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SCIENTIFIC INVESTIGATIONS

Ventilatory response to exercise is preserved in patients with obesity hypoventilation syndrome

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Study Objectives: Blunted ventilatory responses to hypoxia and hypercapnia during resting conditions are common findings in patients with obesity hypoventilation syndrome (OHS). Exercise increases the work and oxygen cost of breathing and produces excessive carbon dioxide (CO_2). The aim of this investigation was to study ventilatory responses to incremental exercise in patients with OHS.

Methods: Sixty-eight obese adults with OHS (n = 15), eucapnic obstructive sleep apnea (n = 26), or simple obesity (n = 27) participated in an incremental exercise test on a cycle ergometer and an in-laboratory sleep study.

Results: The peak oxygen uptake (peak VO_2) and peak pulse oxygen was decreased in patients with OHS compared with patients with either obstructive sleep apnea or simple obesity. The ventilatory response to exertional metabolic demand (nadir VE/VCO_2, $\Delta VE/\Delta VCO_2$ slope, and VE/VCO_2 at peak exercise) did not significantly differ among the 3 groups. Minute ventilation, tidal volume, respiratory frequency, tidal volume/respiratory frequency, and inspiratory time/total time ratio at a given work rate were comparable among the 3 groups. Among the whole cohort, apnea-hypopnea index was not independently associated with peak VO_2, and no association was found between the $\Delta VE/\Delta VCO_2$ slope and resting arterial partial pressure of CO_2.

Conclusions: The ventilatory response to incremental exercise is preserved in patients with OHS compared with patients with obstructive sleep apnea and simple obesity who were matched for age and body mass index. This result highlights the complexity of the respiratory control system during exercise for patients with OHS, which may be uncoupled with the ventilatory response during sleep and resting conditions.

Keywords: obesity hypoventilation syndrome; ventilatory response; cardiopulmonary exercise test

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BRIEF SUMMARY

Current Knowledge/Study Rationale: A depressed ventilatory response to hypercapnia and hypoxemia is one of the most important predisposing factors of obesity hypoventilation syndrome, and exercise, which is a crucial component for weight management, places extra challenges on the respiratory system. The objective of this study was to investigate the ventilatory response to incremental exercise in patients with obesity hypoventilation syndrome.

Study Impact: Ventilatory responses to exercise have scarcely been reported in patients with obesity hypoventilation syndrome. We found that patients with obesity hypoventilation syndrome had a reduced cardiovascular response to exercise; however, the ventilatory responses to incremental exercise were similar to those of patients with obstructive sleep apnea and simple obesity, which indicates the ability to maintain homeostatic regulation of ventilation in response to augmented exercise challenges.

INTRODUCTION

Obesity has markedly increased worldwide during the last 3 decades and is now a prevalent global epidemic.[1,2] Obesity poses unique challenges on the respiratory system and is one of the most important precipitating factors for obstructive sleep apnea (OSA) and obesity hypoventilation syndrome (OHS). OHS is defined as daytime hypercapnia during wakefulness combined with obesity and is accompanied by sleep hypoventilation or OSA.[3] Compared with patients with eucapnic OSA, patients with OHS are at an increased risk for developing cardiopulmonary complications and early mortality and have a poorer quality of life and higher health care expenses.[4–6]

Most individuals who are severely obese can maintain blood gas homeostasis through augmentation of alveolar ventilation and carbon dioxide (CO_2) output, thereby preventing the development of OHS. Many physiologic differences exist between individuals with OHS and those with eucapnic OSA or simple obesity, and an abnormal ventilatory response to hypercapnia and hypoxemia is one of the most important predisposing factors of chronic alveolar hypoventilation,

which is the characteristic of OHS.[7] Studies of individuals with OHS during resting conditions have found blunted ventilatory responses to hypoxia and hypercapnia compared with the responses of those with eucapnic OSA and simple obesity.[8,9]

Physical activity is a crucial component for weight management in patients with OHS. Exercise may increase the work and oxygen cost of breathing and produce excessive CO_2. Considering the depressed regulation of ventilation observed at rest and the additional load on the ventilation system during exercise, whether there are any alterations in the ventilatory responses to exercise in patients with OHS warrants investigation. An abnormal ventilatory response can influence the exercise capacity and the safety of exercise rehabilitation. Thus, the aim of this investigation was to study ventilatory responses to incremental exercise in patients with OHS. We hypothesized that patients with OHS have depressed exercise ventilatory responses compared with those with eucapnic obesity and OSA and healthy individuals with obesity.

METHODS

Study population

Sixty-eight obese adults with OHS (n = 15), eucapnic OSA (n = 26), or simple obesity (n = 27) were recruited from the Bariatric Surgery Center of China-Japan Friendship Hospital. The diagnosis for OHS is defined by the combination of daytime hypercapnia (partial pressure of arterial carbon dioxide ≥ 45 mm Hg during wakefulness and obesity; body mass index [BMI] ≥ 30 kg/m^2) occurring without other mechanical, neuromuscular, or metabolic causes of hypoventilation.[3] OSA is defined as an apnea-hypopnea index (AHI) ≥ 15 events/h based on an in-laboratory polysomnographic (PSG) study. Individuals with significant pulmonary, cardiovascular, musculoskeletal, or metabolic disorders that may preclude maximal exercise testing were excluded from the study. Individuals who had accepted noninvasive positive airway pressure treatment or had taken part in regular physical activity (>30 min/day, >3 days/wk) during the past 6 months were excluded. All participants provided written informed consent, and the Institutional Review Board of China-Japan Friendship Hospital approved the protocol.

Pulmonary function testing and cardiopulmonary exercise testing

Resting lung function tests, including spirometry, lung volumes, and diffusing capacity, were measured according to current recommendations, and the percent predicted values were calculated according to relevant reference equations.[10–13]

After the pulmonary function tests, all participants performed a stepwise incremental exercise test on an electrically braked cycle ergometer (VIAsprint 150P; Ergoline, Bitz, Germany). The cardiopulmonary exercise testing consisted of 3-minute rest and 1-minute unloaded pedaling, followed by an incremental test in which the workload was increased in 15-W/min intervals to symptom limitation. Respiratory gas exchanges were measured through an online breath-by-breath air analyzing system (Jaeger MasterScreen CPX, CareFusion, San Diego, United States) during the entire exercise test. Oxygen uptake (VO_2), carbon dioxide output (VCO_2), tidal volume (VT), respiratory frequency, minute ventilation (VE), pulse oximetry (SpO_2), blood pressure, and electrocardiogram were recorded throughout the exercise test. The ventilatory responses to exercise were measured at several submaximal workloads: 30, 45, 60, 75, 90, 105, 120, and 135 W. The slope of VE/VCO_2 ($\Delta VE/\Delta VCO_2$) was calculated from the lower linear part of the plot of VE as a function of VCO_2.[14] Anaerobic threshold was assessed using the V-slope method.[15] Breathing reserve was expressed as VE/maximum voluntary ventilation, and maximum voluntary ventilation was expressed as maximum voluntary ventilation = forced expiratory volume in 1 second × 40. Dyspnea intensity was assessed with the modified 10-point Borg scale. The Wasserman formula was used to calculate the predicted values of peak VO_2.[16] The predicted maximal heart rate for cycle ergometry was determined using the following equation: 208 − 0.70(age).[17]

PSG study

Full overnight PSG (Alice 6, Philips Respironics, Murrysville, Pennsylvania, United States) was performed in a sleep center. All data were analyzed by experienced technologists according to the 2012 American Academy of Sleep Medicine criteria.[3]

Statistical analysis

Two-way analysis of variance and appropriate post hoc analysis were conducted to compare between-group differences. χ^2 tests were used to compare frequencies. Analysis of variance with repeated measures was used to compare cardiorespiratory variables during isowork rates. Bivariate correlation coefficients were used to determine the association of potential predictor variables with VO_2max and $\Delta VE/\Delta VCO_2$. Predictor variables with $P < .10$ according to the bivariate analysis were selected for multivariate stepwise regression analysis. $P < .05$ was considered statistically significant. All analyses were conducted with SPSS 25.0 (SPSS Inc., Chicago, IL).

RESULTS

Clinical, resting functional, and PSG characteristics

Among the recruited 68 patients, most were in their 40s and severely obese with metabolic syndromes. Age, sex distribution, BMI, resting pulmonary function parameters, frequencies of comorbidities, and medications were similar among the OHS, eucapnic OSA, and simple obesity groups, with arterial carbon dioxide partial pressure and bicarbonate (HCO_{3-}) being higher and arterial oxygen partial pressure being lower in the OHS group compared with those in the OSA and simple obesity groups. Systolic blood pressure was higher in the OHS and OSA groups than in the simple obesity group, and diastolic blood pressure was higher in the OHS group than in the OSA and simple obesity groups. No significant differences were found in key PSG variables in the patients with OHS and patients with eucapnic OSA. The AHI and oxygen desaturation index were higher and the mean and nadir SpO_2 during sleep were lower in the patients with OHS and patients with eucapnic OSA than in participants with simple obesity (**Table 1**).

Table 1—Anthropometric, resting functional, and polysomnography parameters.

Variables	OHS (n = 15)	OSA (n = 26)	OB (n = 27)
Demographic			
Age, years	41.7 ± 6.7	43.5 ± 6.8	40.7 ± 8.3
Male/female	5/10	8/18	4/23
BMI, kg/m^2	39.4 ± 7.2	39.2 ± 6.3	37.5 ± 4.2
ESS, mean	12.0 ± 3.5[a]	11.6 ± 4.1[a]	7.9 ± 3.8
SBP, mm Hg	138.8 ± 22.3[a]	127.4 ± 14.8	122.9 ± 20.5
DBP, mm Hg	98.2 ± 12.0[a,b]	87.2 ± 13.1	82.3 ± 9.8
Hypertension n, %)	8 (53.3%)	10 (38.5%)	8 (29.6%)
Diabetes (n, %)	5 (33.3%)	5 (19.2%)	6 (22.2%)
IHD (n, %)	2 (13.3%)	2 (7.7%)	2 (7.4%)
Lung function			
FEV_1, % predicted	79.7 ± 10.6	83.6 ± 13.6	83.0 ± 13.5
FVC, % predicted	86.0 ± 9.0	90.0 ± 14.2	90.3 ± 13.8
FEV_1/FVC, %	79.1 ± 3.3	79.4 ± 6.2	79.9 ± 5.6
TLC, % predicted	80.8 ± 12.9	84.0 ± 13.3	83.1 ± 11.9
RV/TLC, %	32.0 ± 5.6	31.7 ± 5.0	29.5 ± 7.5
DLCO, % predicted	87.3 ± 11.5	89.2 ± 12.2	89.1 ± 11.8
Arterial blood gas			
pH	7.39 ± 0.04	7.40 ± 0.04	7.39 ± 0.03
PaO_2, mm Hg	82.9 ± 7.7[a]	88.1 ± 5.9	90.1 ± 5.3
$PaCO_2$, mm Hg	48.3 ± 2.4[a,b]	39.5 ± 2.8	39.7 ± 3.0
HCO_{3-}, mmol/L	27.4 ± 1.4[a,b]	24.2 ± 1.6[a]	22.9 ± 1.5
PSG parameters			
AHI, events/h	40.4 ± 26.8[a]	45.6 ± 22.4[a]	3.9 ± 2.9
ODI, events/h	41.4 ± 26.9[a]	43.3 ± 15.9[a]	6.9 ± 5.1
SpO_2mean, %	90.9 ± 3.8[a]	91.9 ± 1.9[a]	94.4 ± 2.6
SpO_2nadir, %	71.9 ± 11.1[a]	72.4 ± 13.2[a]	85.0 ± 6.5
Medication			
β-Blockers (n, %)	2 (13.3%)	2 (7.7)	2 (7.4%)
RAAS blockers (n, %)	7 (46.7%)	9 (34.6%)	6 (22.2%)
CCB (n, %)	1 (6.7%)	1 (3.8%)	1 (3.7%)

Data expressed as mean ± standard deviation, ratio, percentage, or count (percentage). [a]$P \leq .05$ compared with OB. [b]$P \leq .05$ compared with OSA. AHI = apnea-hypopnea index, BMI = body mass index, CCB = calcium channel blocker, DBP = diastolic blood pressure, DLCO = diffusion capacity of the lung for carbon monoxide, ESS = Epworth Sleepiness Scale, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, IHD = ischemic heart disease, ODI = oxygen desaturation index, OHS = obesity hypoventilation syndrome, OSA = obstructive sleep apnea, OB = obesity, PaO_2 = arterial oxygen partial pressure, $PaCO_2$ = arterial carbon dioxide partial pressure, PSG = polysomnogram, RV = residual volume, SBP = systolic blood pressure, SpO_2 = pulse oxygen saturation, TLC = total lung capacity.

Cardiopulmonary exercise testing metabolic and cardiovascular responses

Maximal exercise was achieved in all the groups, as indicated by the peak respiratory exchange ratio ≥ 1.1. The OHS group had reduced peak VO_2, either expressed in mL/kg/min or in percentage predicted, compared with patients with either OSA or simple obesity. The peak heart rate, either expressed in absolute value or in percentage predicted, was lower in patients with OHS than in patients with simple obesity. The peak O_2 pulse, either expressed in mL/min/bpm or in percentage predicted, was lower, and the peak diastolic blood pressure was higher in patients with OHS than in patients with OSA and participants with simple obesity (**Table 2**). For the whole cohort, the peak VO_2 (mL/kg/min) was associated with male sex, BMI, AHI, oxygen desaturation index, and forced expiratory volume in 1 second according to unadjusted analysis (**Table 3**). In stepwise multiple linear regression analysis with the peak VO_2 (mL/kg/min) as the dependent variable and male sex, BMI, AHI, oxygen desaturation index, forced expiratory volume in 1 second, and forced vital capacity as independent variables, only BMI and male sex were found to be independently associated with the peak VO_2 (**Table 4**). The formula

Table 2—Physiologic responses to incremental exercise testing.

Variables	OHS (n = 15)	OSA (n = 26)	OB (n = 27)
Metabolic/cardiovascular responses			
Peak VO_2, mL/min/kg	17.5 ± 2.2[a,b]	19.8 ± 2.8	20.9 ± 3.1
Peak VO_2, % predicted	77.1 ± 10.5[a,b]	86.0 ± 11.7	88.5 ± 11.2
Peak RER	1.1 ± 0.1	1.1 ± 0.1	1.1 ± 0.1
AT VO_2, mL/min/kg	14.6 ± 5.3	14.3 ± 4.2	15.7 ± 4.0
AT VO_2, % predicted	50.0 ± 10.8	54.7 ± 11.9	52.8 ± 10.8
$\Delta VO_2/\Delta WR$, mL/min/W	11.6 ± 2.8	10.9 ± 2.4	10.1 ± 1.7
Peak HR, bpm	138.3 ± 15.6[a]	140.7 ± 14.0	150.0 ± 14.5
Peak HR, % predicted	77.2 ± 8.6[a]	78.9 ± 7.7	83.3 ± 8.1
Peak O_2pulse, mL/min/bpm	11.6 ± 2.5[a,b]	14.3 ± 3.4	14.5 ± 3.0
Peak O_2pulse, % predicted	76.6 ± 11.6[a,b]	88.3 ± 13.9	88.5 ± 14.8
SBP at peak, mm Hg	172.6 ± 15.7	167.8 ± 16.1	162.9 ± 21.3
DBP at peak, mm Hg	95.1 ± 9.7[a,b]	84.6 ± 11.8	86.0 ± 10.1
Ventilatory responses			
Peak VE/MVV, %	57.2 ± 10.8	54.3 ± 11.5	49.6 ± 9.6
Peak VT, L	1.71 ± 0.31	1.78 ± 0.39	1.61 ± 0.27
Peak fR, rpm	30.4 ± 6.4	31.3 ± 10.5	33.7 ± 7.5
Rest VE/VCO_2	33.2 ± 6.2	31.5 ± 5.2	33.4 ± 4.7
Peak VE/VCO_2	28.8 ± 3.2	28.4 ± 3.6	28.6 ± 2.9
Nadir VE/VCO_2	24.4 ± 2.4	24.6 ± 3.3	25.4 ± 3.3
$\Delta VE/\Delta VCO_2$ slope	27.9 ± 3.9	28.3 ± 4.1	27.3 ± 3.3
Pulmonary gas exchange			
Peak $PetCO_2$, mm Hg	43.1 ± 3.2[a,b]	38.4 ± 4.4	37.3 ± 3.2
$\Delta PetCO_2$peak-rest, mm Hg	2.9 ± 1.8	3.2 ± 2.1	2.7 ± 1.9
Peak VD/VT	0.21 ± 0.06	0.18 ± 0.05	0.22 ± 0.07
Peak SpO_2, %	98.8 ± 1.14	98.5 ± 2.04	98.0 ± 2.56
ΔSpO_2peak-rest, %	0.5 ± 1.3	0.7 ± 2.3	0.3 ± 0.7
Peak dyspnea score	7.2 (5–9)	6.7 (4–10)	7.8 (3–9)

Data expressed as mean ± standard deviation for numerical variables with a normal distribution or as the median and interquartile range for data with a skewed distribution. [a]$P \leq .05$ compared with OB. [b]$P \leq .05$ compared with OSA. AT = anaerobic threshold, DBP = diastolic blood pressure, fR = respiratory frequency, HR = heart rate, MVV = maximum voluntary ventilation, O_2pulse = oxygen pulse, $PetCO_2$ = end-tidal partial pressure of carbon dioxide, RER = respiratory exchange rate, SBP = systolic blood pressure, SpO_2 = pulse oxygen saturation, VCO_2 = carbon dioxide output, VD = dead space ventilation, VE = minute ventilation, VO_2 = oxygen uptake, VT = tidal volume, WR = work rate.

generated by the multivariate regression analysis was as follows: peak VO_2 (mL/kg/min) = 36 − 0.365 × BMI − 3.317 × sex (male = 0, female = 1) (adjusted R^2 = 0.495, F = 33.286, $P < .001$).

Cardiopulmonary exercise testing ventilatory and gas exchange responses

No ventilation limitation to exercise was noted, as reflected by adequate breathing reserve for the participants in the 3 groups. VE, VT, respiratory frequency, VT/respiratory frequency, inspiratory time/total time for each respiration, VE/VCO_2, and VE/VO_2 at a given work rate throughout exercise were not significantly different among the 3 groups (**Figure 1**). The nadir VE/VCO_2, $\Delta VE/\Delta VCO_2$ slope, and VE/VCO_2 at peak exercise did not significantly differ among the 3 groups (**Figure 2**). No associations were found between $\Delta VE/\Delta VCO_2$ and the anthropometric, resting functional and PSG parameters, except for age. The exercise gas exchange parameters at peak exercise, including dead space ventilation/VT and SpO_2, were not significantly different among the 3 groups. No significant differences were found in end-tidal partial pressure of carbon dioxide and SpO_2 from rest to peak exercise in any of the 3 groups ($P > .05$). The peak dyspnea scores were similar among the 3 groups (**Table 2**).

DISCUSSION

OSA and OHS are known to impair cardiorespiratory fitness; however, little is known about their impact of sleep-disordered

Table 3—Correlates of peak VO_2 and $\Delta VE/\Delta VCO_2$.

Unadjusted analysis	Peak VO_2 (mL/kg/min)		$\Delta VE/\Delta VCO_2$	
	r	*P*	*r*	*P*
Group (OHS, OSA, OB)	−0.13	.31	−0.06	.63
Age, years	−0.01	.96	0.30	.01
Male sex	−0.57	<.01	−0.04	.72
BMI, kg/m^2	−0.52	<.01	−0.08	.51
SBP, mm Hg	0.16	.22	−0.14	.29
DBP, mm Hg	0.10	.48	0.07	.62
FEV_1, % predicted	0.29	.02	0.09	.44
FVC, % predicted	0.21	.08	0.11	.38
FEV_1/FVC, %	0.07	.56	−0.07	.55
TLC, % predicted	0.12	.47	0.23	.15
DLCO, % predicted	0.07	.67	−0.16	.31
PaO_2, mm Hg	0.03	.83	−0.20	.11
$PaCO_2$, mm Hg	0.11	.37	−0.12	.34
HCO_{3-}, mmol/L	−0.07	.60	0.12	.34
AHI, events/h	0.30	.01	0.17	.17
ODI, events/h	0.24	.05	0.17	.16
SpO_2mean, %	0.04	.80	−0.01	.97
SpO_2nadir, %	0.00	.99	−0.11	.40
Medication of β-blockers	−0.14	.25	−0.07	.58

AHI = apnea-hypopnea index, BMI = body mass index, DLCO = diffusion capacity of the lung for carbon monoxide, DBP = diastolic blood pressure, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, OB = obesity, ODI = oxygen desaturation index, OHS = obesity hypoventilation syndrome, OSA = obstructive sleep apnea, $PaCO_2$ = arterial carbon dioxide partial pressure, PaO_2 = arterial oxygen partial pressure, SBP = systolic blood pressure, SpO_2 = pulse oxygen saturation, TLC = total lung capacity, VCO_2 = carbon dioxide output, VE = minute ventilation, VO_2 = oxygen uptake.

Table 4—Regression with peak VO_2 (mL/kg/min stepwise multiple linear regression analysis).

Variables	Beta	*P*
Male sex	−0.44	<.01
BMI	−0.60	<.01
FEV_1, % predicted	−0.01	.95
FVC, % predicted	−0.13	.90
AHI	0.12	.23
ODI	0.07	.48

Inclusion criteria = 0.05; exclusion criteria = 0.20. AHI = apnea-hypopnea index, BMI = body mass index, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, ODI = oxygen desaturation index, VO_2 = oxygen uptake.

breathing (SDB) on the physiologic response to exercise, especially for patients with OHS. This study investigated the cardiorespiratory responses to exercise in patients with OHS without the presence of confounding factors such as significant cardiopulmonary dysfunction. The main findings of this study indicate the following. (1) The maximal aerobic capacity, assessed by VO_2 peak either in mL/min/kg or in percentage predicted, and the cardiovascular responses to exercise are decreased in patients with OHS compared with those values in patients with eucapnic OSA and simple obesity. (2) The ventilatory responses to incremental exercise testing are preserved in patients with OHS, which is reflected by comparable VE, VE/VCO_2, and VE/VO_2 measures throughout the exercise test compared with those responses in participants with eucapnic OSA and simple obesity.

Reduced cardiopulmonary fitness is closely related to an increased risk of cardiovascular disease and all-cause mortality in healthy participants and patients with different disease entities.[18,19] OSA and OHS have many detrimental effects on cardiovascular and respiratory mechanisms; therefore, these 2 types of SDB are predicted to have a negative impact on cardiopulmonary fitness. Nevertheless, controversy still exists as to the impact of SDB on maximal aerobic capacity. Previous investigations have obtained conflicting findings, with some

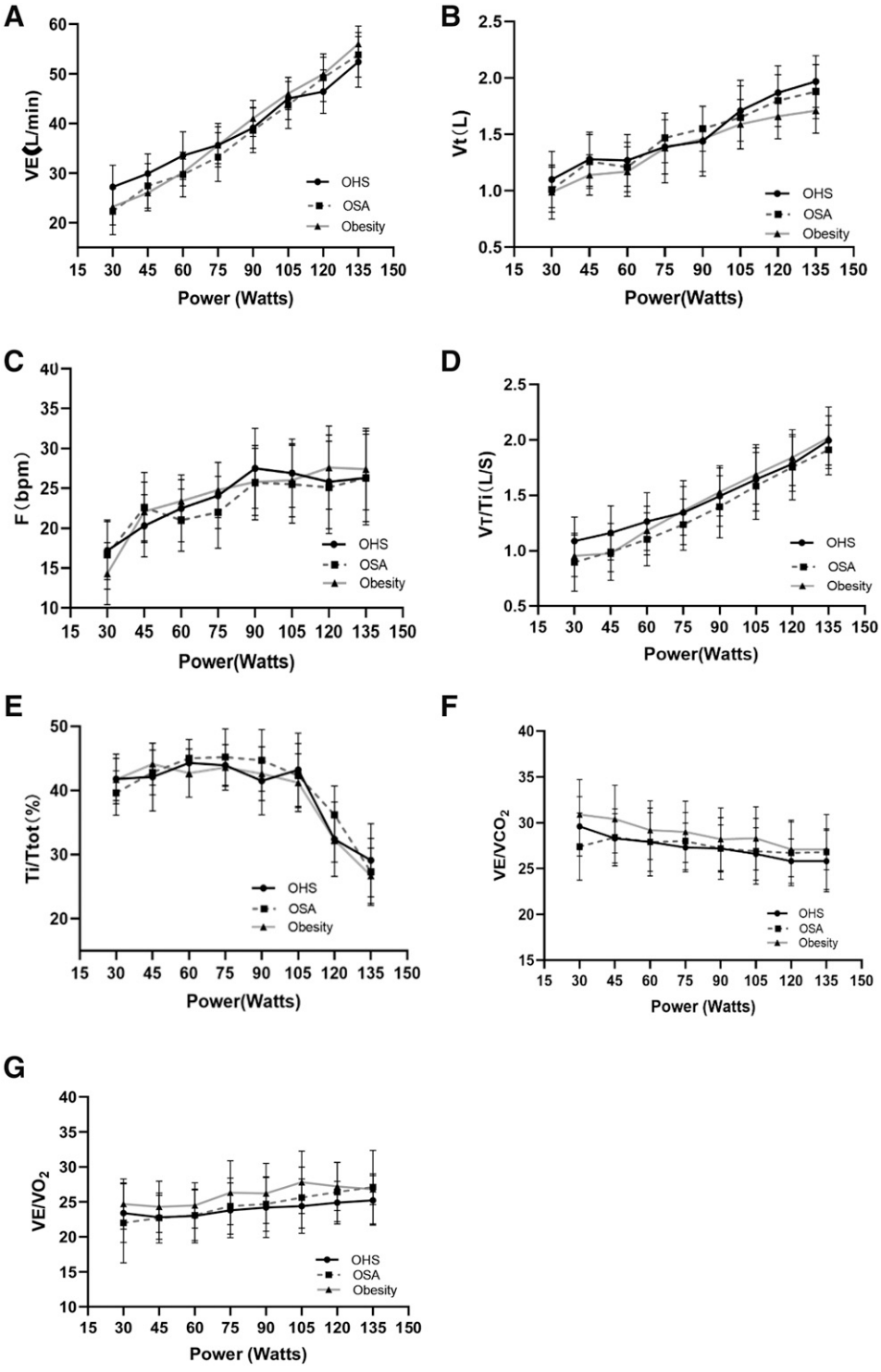
investigations indicating no impairment in maximal aerobic capacity in patients with OSA,[20,21] and others indicating decreased maximal exercise capacity compared with that in control participants.[22–25] These discrepancies may be because of the varying status of comorbidities and the differences of OSA severity and sample size. A retrospective study performed by Mansukhani et al[23] reported decreased exercise capacity and a negative correlation between AHI and functional exercise capacity in patients with OSA; however, the patients with OSA were older, more obese, and more hypertensive than the participants without OSA. In the present study, the VO_2 peak was similar between the participants with eucapnic OSA and those with simple obesity, and AHI was not an independent predictor of VO_2 peak among the whole cohort (**Figure 3A**). In line with the results of our study, Powell et al[26] found that the exercise capacity did not decrease in participants with moderate to severe OSA compared with that in controls among younger active military personnel. de Carvalho et al[27] studied treadmill exercise capacity among middle-aged female individuals, and they found that the presence of obesity without OSA was associated with low exercise capacity, whereas the presence of OSA without obesity was not, which indicates that the effect of OSA on exercise tolerance may be through intermediate factors, such as comorbid cardiovascular disease or deconditioning, rather than an independent effect. The cardiopulmonary response to exercise in patients with OHS has scarcely been reported. Schönhofer et al[28] studied 14 patients with OHS and found that their load tolerance was compromised. In the present study, the VO_2 peak was lower in patients with OHS than in individuals with eucapnic OSA and simple obesity. Additionally, the peak O_2 pulse, either in mL/min bpm or in percentage predicted, was decreased in patients with OHS, which indicates an impaired cardiovascular response to exercise. Cardiovascular morbidity is of particular concern in patients with OHS. In our cohort, the patients with OHS were more hypertensive than the patients with OSA and simple obesity both at rest and during peak exercise, especially for the diastolic pressure level. A previous study found that left ventricular diastolic dysfunction is more prevalent in severe SDB and is associated with impaired exercise performance.[29] Therefore, the increased afterload and secondary diastolic dysfunction of the left ventricle may explain the decreased peak O_2 pulse and maximal exercise capacity.

Peak heart rate was similar in the individuals with OHS and OSA but was lower in the former than in individuals with simple obesity. The possibility of submaximal exercise maneuvers was small because the peak respiratory exchange rate attained 1.1 in all 3 groups. In line with the results of our study, Aguillard et al[21] and Kaleth et al[30] also reported a blunted heart rate response to graded exercise in individuals with OSA. The reasons for the diminished chronotropic response during exercise in individuals with OSA are unclear. Possible explanations include the sustained increased sympathetic activity secondary to hypoxia and sleep fragmentation that can result in the downregulation of cardiac β-adrenergic receptors, which impairs sufficient heart rate elevation in response to the rapidly increased exercise work load. In addition, β-blockers have negative chronotropic effects on heart rate. In the current study, the use of β-blockers was not significantly different among the 3 groups ($\chi^2 = 0.49$. $P = .78$), and no association was found between the administration of β-blockers and peak VO_2max. Similar to the results of our study, a large-scale, population-based survey reported that chronic β-blockade has no effect on peak exercise capacity or ventilatory efficiency among the general population.[31] The effects of β-blockers on the cardiovascular response to exercise in patients with SDB require further investigation.

Obesity has profound adverse effects on the respiratory system, and hypoventilation in individuals who are obese includes a diversity of mechanisms frequently implicated, among which the 2 most important are obesity-related mechanical limitation and blunted ventilatory drive. In the present cohort, the ventilatory reserve and breathing pattern did not significantly differ among the 3 groups. The adequate ventilatory reserve indicates no mechanical ventilatory limitation to exercise. Limited data are available on the ventilatory responses to incremental exercise testing in individuals with OSA, and documented reports have scarcely studied the exercise ventilatory responses in individuals with OHS. Hargens et al[32] reported augmented exercise ventilatory responses in obese young men with OSA, represented by significantly higher VE, VE/VO_2, and VE/VCO_2 measures at submaximal exercise work rates and peak exercise. Bruni et al[33] found that OSA has no impact on ventilatory responses to incremental exercise in patients who are morbidly obese with OSA compared with individuals who are obese without OSA and lean healthy individuals. Bernhardt et al[34] reported that the ventilatory response to constant-load submaximal cycling exercise is preserved in patients with OSA; however, the $\Delta VE/\Delta VCO_2$ slope and end-tidal partial pressure of carbon dioxide were increased with added dead space in 2 suspected patients with OHS, which suggests that the respiratory control may reach its limit for increasing ventilation to maintain constant end-tidal partial pressure of carbon dioxide homeostasis. In the present study, the $\Delta VE/\Delta VCO_2$ slope, the nadir and peak VE/VCO_2, and submaximal VE and VE/VCO_2 at given work rates were similar among the 3 groups, which suggests a comparable ventilatory response to incremental exercise testing in individuals with OHS, OSA, and simple obesity, matched for age and BMI. In line with our study, Menitove et al[35] studied the exercise ventilatory response in 6 patients with OHS with a severely reduced response to CO_2 rebreathing at rest and 20 healthy controls, and they found that $\Delta VE/\Delta VCO_2$ was similar between the 2 groups. These inconsistent findings as to the impact of SDB on exercise ventilatory responses may be because of differences in patient selection (our patients had less comorbidities and were relatively younger) or exercise protocol (maximal ramp or steady state submaximal exercise).

Different from the ventilatory regulation during sleep and wakeful resting, which mainly relies on the chemical control of breathing, other important inputs and sensors are involved in the regulation of the depth and rate of breathing during exercise. Receptors in the joints and limb muscles, stretch receptors in the lungs, and higher brain centers (cerebral cortex) can respond to movement to augment ventilation during exercise. Thus, the blunted ventilatory response during sleep and rest may be uncoupled with the exercise ventilatory responses in patients

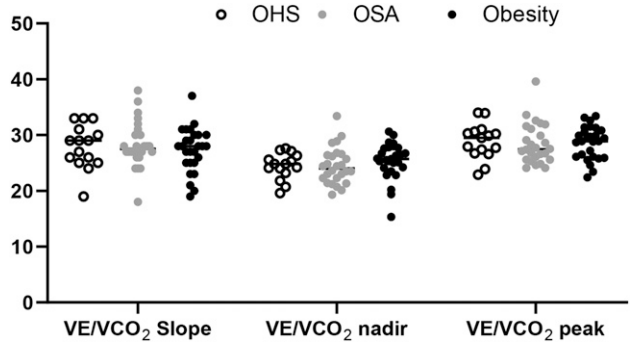
Figure 1—Ventilatory responses to incremental exercise testing in patients with OHS, OSA, and simple obesity.



Patients with OHS represented by circle symbols (n = 15), patients with OSA represented by square symbols (n = 26), and patients with simple obesity represented by triangle symbols (n = 27). The values are expressed as the means ± standard error of the mean. fR = respiratory frequency, OHS = obesity hypoventilation syndrome, OSA = obstructive sleep apnea, $PaCO_2$ = arterial carbon dioxide partial pressure, Ti = inspiratory time, Ttot = total time for each respiration, VCO_2 = carbon dioxide output, VE = minute ventilation, VO_2 = oxygen uptake, VT = tidal volume.

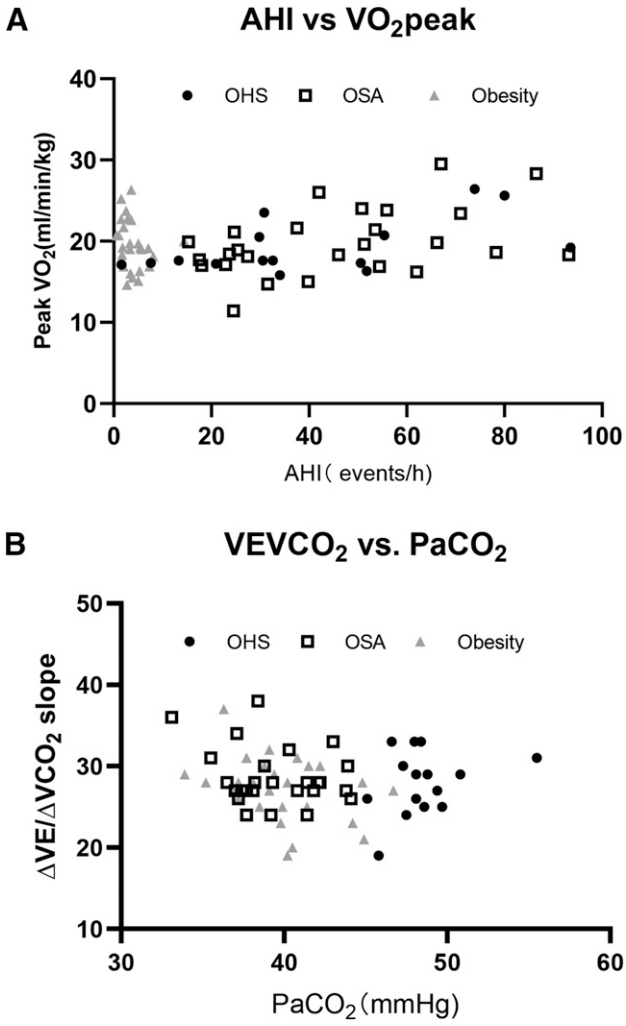
with OHS. Menitove et al[35] found no correlation between the CO_2 rebreathing response at rest and exercise ventilatory response in patients with OHS and normal individuals. In the present study, we found that the end-tidal partial pressure of carbon dioxid was not significantly different from rest to peak exercise in any of the 3 groups and that the slope of $\Delta VE/\Delta VCO_2$

Figure 2—Individual values for different metrics of exercise ventilatory response to exertional metabolic demand (VE/VCO_2).



Patients with OHS (open symbols; n = 15), OSA (gray symbols; n = 26), and simple obesity (solid symbols; n = 27) are identified. OHS = obesity hypoventilation syndrome, OSA = obstructive sleep apnea.

Figure 3—Relationship between AHI and peak VO_2 and resting $PaCO_2$ and $\Delta VE/\Delta VCO_2$ slope.



(A) Relationship between AHI and peak VO_2. **(B)** Relationship between resting $PaCO_2$ and $\Delta VE/\Delta VCO_2$ slope. Patients with OHS (solid circle symbols; n = 15), OSA (open square symbols; n = 26), and simple obesity (gray triangle symbols; n = 27) are identified. AHI = apnea-hypopnea index, OHS = obesity hypoventilation syndrome, OSA = obstructive sleep apnea, $PaCO_2$ = arterial carbon dioxide partial pressure, VCO_2 = carbon dioxide output, VE = minute ventilation, VO_2 = oxygen uptake.

was not correlated with resting arterial carbon dioxide partial pressure **(Figure 3B)**, which indicates that chemoreflexes may not be the solo (dominant) mechanism of exercise ventilatory control in patients with OHS. The respiratory control system shows considerable plasticity or compensatory capacity to maintain the homeostasis of blood PCO_2 and pH in response to physiologic (eg, obesity, OSA) and imposed (eg, exercise) conditions despite damage to key breathing control elements. The current findings cannot exclude the possibility that the patients recruited in our study are in a relatively early state of the OHS process, and patients with more advanced severity may show some degree of impaired ventilatory response to exercise, which warrants further investigation.

It is conventionally thought that the blunted chemoreflex sensitivity in patients with OHS may impair the perceptual response to exercise; however, in the present study, the peak dyspnea scores were similar among the 3 groups. Exertional dyspnea is the complex interaction of neural, mechanical, and metabolic factors that influence the relationship between central motor activation and respiratory muscle activity. We did not observe significant differences in respiratory neutral drive or ventilatory mechanical constrains among the 3 groups during exercise. In addition, although exertional dyspnea is mainly related to effort, the activation of other sensory receptors may also contribute to conscious sensation and the sensory quality of breathing.

Several limitations of the present study should be mentioned. First, OHS is frequently underappreciated, and diagnosis is usually made at advanced and unsteady states in clinical practice; thus, the specific characteristics of the present study population are worth noting. Unlike the OHS patients in most previous studies, we recruited patients without significant cardiopulmonary comorbidities from a bariatric surgery center, which may decrease the confounding effects of significant cardiopulmonary dysfunction on responses to exercise testing. In addition, the sample in the present study was limited to individuals who are Asian and, more uniquely, predominantly women. Sex- and race-specific determinants of ventilatory drive are known to exist. Therefore, considering the large heterogeneity in OHS and the relatively limited sample size, as well as the specific demographics of the study population of the current study, our findings cannot be generalized to patients with OHS of different severities and demographics characteristics. The present study investigated patients with OHS, eucapnic OSA, or simple obesity; however, it did not contain a lean, healthy group. Thus, whether the exercise ventilatory response could be influenced by obesity is unclear, although a previous study reported no differences in exercise ventilatory response between obese otherwise healthy participants and healthy lean controls.[33] Third, although the present study matched patients with OHS and with OSA and simple obesity individuals with respect to BMI, there may be differences in fat content across

individuals, and given lower adipose oxygen use, a higher fat content would be expected to lead to a lower overall mean VO_2/kg. Additional studies with reliable body composition assessment are warranted to provide a better understanding of the impact of SDB on aerobic exercise capacity. Fourth, the baseline measures of central respiratory drive to hypoxia or hypercapnia were not included in the present study. The association of the resting ventilatory drive to exercise ventilatory responses cannot be determined. Last, considering the relatively small sample size of this study, the comparisons among OHS, OSA, and simple obesity groups might be at risk of type II error, a possibility that cannot be disregarded.

In conclusion, patients with OHS demonstrated similar ventilatory responses to incremental exercise testing compared with individuals with OSA and simple obesity, which indicates the ability to maintain homeostatic partial pressure of carbon dioxide (PCO_2) regulation in response of augmented exercise challenges. The current findings may improve our understanding of the complexity of the respiratory control system during exercise for patients with OHS.

ABBREVIATIONS

AHI, apnea-hypopnea index
BMI, body mass index
CO_2, carbon dioxide
OHS, obesity hypoventilation syndrome
OSA, obstructive sleep apnea
O_2 pulse, oxygen pulse
PSG, polysomnography
SDB, sleep-disordered breathing
SpO_2, pulse oxygen saturation
VO_2, oxygen uptake
VCO_2, carbon dioxide output
VE, minute ventilation
VT, tidal volume

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DISCLOSURE STATEMENT

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