

# Factors Influencing Cardiopulmonary Exercise Testing in Obstructive Sleep Apnea Syndrome Patients

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**Summary.** The exercise capacity of obstructive sleep apnea syndrome (OSAS) patients has been demonstrated to be impaired, but the factors responsible are still unclear. In addition, ventilatory efficiency during exercise has never been studied in OSAS. Hypertension (HT), commonly found in OSAS patients, could be a contributing factor to exercise capacity. The aim of the study is: 1) to determine possible factors that could influence the exercise in OSAS patients, and 2) to compare the exercise capacity and ventilatory efficiency of patients with and without HT. Twenty-two male OSAS patients were submitted to cardiopulmonary exercise testing. Multiple linear regression analyses were used to find possible factors that could influence the exercise capacity and ventilatory efficiency of OSAS patients. Patients were divided into two groups according to the presence of HT, and cardiopulmonary exercise testing (CPET) results were compared between them. No factors emerged as predictors of oxygen consumption at peak exercise ( $\dot{V}O_{2peak}$ ). The slope of increase of ventilation relative to carbon dioxide production ( $\dot{V}E/\dot{V}CO_2$ -slope) was associated with body mass index (BMI) negatively and with apnea-hypopnea index (AHI) positively ( $p = 0.019$  and  $p = 0.047$ , respectively). There were no differences in either  $\dot{V}O_{2peak}$  or anaerobic threshold (AT) between OSAS with and without HT, but the  $\dot{V}E/\dot{V}CO_2$ -slope was higher in the HT group ( $p = 0.008$ ). Our results suggest that the severity of sleep apnea can influence the ventilatory efficiency of OSAS patients along with BMI and HT.

**Key words**— body mass index, exercise test, hypertension, obstructive sleep apnea, severity of illness index.

## INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) patients always complain of diurnal sleepiness and fatigue.<sup>1)</sup> Cardiopulmonary exercise testing (CPET) is a valuable tool in the evaluation of cardiac, pulmonary, and muscle function.<sup>2)</sup> In OSAS patients, it can help to quantify the level of the patient's exercise limitations and to assess improvement after treatment. There are a limited number of studies addressing exercise capacity in OSAS patients. Some of these have shown diminished exercise ability in OSAS, with lower maximum oxygen consumption ( $\dot{V}O_{2max}$ )<sup>3,4)</sup> and anaerobic threshold (AT)<sup>4,5)</sup> during exercise compared with normotensive patients. Factors responsible for this decrease in exercise capacity are still unclear because each may reciprocally influence other factors; thus, the most influential factor on exercise capacity can not be easily determined.

Hypertension (HT), commonly found in OSAS, could be one confounding factor in some of the studies addressing exercise capacity in OSAS. As improvement of exercise capacity after continuous positive airway pressure (CPAP) treatment<sup>6,7)</sup> has also been reported, the severity of the disease could probably be reflected in the exercise limitations of these patients. The only report showing a correlation between exercise capacity

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**Abbreviations**— AHI, apnea-hypopnea index; AT, anaerobic threshold; BMI, body mass index; HT, hypertension; OSAS, obstructive sleep apnea syndrome; SPB and DBP, systolic and diastolic blood pressure;  $\dot{V}E/\dot{V}CO_2$ -slope, slope of increase of ventilation relative to carbon dioxide production;  $\dot{V}O_{2peak}$ , oxygen consumption at peak exercise.

and severity of sleep apnea included just 11 patients and checked only the  $\dot{V}O_2$  at peak exercise. Anthropometric characteristics such as age and weight are also factors that could influence exercise capacity.<sup>8)</sup> The correlation between body mass index (BMI) and apnea-hypopnea index (AHI) in OSAS<sup>9)</sup> is well known, however, studies including OSAS patients and exercise capacity usually exclude severely obese patients due to the influence of BMI on the exercise capacity. One other valuable parameter that can be assessed during exercise is the ventilatory efficiency, demonstrated by the slope of increase of ventilation relative to carbon dioxide production ( $\dot{V}E/\dot{V}CO_2$ -slope). The  $\dot{V}E/\dot{V}CO_2$ -slope has been widely used to help in the interpretation of CPET in addition to  $\dot{V}O_{2max}$  and AT in cardiac impairments.<sup>10,11,12)</sup> However, the  $\dot{V}E/\dot{V}CO_2$ -slope has never been addressed in OSAS patients.

In order to determine influences of anthropometric factors (age, BMI), severity of sleep apnea, and blood pressure (BP) on the exercise capacity and ventilatory efficiency of OSAS patients, we performed multiple linear regression analyses including independent variables of these parameters. We also compared the exercise capacity and ventilatory efficiency of OSAS patients with and without HT.

## METHODS

### Patients

Twenty-two men complaining of habitual snoring and/or daytime sleepiness hospitalized for a diagnosis of OSAS were included in the study. All of them were diagnosed from mild to severe OSAS on the basis of polysomnography (PSG). Exclusion criteria included: diabetes mellitus, heart failure, chronic obstructive lung disease, renal failure, anemia, myopathy, and other musculoskeletal disabilities as evaluated by clinical history, physical examination, electrocardiography (ECG), and spirometry. Patients were divided into two groups according to the presence of HT. HT was defined as systolic BP (SBP) > 140 mmHg and/or diastolic BP (DBP) > 90 mmHg. In the hypertensive group, we included patients currently taking antihypertensive medications and patients with HT in their medical records. Five patients with HT were on antihypertensive drugs, which included: calcium antagonists, angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, and diuretics. Some patients were taking more than one drug at the same time. The CPET was performed as a routine clinical evaluation of the exercise ability of OSAS patients at Niigata University Medical and Dental Hospital. All participants were duly informed

about the exercise protocol and the written consent was also obtained before the study.

### Pulmonary function test

Spirometry was performed prior to entry into the study with the model Chestac-55V (Chest M.I. Inc., Tokyo), according to the American Thoracic Society standardization.<sup>13)</sup> The following function tests were performed: vital capacity (VC), and forced expiratory volume in 1s (FEV<sub>1</sub>). In addition, the FEV<sub>1</sub>/FVC (forced vital capacity) was determined. The maximum ventilatory ventilation (MVV) was indirectly estimated multiplying FEV<sub>1</sub> by 40.<sup>8)</sup>

### Polysomnography

Overnight sleep studies were performed with full PSG (Somnostar; SensorMedics, Yorba Linda, CA, USA), including the following measurements: electroencephalography (EEG), electromyography, electrooculography, ECG, airflow by oronasal thermistor, chest and abdominal wall movements, oxygen saturation (SpO<sub>2</sub>) by pulse oxymeter, snoring sounds by tracheal microphone, and body position. The findings were defined according to the recommendations advocated by the American Academy of Sleep Medicine (AASM) in 1999.<sup>14)</sup> Briefly, apnea was defined as the complete absence of oronasal airflow for at least 10s. Hypopnea was defined as a > 50 % decrease in oronasal airflow accompanied by a 3% fall in SpO<sub>2</sub> from the baseline or an EEG arousal from sleep. Sleep-disordered breathing was assessed by apnea-hypopnea index (AHI), the cumulative percentage of sleep time with SpO<sub>2</sub> below 90% (CT 90%) and the lowest SpO<sub>2</sub> (LoSpO<sub>2</sub>).

### Exercise testing

Symptom-limited CPET was performed on a stationary cycle ergometer (Combi 232CXL, Tokyo). After a three min rest period, followed by three min of unloaded cycling (warm-up) on 55 revolutions/min, exercise intensity was increased incrementally by 10 to 20 W/min, depending on the patient's age and condition, to allow each subject to reach a maximum within 8 – 12 min. All patients were encouraged to exercise to exhaustion.  $\dot{V}O_2$ , CO<sub>2</sub> production ( $\dot{V}CO_2$ ), minute ventilation ( $\dot{V}E$ ) and respiratory frequency (f) were continuously measured using a breath-by-breath gas analyzer (Minato AE280S, Osaka) with paramagnetic oxygen and photometric CO<sub>2</sub> gas analyses. Gas exchange variables were calculated and summarized every 30s. The respiratory exchange ratio (RER) was calculated as the ratio of  $\dot{V}CO_2/\dot{V}O_2$ . The AT was determined using the V-slope method, as previously described.<sup>8,15)</sup> The  $\dot{V}O_2$  at peak exercise ( $\dot{V}O_{2peak}$ ) was

**Table 1.** Anthropometric characteristics, spirometry, and polysomnography data of the study subjects

Parameters	Mean $\pm$ SD (n = 22)
Age, years	51.1 $\pm$ 13.7
Height, cm	167.6 $\pm$ 6.1
Weight, kg	83.2 $\pm$ 17.9
BMI, kg/m <sup>2</sup>	29.5 $\pm$ 5.5
VC, % predicted	111.9 $\pm$ 18.0
FEV <sub>1</sub> /FVC, %	78.1 $\pm$ 7.1
FEV <sub>1</sub> , % predicted	102.8 $\pm$ 18.7
MVV, L/min	126.5 $\pm$ 31.9
AHI, events/h	47.4 $\pm$ 30.4
CT90%, %	20.7 $\pm$ 27.2
LoSpO <sub>2</sub> , %	79.9 $\pm$ 10.1

Values represent mean  $\pm$  SD. MVV, maximum voluntary ventilation; AHI, apnea-hypopnea index; CT90%, cumulative percentage of sleep time with oxygen saturation below 90%; LoSpO<sub>2</sub>, lowest oxygen saturation.

**Table 2.** Comparison of anthropometric characteristics, spirometry, and polysomnography data between no-hypertension (HT) and HT groups

Parameters	No-HT group (n = 8)	HT group (n = 14)	<i>p</i> -values
Age, years	44.1 $\pm$ 14.9	55.0 $\pm$ 11.7	0.109
BMI, kg/m <sup>2</sup>	29.5 $\pm$ 6.6	29.5 $\pm$ 5.0	0.633
VC, % predicted	112.9 $\pm$ 15.6	111.3 $\pm$ 19.8	0.973
FEV <sub>1</sub> /FVC, %	81.1 $\pm$ 6.1	78.6 $\pm$ 8.0	0.088
FEV <sub>1</sub> , % predicted	105.7 $\pm$ 14.4	104.5 $\pm$ 21.1	0.339
MVV, L/min	140.8 $\pm$ 36.6	118.4 $\pm$ 26.9	0.172
AHI, events/h	45.7 $\pm$ 28.1	48.3 $\pm$ 33.2	0.785
CT90%, %	23.8 $\pm$ 26.7	19.0 $\pm$ 28.3	0.375
LoSpO <sub>2</sub> , %	77.1 $\pm$ 12.1	81.4 $\pm$ 8.9	0.306

Mann-Whitney U test between no-HT and HT groups. Values represent mean  $\pm$  SD. MVV, maximum voluntary ventilation; CT90%, cumulative percentage of sleep time with oxygen saturation below 90%; LoSpO<sub>2</sub>, lowest oxygen saturation.

**Table 3.** Comparisons of cardiopulmonary exercise testing (CPET) data between no-HT and HT groups

Parameters	No-HT group (n = 8)	HT group (n = 14)	<i>p</i> -values
Rest			
RER <sub>rest</sub>	0.89 ± 0.1	0.9 ± 0.1	0.785
HR <sub>rest</sub> , beats/min	79.0 ± 8.0	74.9 ± 10.7	0.125
SBP <sub>rest</sub> , mmHg	128.2 ± 8.2	142.9 ± 11.7	0.009
DBP <sub>rest</sub> , mmHg	81.8 ± 7.8	95.0 ± 9.3	0.002
Peak exercise			
RER <sub>peak</sub>	1.21 ± 0.1	1.15 ± 0.1	0.172
$\dot{V}E$ , L/min	66.9 ± 19.8	68.9 ± 13.4	0.733
f, cycles/min	30.7 ± 5.5	34.0 ± 5.4	0.133
BR, %	47.9 ± 9.2	61.3 ± 19.7	0.101
O <sub>2</sub> pulse, mL/beat/min	12.2 ± 2.6	12.9 ± 2.6	0.413
maximal load, W	143.9 ± 38.7	148.7 ± 30.8	> 0.999
SpO <sub>2</sub> , %	97.0 ± 2.5	96.2 ± 1.5	0.056
PETCO <sub>2</sub> , mmHg	42.2 ± 3.0	40.0 ± 3.1	0.095
HR <sub>peak</sub> , beats/min	148.6 ± 26.0	145.7 ± 16.6	0.838
SBP <sub>peak</sub> , mmHg	212.8 ± 31.5	218.0 ± 25.9	0.785
SDB <sub>peak</sub> , mmHg	106.4 ± 19.0	117.4 ± 17.1	0.322
$\dot{V}O_{2peak}$ , mL/min	1792.6 ± 394.0	1881.6 ± 419.5	0.838
$\dot{V}O_{2peak}$ , mL/kg/min	21.7 ± 4.2	23.1 ± 4.9	0.585
Others			
AT, mL/min	1006.8 ± 267.2	1015.2 ± 267.2	0.891
AT, mL/kg/min	12.0 ± 1.5	12.5 ± 1.6	0.517
$\dot{V}E/\dot{V}CO_{2-slope}$	23.6 ± 2.0	27.0 ± 2.6	0.008

Mann-Whitney U test between no-HT and HT groups. Values represent mean ± SD. RER, respiratory exchange ratio; SPB<sub>rest</sub>, DBP<sub>rest</sub>, SBP<sub>peak</sub>, DBP<sub>peak</sub>, systolic and diastolic blood pressure at rest and at peak exercise, respectively;  $\dot{V}E$ , minute ventilation, f, respiratory frequency; BR, breathing reserve; O<sub>2</sub> pulse, oxygen pulse; PETCO<sub>2</sub>, end-tidal PCO<sub>2</sub>,  $\dot{V}O_{2peak}$ , oxygen consumption at peak exercise; AT, anaerobic threshold;  $\dot{V}E/\dot{V}CO_{2-slope}$ , slope of increase of ventilation relative to carbon dioxide production.

calculated by averaging values obtained during the final 30s of exercise. The ECG and heart rate (HR) were monitored throughout the test. The oxygen pulse (O<sub>2</sub> pulse) was obtained by dividing the  $\dot{V}O_{2peak}$  in mL/min by maximum HR in beats/min. The breathing reserve (BR), defined as the percentage of MVV achieved at peak exercise, was calculated as BR = ( $\dot{V}E_{peak}/MVV$ ) x100. Cuff BP was also measured twice before the test

by the examining physician using a mercury column sphygmomanometer, and the average values were used to derive the SBP and DBP at rest (SBP<sub>rest</sub> and DBP<sub>rest</sub>, respectively). BP was measured throughout the test every minute. The  $\dot{V}E/\dot{V}CO_{2-slope}$  was calculated by a linear regression analysis excluding data above the ventilatory compensation point.<sup>10,16</sup> There were no complications from the exercise tests, and all patients stopped

exercising due to leg fatigue and/or dyspnea. These data of the exercise test were obtained in accordance with the guidelines of the American Thoracic Society.<sup>2)</sup>

### Statistical analysis

All descriptive data are expressed as the mean  $\pm$  SD. The multiple linear regression analysis — including all independent variables — was performed to determine the most influential predictor(s) of exercise ability. The Mann-Whitney U test was utilized to assess differences between patients with and without HT. A value of  $p < 0.05$  was considered to be statistically significant.

## RESULTS

The clinical characteristics of the patients are shown in Table 1. In CPET, all subjects were able to achieve a maximal respiratory exchange ratio ( $\dot{V}CO_2/\dot{V}O_2$ )  $\geq 1.04$ , indicating achievement of at least near maximal exercise.

The multiple linear regression analysis was performed to evaluate the effect of age, BMI, SBP<sub>rest</sub>, DBP<sub>rest</sub>, AHI, CT 90%, and LoSpO<sub>2</sub> on the dependent variables of the  $\dot{V}O_{2peak}$ , and  $\dot{V}E/\dot{V}CO_2$ -slope. No factors emerged as predictive values of  $\dot{V}O_{2peak}$ . The factors that emerged as the predictive variables of the  $\dot{V}E/\dot{V}CO_2$ -slope in the multiple linear regression analysis were BMI as a significant negative predictor ( $p = 0.019$ ), and AHI as a significant positive predictor ( $p = 0.047$ ). The equation that describes this relationship is  $\dot{V}E/\dot{V}CO_2\text{-slope} = -0.53 \times \text{BMI} + 0.09 \times \text{AHI} + 16.2$  ( $r^2 = 0.28$ ). The remaining factors were not included as predictive factors.

We then divided 22 patients with OSAS into two groups: OSAS without HT (no-HT group), and OSAS with HT (HT group). Comparison between the no-HT and HT groups revealed no differences between them regarding the anthropometric characteristics and severity of sleep apnea (Table 2). Comparisons of CPET results between no-HT and HT groups indicated that, although no differences were found in either the  $\dot{V}O_{2peak}$  or AT between them, whether or not correcting the values for body weight, the HT group presented higher  $\dot{V}E/\dot{V}CO_2$ -slope ( $p = 0.008$ ) when compared with the no-HT group (Table 3). Even after excluding five patients from the HT group taking antihypertensive medications the  $\dot{V}E/\dot{V}CO_2$ -slope was significantly different between the two groups ( $p = 0.012$ ).

## DISCUSSION

In the present study we examined the factors that could influence the exercise capacity and ventilatory efficiency of OSAS patients, giving special attention to the presence

of HT. The major findings of this study were that BMI and AHI could be included as predictive variables of the  $\dot{V}E/\dot{V}CO_2$ -slope, whereas no factors emerged as predictors of  $\dot{V}O_{2peak}$ . Comparisons of CPET results between HT and no-HT patients showed that the  $\dot{V}CO_2$ -slope was higher in the HT group. These results suggest that AHI can influence the ventilatory efficiency in addition to BMI and HT.

Previous studies addressing exercise capacity in OSAS patients focused on AT and  $VO_{2max}$ .<sup>3,4,6,17)</sup> Vanuxem et al. showed about 20% lower maximal oxygen consumption in OSAS patients than in the control subjects.<sup>3)</sup> Lin et al. also reported a significant decrease in  $\dot{V}O_{2peak}$  and AT in OSAS patients compared with normal controls.<sup>4)</sup> However, no study of OSAS patients has ever included the  $\dot{V}E/\dot{V}CO_2$ -slope. The  $\dot{V}E/\dot{V}CO_2$ -slope is a CPET-derived variable that is generally independent from subject effort, easily calculated, and has potential to supply additional information to the interpretation of exercise testing. We therefore looked at the ventilatory efficiency demonstrated by the  $\dot{V}E/\dot{V}CO_2$ -slope in patients with OSAS. Central and peripheral chemoreceptors exert a powerful influence on breathing; the peripheral chemoreceptors respond primarily to hypoxic stimulation whereas the central chemoreceptors respond primarily to hypercapnia. The  $\dot{V}E/\dot{V}CO_2$ -slope is used as an index of the ventilatory response to exercise.<sup>10)</sup> The ventilatory response to exercise is related to both hypoxic and hypercapnic chemosensitivity in healthy subjects<sup>18,19)</sup> and in chronic heart failure patients.<sup>20)</sup> In other words, the  $\dot{V}E/\dot{V}CO_2$ -slope may reflect the way the patient's ventilation responds to changes in arterial blood gases. The higher the stimulus to ventilation due to enhanced chemosensitivity, the higher the values of the  $\dot{V}E/\dot{V}CO_2$ -slope.<sup>20)</sup>

In the multiple linear regression analysis, BMI appeared as a negative predictor of the  $\dot{V}E/\dot{V}CO_2$ -slope. It has been shown that obesity could in certain cases lead to hypoventilation, this being especially true in cases of obesity-hypoventilation syndrome, i.e. obesity with hypercapnia, due to the depression of ventilatory control.<sup>21)</sup> In addition, Lopata and Onal<sup>22)</sup> have shown that obese OSAS patients with or without hypercapnia are unable to increase the respiratory muscle drive and output as expected, which could explain the possible negative influence of BMI on the  $\dot{V}E/\dot{V}CO_2$ -slope. We also found that AHI appeared as a positive predictor of the  $\dot{V}E/\dot{V}CO_2$ -slope. Studies addressing chemosensitivity in OSAS patients have primarily examined the ventilatory response to hypoxia and have reported conflicting results. Some of them showed an increased<sup>23,24)</sup> but others a decreased ventilatory response to hypoxia.<sup>25,26)</sup> One of these studies found a positive correlation between AHI and peripheral chemosensitivity in OSAS patients;<sup>26)</sup> therefore, chemoreceptors might be related to an altered

ventilatory response in these patients. In addition to the pharyngeal anatomy and muscle regulation during sleep, ventilatory control is supposed to be one of the factors contributing to obstructive sleep apnea.<sup>27)</sup> The quantity and pattern of ventilation in normal subjects are tightly regulated to both maintain oxygen and carbon dioxide levels within narrow limits and to minimize the respiratory work. This is a product of multiple feedback loops, including the chemoreceptors (O<sub>2</sub> and CO<sub>2</sub>), intrapulmonary receptors, and respiratory muscle afferents and others. Especially, a change in PCO<sub>2</sub> will initiate a series of events to quickly correct the change and return PCO<sub>2</sub> to the desired level. To evaluate this response, a “loop gain” index is used. A higher loop gain in patients with sleep apnea than in control subjects was demonstrated,<sup>28)</sup> and the higher the AHI, the higher the loop gain.<sup>29)</sup> This loop gain is the product of the plant gain and the controller gain. The plant gain is the ability to eliminate CO<sub>2</sub>, and the controller gain is the response of ventilation to the change in arterial CO<sub>2</sub> tension.<sup>30)</sup> The  $\dot{V}E/\dot{V}CO_2$ -slope measured in our study is similar to the controller gain because it evaluates the response of the ventilation to the change in CO<sub>2</sub>. It is possible that a higher  $\dot{V}E/\dot{V}CO_2$ -slope may increase the respiratory output, enhancing the negative pressure which could collapse the upper airway causing even more severe sleep apnea.

As BMI is positively correlated to AHI<sup>9)</sup>— this being also true in our sample group (data not shown), this opposite influence of both parameters on  $\dot{V}E/\dot{V}CO_2$ -slope seems controversial. It has been reported, however, that the ventilatory response in OSAS varies according to the degree of underlying HT,<sup>31)</sup> and the presence of HT was not exclusive to obese patients in our study group. The  $\dot{V}E/\dot{V}CO_2$ -slope was higher in the HT group when compared with the no-HT group (Table 3), despite the absence of any differences in age, respiratory function, or BMI between the groups (Table 2). The  $\dot{V}E/\dot{V}CO_2$ -slope was not abnormally high in the HT group,<sup>32)</sup> but it was statistically higher than the no-HT group, a difference which could possibly arise from the higher peripheral chemosensitivity demonstrated in hypertensive subjects.<sup>33)</sup>

Our study has several limitations. First of all, HT in hypertensive patients was mild or moderate; possible differences in exercise capacity could be found in patients with severe HT. Second, we did not directly measure the chemosensitivity to hypoxia or hypercapnia. Decreased pulmonary perfusion<sup>34,35)</sup> and cardiac output<sup>12,34,36)</sup> could alter the  $\dot{V}E/\dot{V}CO_2$ -slope; however, we excluded subjects with pulmonary and/or cardiac dysfunction and therefore believe that the results of our study were most probably influenced by chemosensitivity.

Our results suggest that the severity of sleep apnea (AHI), obesity, and the presence of HT can influence

the ventilatory efficiency ( $\dot{V}E/\dot{V}CO_2$ -slope) of OSAS patients.

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