Respiratory Physiology & Neurobiology 236 (2017) 42–50

Contents lists available at ScienceDirect

Respiratory Physiology & Neurobiology

journal homepage: www.elsevier.com/locate/resphysiol

Short-term modulation of the ventilatory response to exercise is preserved in obstructive sleep apnea

Vipa Bernhardt[a,b], Gordon S. Mitchell[c], Won Y. Lee[d], Tony G. Babb[a,*]

[a] Institute for Exercise and Environmental Medicine, Texas Health Presbyterian Hospital Dallas and UT Southwestern Medical Center, Dallas, TX, USA
[b] Texas A&M University-Commerce, Department of Health and Human Performance, Commerce, TX, USA
[c] University of Florida, Department of Physical Therapy, Gainesville, FL, USA
[d] Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX, USA

ARTICLE INFO

Article history:
Received 11 April 2016
Received in revised form 2 November 2016
Accepted 7 November 2016
Available online 10 November 2016

Keywords:
Obesity
Sleep apnea
P_{CO2}
Obesity hypoventilation syndrome

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/h [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} (PET_{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, $p > 0.05$); PET_{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 ($p < 0.05$) and the PET_{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.

1. 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

* Corresponding author at: Institute for Exercise and Environmental Medicine, 7232 Greenville Ave, Ste 435, Dallas, TX 75231, USA.
E-mail addresses: Vipa.Bernhardt@tamuc.edu (V. Bernhardt), gsmitche@phhp.ufl.edu (G.S. Mitchell), Won.Lee@utsouthwestern.edu (W.Y. Lee), TonyBabb@TexasHealth.org (T.G. Babb).

http://dx.doi.org/10.1016/j.resp.2016.11.003
1569-9048/

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.

2. Methods

2.1. 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 (Anon, 1995; Pellegrino et al., 2005).

2.2. 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} (PET_{CO2}) and breathing frequency (Rf) was manually recorded from a capnograph every 15 s. Tidal volume (VT) was calculated as $\dot{V}E$/Rf.

2.3. 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 $\Delta\dot{V}E/\Delta PET_{CO2}$ linear regression. All statistical analyses were performed with IBM SPSS Statistics Version 22. Data are presented as mean ± SD.