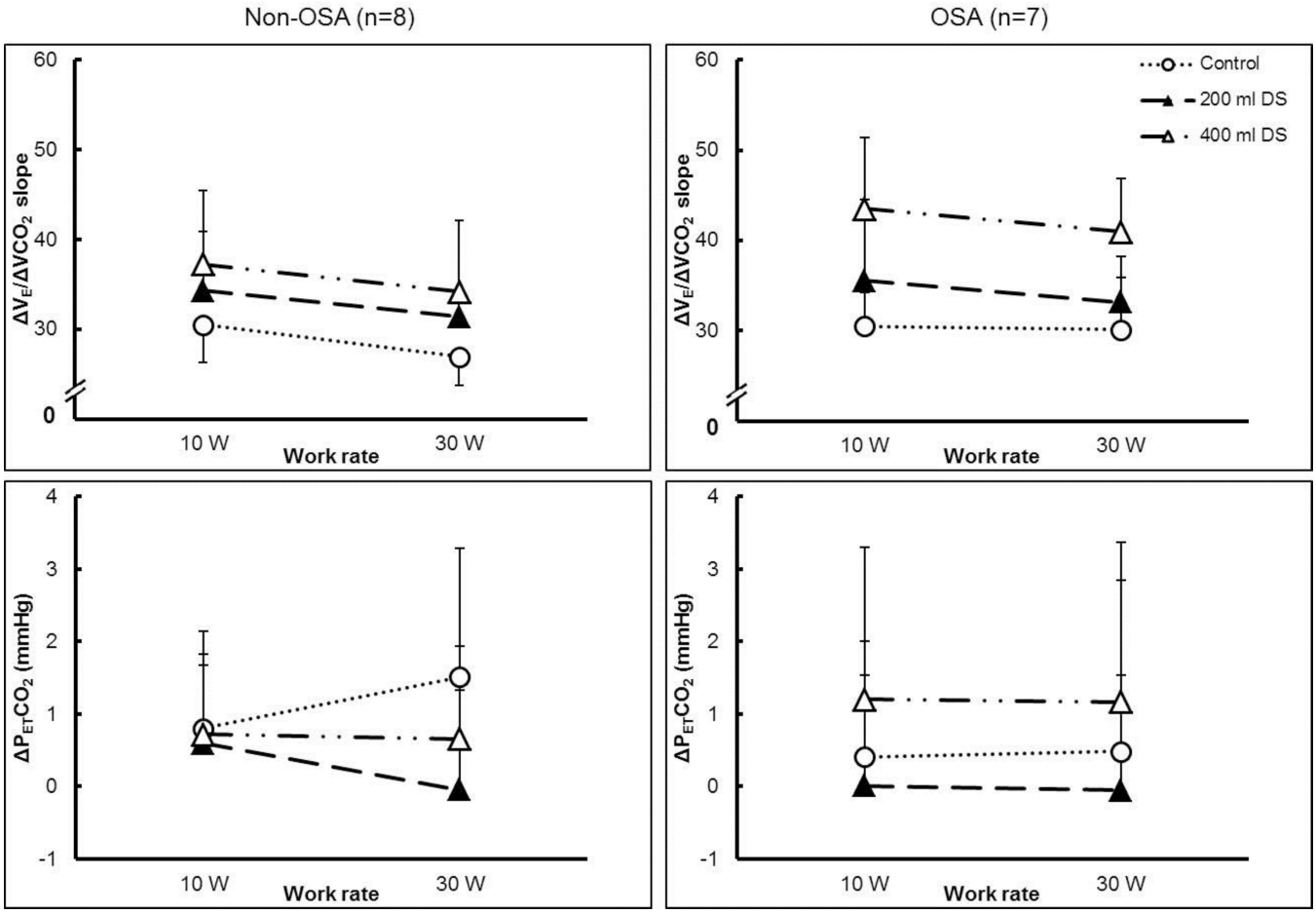

Figure 7.

Interaction between the effects of exercise and dead space level on slope of the exercise ventilatory response ($\Delta \dot{V}_E/\Delta \dot{V}_{CO2}$), and change in P_{ETCO2} (ΔP_{ETCO2}) from rest to each work rate for Non-OSA (left-hand panels) and OSA (right-hand panels) groups. DS, dead space. Dotted line with open circles, control (no added dead space); dashed line with filled triangles, 200 mL added dead space; dashed and dotted line with open triangles, 400 mL added dead space. Mean ± S.D.

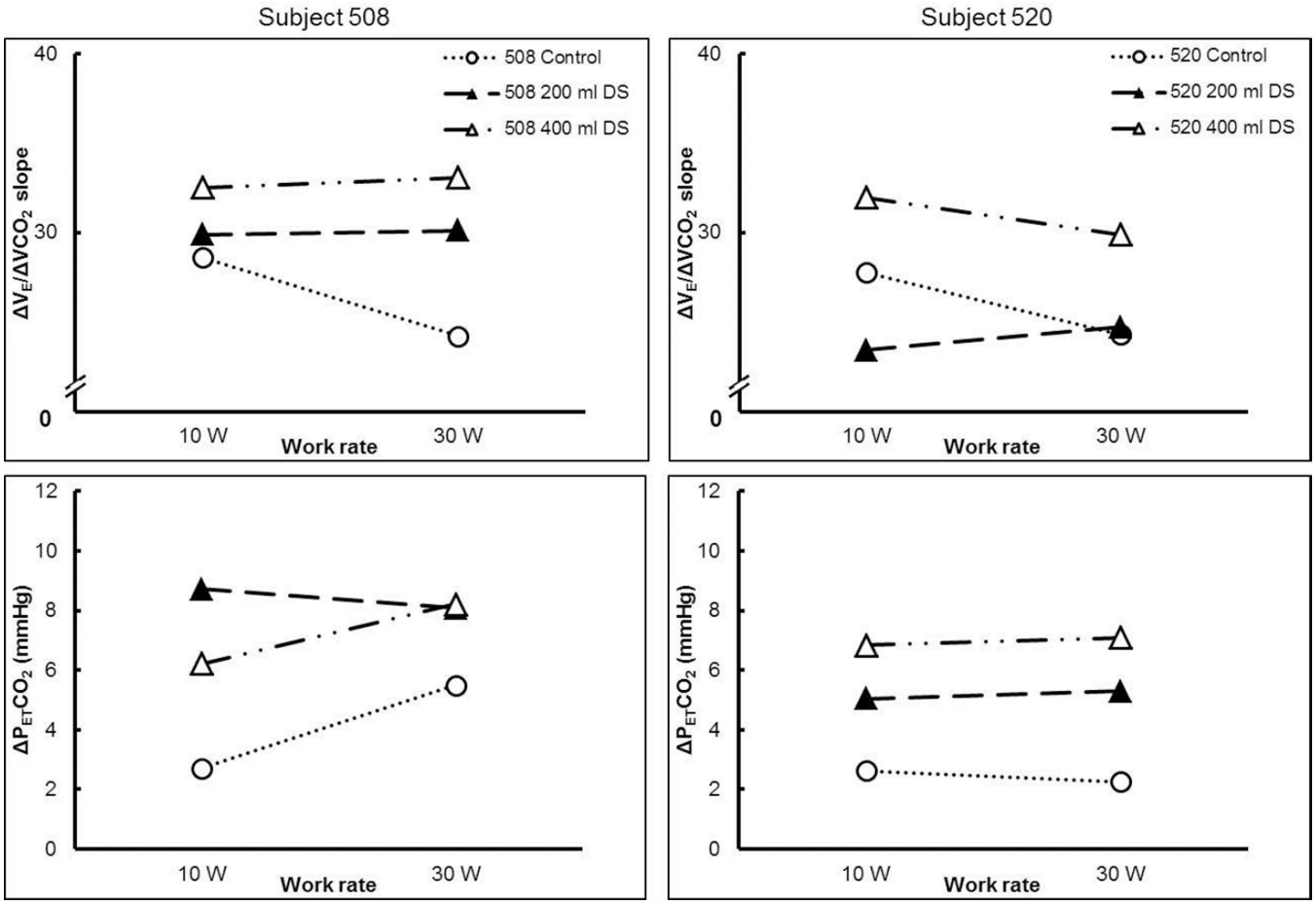

Figure 8.

Interaction between the effects of exercise and dead space level on slope of the exercise ventilatory response ($\Delta \dot{V}_E/\Delta \dot{V}_{CO2}$), and change in $P_{ET_{CO2}}$ ($\Delta P_{ET_{CO2}}$) from rest to each work rate for subject 508 (left-hand panels) and 520 (right-hand panels). DS, dead space. Dotted line with open circles, control (no added dead space); dashed line with filled triangles, 200 mL added dead space; dashed and dotted line with open triangles, 400 mL added dead space.

Table 1

Subject characteristics and pulmonary function.

	Non-OSA (n=8)	OSA(n=8)
Age (yr)	38 ± 10	39 ± 6
Height (cm)	170.0 ± 9.2	175.0 ± 5.8
Weight (kg)	106.8 ± 15.8	121.9 ± 17.5
BMI (kg/m^2)	37.1 ± 6.3	39.8 ± 5.2
AHI (events/hr)	1.3 ± 1.7	25.4 ± 23.6
Neck circumference (cm)	39.5 ± 4.2	44.5 ± 3.7*
FVC (%pred)	98 ± 7	95 ± 13
FEV_1 (%pred)	94 ± 11	95 ± 11
FEV_1/FVC (%)	79 ± 7	82 ± 3
TLC (%pred)	96 ± 8	89 ± 11
FRC (%TLC)	45 ± 2	39 ± 7
IC (%pred)	94 ± 11	98 ± 15
ERV (L)	1.0 ± 0.4	0.8 ± 0.4
RV (%pred)	76 ± 8	72 ± 12
DLCO (%pred)	86 ± 12	89 ± 18
DLCO/V_A (%pred)	113 ± 11	126 ± 24

BMI, body mass index; AHI, apnea-hypopnea index; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1s; TLC, total lung capacity; FRC, functional residual capacity; IC, inspiratory capacity; ERV, expiratory reserve volume; RV, residual volume; DLCO, lung diffusing capacity; V_A, alveolar volume; %pred, as a percent of predicted. Values are means ± SD.

*$p<0.05$

Table 2

Ventilation, breathing pattern and gas exchange at rest and during exercise (i.e., control condition).

	Non-OSA (n=8)	OSA (n=8)	p-value group	p-value interaction
$\dot{V}_E/\dot{V}CO_2$ slope				
Rest-10W	30.5 ± 4.2	30.5 ± 3.8	0.465	NS
Rest-30W	27.0 ± 3.3	30.1 ± 5.8		
$P_{ET}CO_2$ (mmHg)				
Rest	39.6 ± 1.9	38.6 ± 3.7	0.383	NS
10W	40.7 ± 2.2	39.4 ± 3.7		
30W	41.3 ± 2.3	39.5 ± 4.7		
$\Delta P_{ET}CO_2$ (mmHg)				
Rest-10W	0.8 ± 1.3	0.8 ± 2.4	0.793	NS
Rest-30W	1.5 ± 1.8	0.9 ± 2.6		
$\dot{V}_E$ (L/min)				
Rest	12.2 ± 1.9	14.7 ± 3.8	0.129	NS
10W *a*	22.3 ± 5.0	27.2 ± 9.1		
30W *a,b*	26.2 ± 5.3	31.8 ± 8.3		
$\dot{V}CO_2$ (mL/min)				
Rest	289 ± 69	345 ± 82	0.218	NS
10W *a*	620 ± 158	744 ± 235		
30W *a,b*	802 ± 162	904 ± 203		
$\dot{V}O_2$ (mL/min)				
Rest	353 ± 77	414 ± 77	0.165	NS
10W *a*	756 ± 180	912 ± 278		
30W *a,b*	926 ± 172	1085 ± 252		
R_f (b/min)				
Rest	15.6 ± 5.2	15.2 ± 2.9	0.507	NS
10W *a*	20.0 ± 7.8	21.9 ± 7.1		
30W *a*	20.3 ± 7.7	25.6 ± 8.1		
V_T (mL)				
Rest	852 ± 299	984 ± 273	0.947	NS
10W *a*	1212 ± 372	1256 ± 174		
30W *a*	1421 ± 473	1277 ± 242		

$\dot{V}E/\dot{V}CO_2$, slope of the exercise ventilatory response ($\Delta \dot{V}E/\Delta \dot{V}CO_2$) from rest to each level of exercise; $P_{ET}CO_2$, end-tidal PCO_2; $\Delta P_{ET}CO_2$, change in end-tidal PCO_2; $\dot{V}E$ ventilation; $\dot{V}CO_2$,CO_2 production; $\dot{V}O_2$, oxygen consumption; R_f, respiratory frequency; V_T, tidal volume. Values are means ± SD.

a significantly different from rest;

b significantly different from exercise at 10W.

Table 3

Ventilatory response to added dead space at rest.

	Non-OSA	OSA	p-value GRP	p-value interaction
$P_{ET}CO_2$ (mmHg)				
Control	39.4 ± 1.8	38.6 ± 3.7	0.348	0.051
200 ml DS [a]	41.5 ± 1.9	40.8 ± 3.2		
400 ml DS [a]	42.4 ± 1.3	40.2 ± 3.0		
$\dot{V}_E$ (L/min)				
Control	12.5 ± 1.4	14.7 ± 3.8	0.118	NS
200 ml DS [a]	16.4 ± 2.0	18.4 ± 2.5		
400 ml DS [a,b]	19.3 ± 3.6	24.9 ± 4.2		
$\dot{V}CO_2$ (mL/min)				
Control	294 ± 65	345 ± 82	0.144	NS
200 ml DS	291 ± 62	350 ± 57		
400 ml DS	284 ±83	340 ± 83		
R_f (b/min)				
Control	15.6 ± 5.2	15.2 ± 2.9	0.857	NS
200 ml DS	16.2 ± 5.5	17.2 ± 3.9		
400 ml DS	16.3 ± 5.3	17.0 ± 4.6		
V_T (mL)				
Control	852 ± 299	984 ± 273	0.503	NS
200 ml DS [a]	1055 ± 256	1105 ± 227		
400 ml DS [a,b]	1236 ± 271	1326 ± 243		

For abbreviations, see Table 2. DS, dead space. Values are means ± SD.

[a] significantly different from control trial;

[b] significantly different from 200ml trial.

Table 4

Ventilatory variables from STM protocol: values relative to rest.

	Non-OSA			OSA		
	Control	**200 mL DS**	**400 mL DS**	**Control**	**200 mL DS**	**400 mL DS**
$\Delta\dot{V}_E/\Delta\dot{V}CO_2$ slope$^{(p<0.001)//}$						
10 W	30.5 ± 4.2	34.3 ± 6.5	37.3 ± 8.2	30.5 ± 3.8	35.6 ± 9.0	43.5 ± 7.9
30W	27.0 ± 3.3	31.5 ± 2.9	34.2 ± 8.0	30.1 ± 5.8	33.2 ± 5.1	41.0 ± 5.9
$\Delta P_{ET}CO_2$ (mmHg)						
10 W	0.8 ± 1.6	0.6 ± 1.1	0.7 ± 1.1	1.7 ± 4.6	0.0 ± 1.5	1.2 ± 2.1
30W	1.5 ± 1.8	0.0 ± 1.4	0.7 ± 1.3	1.8 ± 5.7	0.0 ± 1.6	1.2 ± 2.2
$\Delta\dot{V}_E$ (L/min)$^{(p<0.001)/, (p=0.002)//}$						
10 W	10.0 ± 3.9	9.4 ± 5.6	11.7 ± 5.5	12.6 ± 7.6	14.2 ± 9.0	17.0 ± 8.3
30W	13.9 ± 4.7	11.8 ± 12.4	16.7 ± 7.4	17.2 ± 7.2	19.2 ± 12.2	26.0 ± 9.6
$\Delta\dot{V}CO_2$ (mL/min)$^{(p<0.001)/}$						
10 W	331 ± 131	328 ± 119	343 ± 118	400 ± 200	443 ± 177	400 ± 205
30W	513 ± 150	450 ± 306	531 ± 170	560 ± 161	624 ± 238	643 ± 253
ΔR_f (breaths/min)$^{(p=0.006)/}$						
10 W	4.4 ± 2.8	4.1 ± 2.7	5.6 ± 4.0	6.7 ± 4.5	8.2 ± 5.5	8.3 ± 4.9
30W	4.7 ± 3.2	5.9 ± 4.1	7.7 ± 6.8	10.4 ± 6.1	8.7 ± 4.4	11.6 ± 5.1
ΔV_T (L)$^{(p=0.049)/}$						
10 W	0.36 ± 0.14	0.36 ± 0.13	0.40 ± 0.18	0.27 ± 0.24	0.24 ± 0.17	0.24 ± 0.19
30W	0.57 ± 0.22	0.29 ± 0.62	0.57 ± 0.27	0.29 ± 0.20	0.44 ± 0.19	0.37 ± 0.26

For abbreviations, see Table 2. Data were analyzed by 3-way ANOVA comparing effects of group (Non-OSA, OSA), exercise (10W, 30W) and dead space (control, 200 mL, 400 mL). Values are means ± SD.

≠ Significant effect of group.

/ Significant effect of exercise.

// Significant effect of dead space. (p-values shown)

Table 5

Subject characteristics for OHS subjects 508 and 520.

	Subject 508	Subject 520
Sex	F	M
Age (yr)	42	38
Height (cm)	149.7	185.9
Weight (kg)	106.3	175.2
BMI (kg/m^2)	47.4	50.7
AHI (events/hr)	20	43
Neck circumference (cm)	37.6	49.5
FVC (%pred)	91	90
FEV_1 (%pred)	85	83
FEV_1/FVC (%)	78	75
TLC (%pred)	83	83
FRC (%TLC)	35	39
IC (%pred)	82	81
ERV (L)	0.2	0.5
RV (%pred)	78	90
DLCO (%pred)	68	69
DLCO/V_A (%pred)	146	113

For abbreviations, see Table 1.