Heart Rate Recovery and Oxygen Kinetics After Exercise in Obstructive Sleep Apnea Syndrome

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ABSTRACT

Background: Patients who suffer from obstructive sleep apnea (OSA) have a decreased exercise capacity and abnormal autonomic nervous function. However, the kinetics of early oxygen (O_2) and heart rate recovery (HRR) have not been described.

Materials and Methods: We evaluated 21 men with moderate to severe OSA (mean age: 48 ± 11 yrs, mean apnea-hypopnea index [AHI]: 55 ± 13) and without known heart disease and 10 healthy men matched for age and body mass index (BMI; controls). Men with OSA underwent overnight polysomnography, and both groups underwent symptom-limited incremental cardiopulmonary exercise testing (CPET). We recorded the CPET parameters including peak O_2 uptake ($V_{O_2}p$), kinetics of early O_2 recovery by the first degree slope of V_{O_2} during the first minute (V_{O_2}/t slope), the time required for a 50% decline of $V_{O_2}p$ during recovery ($T_{1/2}$), and early heart rate recovery (HRR = HR at maximal exercise − HR at 1 min of recovery), as well as the chronotropic reserve to exercise ([CR] = [peak HR − resting HR/220 − age − resting HR] × 100). Patients with OSA had a lower $V_{O_2}p$ (28.7 ± 4.0 vs 34.7 ± 6.2 mL/kg/min), V_{O_2}/t slope (1.04 ± 0.3 vs 1.4 ± 0.17 mL/kg/min^2), and $T_{1/2}$ (74 ± 10 vs 56 ± 6 sec) compared to controls (all $P < 0.001$). In addition, both HRR and CR were lower in the OSA group (22.0 ± 7.0 vs 31.0 ± 6.0 bpm, P:0.003, and 79.0% ± 15% vs 99.0% ± 13.0%, P:0.01, respectively).

Conclusions: Patients with OSA demonstrate reduced exercise capacity, delayed oxygen kinetics, and reduced HRR. These data point to abnormal oxygen delivery and/or oxidative function of the peripheral muscles and impaired autonomic nervous activity in OSA patients.

Introduction

Obstructive sleep apnea (OSA) is a common disorder associated with several adverse comorbidities, especially with respect to the cardiovascular system. Patients with untreated OSA are at increased risk of hypertension,[1,2] myocardial ischemia,[3] myocardial infarction,[4] stroke,[5] heart failure,[6,7] vascular complications,[8,9] and death.[10,11] Patients suffering from OSA are characterized by an impaired exercise tolerance,[12] the mechanisms of which have not been thoroughly determined. Possible causes include various cardiovascular,[13] respiratory,[14,15] and peripheral muscular abnormalities.[16]

On the other hand, OSA is also associated with autonomic nervous system dysfunction. Sympathetic drive is increased during apneic events and during daytime when awake.[17] In normal healthy subjects, the chronotropic response (CR) is the product result of combined parasympathetic withdrawal and sympathetic activation,[18] while heart rate recovery (HRR) immediately after exercise reflects mostly parasympathetic reactivation.[18,19] Heart rate recovery has been shown to entail prognostic significance in the general population[20] and in chronic heart failure.[21] The impairment of the CR to exercise observed in patients suffering from chronic heart failure[22] has been related to a poor prognosis.[23] Moreover, the improvement of CR and HRR are indices of response of these patients to treatment.[24,25]

Evaluation of the early phase of recovery after exercise is of special interest to physicians, as parameters of recovery entail important information on exercise pathophysiology in several disorders. In particular, V_{O_2}/t slope, which expresses the oxygen (O_2) debt, is less steep in several disorders including chronic heart failure[26,27] and cystic fibrosis.[28] However, there is no reported study of the early phase of recovery from exercise in OSA.

This study was funded partly by a grant from the special account for research grants of the National and Kapodestrian University of Athens, Greece and by the Thorax Foundation. All authors have read and approved of the manuscript.

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20707

Received: August 5, 2009
Accepted with revision: October 15, 2009

In this study we hypothesized that patients with OSA are characterized by a greater O_2 debt and an impaired autonomic function reflected by delayed recovery oxygen kinetics and heart rate recovery after exercise in relation to disease severity.

The aim of this study was: (1) to evaluate recovery oxygen kinetics and heart rate recovery after exercise during cardiopulmonary exercise testing in patients with OSA and (2) to determine its correlation to disease severity.

Materials and Methods

Our study population consisted of 21 consecutive male patients referred to the sleep laboratory of our institute for evaluation of daytime sleepiness, prominent snoring, or clinical suspicion of OSA; and 10 healthy males matched for age and body mass index (BMI) (controls). All patients enrolled in the study had an apnea-hypopnea index (AHI) $\geq$25 and were excluded from the study if they had: (1) obstructive or restrictive lung disease documented by pulmonary function testing (forced expiratory volume in the first sec of expiration [FEV_1] <70% and forced vital capacity [FVC] <70%) performed 1 to 2 hours before cardiopulmonary exercise testing (CPET); (2) known valvular heart disease; (3) diabetes mellitus or a fasting blood glucose >110 mg/dL; (4) known neuromuscular disease that could limit their exercise capacity; (5) known hypertension; or (6) abnormal thyroid function. All participants were given a heart ultrasound and they were administered a simple questionnaire about their daily physical activity to exclude those patients and controls that had recently participated in exercise training programs. This project was approved by the ethics committee of our institution and informed consent was signed by all patients and healthy subjects.

Testing Procedures

Polysomnography: A full-night diagnostic polysomnography (Alice 4 System, Respironics Inc. Murrysville, PA) was performed on each subject. In order to determine the stages of sleep, an electroencephalogram (with 4 channels C4-A1, C3-A2, O_2-A1, O1-A2), electro-oculogram (with 2 channels), and electromyogram of the submentalis muscle (with 1 channel) were continuously recorded. Oral and nasal airflow, electrocardiogram, abdominal and thoracic movements, and arterial blood oxyhemoglobin were also continuously recorded. Airflow and electrocardiographic recordings were monitored by an oronasal thermistor placed in front of the nostrils and the mouth and an online 12-leads electrocardiogram, respectively. Thoracoabdominal excursions were measured qualitatively, using respiratory effort sensors (XactTrace belts featuring Respiratory Inductive Plethysmography XactTrace, Broomfield, CO) placed over the ribcage and abdomen (2 channels). In addition, snoring was detected with a vibration snore sensor (1 channel) and body posture with a body position sensor (1 channel).

Analysis: Sleep stage was scored manually in 30-second intervals. Obstructive respiratory events were scored using standard criteria[29] by an experienced technician. Thus, obstructive apnea was defined as the absence of airflow for >10 seconds in the presence of continued respiratory efforts. Hypopnea was defined as a reduction in chest wall movement to an amplitude that was smaller than 70% of the baseline level, lasting >10 seconds, and leading to a decrease in hemoglobin saturation of 4%. The number of episodes of apneas and hypopneas per hour of sleep is referred to as the apnea-hypopnea index (AHI).

Pulmonary function tests: All participants in the study were familiarized with the procedures before any testing was performed. Flow volumes were determined by spirometry according to American Thoracic Society recommendations, including measurements of forced vital capacity (FVC), Forced Expiratory Volume in 1 second (FEV^1), and the ratio of FEV_1/FVC before cardiopulmonary exercise testing (CPET), in the sitting position, by a Vmax model 229, closed-circuit spirometer (SensorMedics, Yorba Linda, CA).

Cardiopulmonary exercise testing: Patients with OSA and the controls underwent a symptom-limited, incremental CPET on a treadmill (model 2000, Marquette Electronics, Milwaukee, WI) with continuous electrocardiographic monitoring supervised by a physician. A modified Bruce ramp exercise protocol was chosen to attain a target test duration of 8 to 12 minutes. Gas exchange was measured with the patient breathing through a low-resistance valve with the nose clamped, with a metabolic measurement system Vmax 229D (SensorMedics, Anaheim, CA) calibrated with a known gas mixture before each test. All participants were encouraged to exercise to exhaustion, defined as intolerable leg fatigue or dyspnea, while the supervising physician had the prerogative to end the test according to predefined criteria, such as development of cardiac arrhythmias, hypotension, or electrocardiographic changes. All study participants completed the test without early termination of exercise.

O_2 uptake (V_{O_2}), carbon dioxide output (V_{CO_2}), and minute ventilation (VE) were measured breath-by-breath with the online system. All variables were recorded during resting 2-minute periods at standing position before exercise, throughout exercise, and during the first 5 minutes of recovery after exercise. In addition, peripheral arterial O_2 saturation, heart rate, and rhythm were monitored continuously by pulse oximetry and a 12-lead electrocardiographic system (MAX 1, Marquette Electronics, General Electric Healthcare, Milwaukee, WI). Blood pressure was also measured every 2 minutes with a mercury sphygmomanometer.

Both baseline and peak values of gas exchange were the average of measurements recorded in the resting 2 minute period and during the last 20 seconds preceding the end of exercise, respectively; O_2 uptake at anaerobic threshold

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20707

was determined using the V-slope technique[30] and was confirmed graphically, by a plot of ventilatory equivalent for both O_2 (V_E/VO_2) and CO_2 (V_E/VCO_2) against time. The ventilatory response to exercise was calculated as the slope of V_E vs VCO_2 since the beginning of exercise till to anaerobic threshold, where the relationship is linear,[31] by linear regression. The breathing reserve at maximal exercise was calculated as maximal voluntary ventilation (MVV) minus ventilation at maximal of exercise (V_Ep) and the result was divided by MVV ([MVV – V_Ep]/MVV). Both MVV and $T_{1/2}$ were calculated by proliferation of FEV_1 value × 40, and as the time where VO_2 had decreased to 50% of its peak value, respectively.

In order to evaluate VO_2 kinetics during early recovery, the first-degree slope of VO_2 decline during the first minute of recovery (VO_2/t slope) was calculated as described in previous studies[26,27] by a linear regression model, assuming that the decline in VO_2 during early recovery is linear. In addition HRR was measured as the difference between heart rate at peak exercise minus heart rate at the first minute of recovery (heart rate peak – heart rate first min of recovery), respectively.

The CR to exercise was evaluated by the percentage of chronotropic reserve (%chronotropic reserve = [peak HR – resting HR/220 – age – resting HR] × 100).

Statistical Analyses

Values are expressed as means ± SD unless otherwise specified. Before analysis, all continuous variables were tested by a Kolmogorov-Smirnov test showing normal distribution. Using the independent samples *t* test, we compared the cardiopulmonary measurements between patients with OSA and controls. Pearson's correlation coefficient was used to evaluate the bivariate relationships. The Pearson's correlation coefficient was used to find a correlation between at least 2 continuous variables. A *P* value <0.05 was considered statistically significant.

Results

The baseline characteristics of the 2 study groups were similar (Table 1). The majority of participants had a sedentary lifestyle without differences between the 2 groups. Peak VO_2 (in mL/kg/min) and peak % of predicted VO_2 were significantly lower in patients with OSA than in controls, although peak VO_2 (in L/min) are similar in the 2 groups. VO_2/t slope, $T_{1/2}$ of the peak VO_2 (VO_2p), and HRR were markedly lower in the group of patients with OSA than in the control group (Table 2, Figures 1 and 2). On the other hand, heart rate at rest was higher in OSA patients than in controls. In 1 patient, VO_2/t slope was not possible to calculate, because of the increased inter-breath fluctuations during the recovery period. In addition, the mean CR was significantly lower in patients with OSA (79.0 ± 15) than in controls (99.0 ± 13.0, *P*:0.01). Heart rate at peak exercise

Table 1. Baseline Characteristics of Patients With Obstructive Sleep Apnea and Controls

	OSA (n = 21)	Controls (n = 10)
Age, yrs	48 ± 11	46 ± 11
Body mass index, kg/m²	29.3 ± 2.2	28.1 ± 1.4
FEV_1, % predicted	94.0 ± 15.0	104 ± 13.0
FVC, %predicted	99.0 ± 12.0	108.0 ± 20.0
FEV_1/FVC	76.0 ± 8.0	80.0 ± 5.0
DLCO, %predicted	93.2 ± 22.3	95.5 ± 19.1
LVEF (%)	59 ± 5	61 ± 2

Abbreviations: DLCO, carbon monoxide lung diffusing capacity; FEV_1, forced expired volume in 1 second; FVC, forced vital capacity; LVEF, left ventricular ejection fraction; OSA, obstructive sleep apnea.
Values are means ± SD. Between-groups differences were statistically not significant.

Table 2. Results of Cardiopulmonary Exercise Testing in Patients With Obstructive Sleep Apnea and Controls

CPET parameters	OSA (n = 21)	Controls (n = 10)	*P* (2-tail)
VO_2p, L/min	2.74 ± 0.58	2.96 ± 0.48	ns
VO_2p, mL/kg/min	28.7 ± 4.0	34.7 ± 6.2	<0.01
VO_2p % predicted	88.2 ± 13.6	97.5 ± 11.1	<0.05
AT, mL/kg/min	20.3 ± 2.6	24.1 ± 5.4	ns
V_E/VCO_2/t slope	26.0 ± 3.0	26.0 ± 2.0	ns
Breathing reserve, %	31.2 ± 15.0	32.6 ± 18.6	ns
VO_2/t slope, mL/Kg/min²	1.04 ± 0.3	1.4 ± 0.17	<0.001
Baseline heart rate, bpm	88.0 ± 17.0	73.0 ± 8.0	0.02
Peak heart rate, bpm	155.0 ± 11.0	172.0 ± 13.0	ns
Chronotropic response %	79.0 ± 15.0	99.0 ± 13.0	0.01
Peak heart rate, %predicted	96.0 ± 8.0	103.0 ± 9.0	ns
Heart rate recovery, bpm	22.0 ± 7.0	31.0 ± 6.0	0.003
$T_{1/2}$, sec	74.0 ± 10.0	56.0 ± 6.0	<0.001
Oxygen pulse (mL/beat)	17.3 ± 3.1	16.5 ± 2.0	ns

Abbreviations: AT, O_2 uptake at the anaerobic threshold; CPET, cardiopulmonary exercise testing; ns, not significant; OSA, obstructive sleep apnea; V_E/VCO_2 slope, regression slope relating V_E and VCO_2 from onset of exercise to anaerobic threshold; VO_2p, average O_2 uptake in the last 20 seconds of exercise; VO_2/t slope, first-degree slope of VO_2 for the first minute of recovery; $T_{1/2}$, time to 50% fall in VO_2 from VO_2p.
Values are means ± SD.

DOI:10.1002/clc.20707

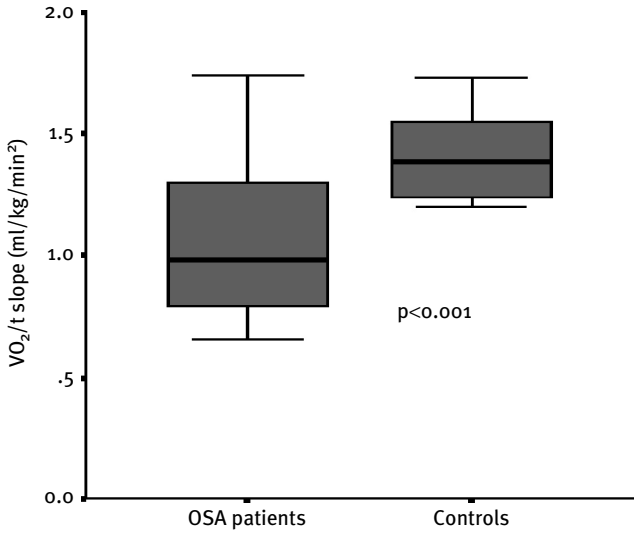

Figure 1. Oxygen recovery kinetics (VO_2/t slope) in patients with OSA vs controls. Data are presented as medians and 25% and 75% quartiles. The whiskers span the total range.

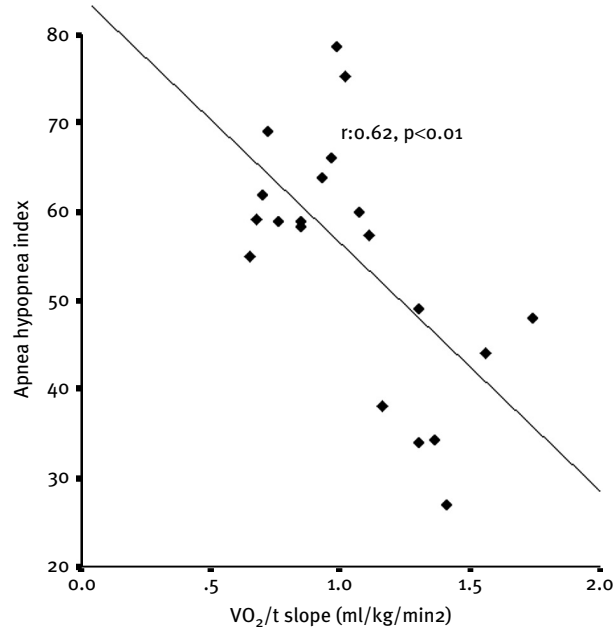

Figure 3. Scatter graph of AHI vs VO_2/t slope in OSA patients.

and % of predicted peak heart rate were not significantly statistically different in patients with OSA and in the controls (Table 2).

Pearson correlation coefficient comparisons between AHI index and indices of exercise capacity revealed statistically significant inverse correlation between AHI with VO_2/t slope, ($r = -0.62$, $P < 0.003$, Figure 3) and with HRR ($r = -0.50, P < 0.02$). However, no statistically significant correlations were found between AHI and BMI, VO_2p, VO_2 at anaerobic threshold, peak heart rate, CR, or $T_{1/2}$. There was also no statistically significant correlation between VO_2p, CR, and HRR.

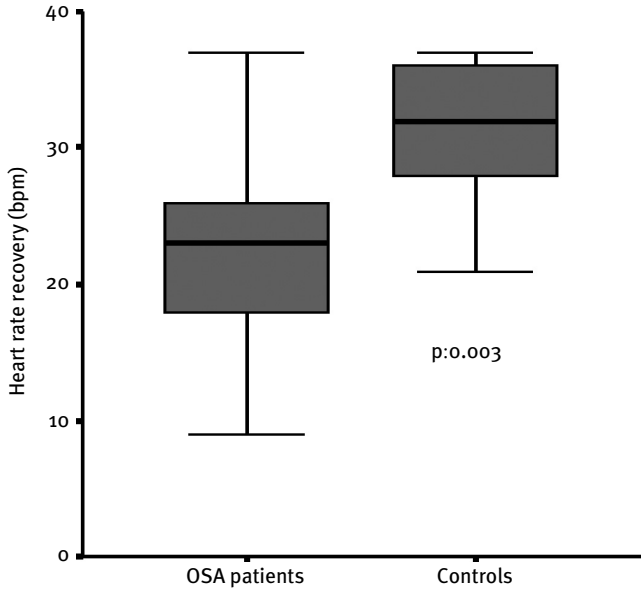

Figure 2. Early heart rate recovery in patients with OSA vs controls. Data are presented as medians and 25% and 75% quartiles. The whiskers span the total range.

Discussion

The main findings of this study are: (1) the delayed recovery of oxygen kinetics, (2) the abnormal CR to exercise, and (3) the prolonged HRR in patients suffering from OSA compared to controls. To our knowledge, this is the first study that evaluates oxygen recovery kinetics after exercise in patients with OSA.

A reduced peak VO_2 in patients suffering from OSA has been observed in previous studies.[12,16,32] Our study confirmed not only a significantly lower peak VO_2 (in mL/kg/min), but also a lower percent predicted VO_2 in patients with OSA than in controls. The causes of reduced exercise capacity in patients with OSA remain unclear. Potential contributing factors include left and right ventricular diastolic dysfunction,[7,8] respiratory dysfunction, restrictive pulmonary disease, pulmonary hypertension,[14,15] and peripheral muscular abnormalities.[16]

Our study population consisted of patients with OSA that were free of symptoms of cardiovascular disease, had a normal heart ultrasound, and had no ST-depressions in the ECG during exercise. Moreover, the similar values of oxygen pulse (VO_2/heart rate) at peak exercise in

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20707

patients with OSA and the control group, and the absence of hypoxemia during exercise in all patients were not consistent with cardiac or pulmonary causes as explanations for the reduced exercise capacity. Our patients with OSA did not have respiratory diseases according to the pulmonary function tests obtained before CPET. From previous studies, the most likely factor limiting the exercise capacity of patients suffering from OSA appears to be peripheral, specifically an abnormal muscular energetic metabolism.[16] These studies have reported higher lactate concentrations during incremental exercise, as well as a lactate threshold reached earlier in patients with OSA than in healthy subjects.[33] A decrease in the rate of lactate elimination during recovery, indicative of a decrease in oxidative metabolism was also observed.[16] This impaired oxidative metabolism might be due to a decrease in the number of type I fibers and in the volume of mitochondria, as well as in the activity of oxidative enzymes, which has been shown in chronic hypoxia.[16,33]

In our study, the early recovery of O_2 kinetics (V_{O_2}/t slope) after exercise was delayed in patients with OSA compared to controls. In healthy subjects, the early recovery of O_2 kinetics represents the O_2 delivery during the alactic phase, and reflects more accurately the oxidative mechanisms of high-energy phosphate repletion during that period.[34] A delayed recovery of O_2 kinetics has also been observed in patients presenting with heart failure, compared with healthy subjects.[27] The prolonged recovery of total body O_2 uptake, reflecting a higher O_2 debt, might be attributed to a slower recovery of muscle energy stores after exercise, probably due to the impaired delivery of O_2 to the peripheral muscles, or to histological and biochemical skeletal muscles alterations, or both.[26]

Other noteworthy observations made in our study were the delayed kinetics of HRR and weaker CR in patients with OSA than in controls. It is well-known that the kinetics of early HRR immediately after exercise is an index of parasympathetic activity in healthy subjects and that CR to exercise is regulated mostly by initial parasympathetic inhibition and subsequently by sympathetic activation.[18,19] It is also known that patients with OSA have a heightened sympathetic activity when awake.[35,36] The results of this study indicate that these patients also have an abnormal parasympathetic activity reflected by a lower HRR in accordance to previous observation.[37–39] In addition, the altered CR to exercise in patients with OSA seems to be mainly due to their high sympathetic drive. The high resting heart rate in patients with OSA is another index of this sympathetic over-activation. Thus, OSA patients appear to have a blunted heart rate response to exercise confirming previous results.[39–41] A possible explanation for this abnormality maybe the desensitization of cardiac β1 receptors by heightened sympathetic activity similar to heart failure.[22] Furthermore, the severity of OSA, as expressed by AHI, correlated with O_2 kinetics, and with HRR indicating that the severity of OSA is associated with both parasympathetic dysfunction and O_2 debt. Both of these indices have been shown to contain significant prognostic information for patients with heart failure[21,26,27]; however, whether these indices are potent prognostic markers in patients with OSA must be confirmed by larger prospective studies. Future studies aiming to evaluate treatment strategies such as β-blockers or exercise training programs in patients with OSA might also be an interesting field of research.

Limitations of the Study

The main limitation of our study was the relatively small number of patients included and the gender. Moreover, patient inclusion was limited to moderate to severe OSA, with a mean AHI of 55. The present study, though prospective, was a cross-sectional study and the conclusions of a possible direct cause-effect cannot be ascertained. Patients with OSA present a blunted CR, a slow HRR, and delayed O_2 recovery kinetics, characteristics that might also be found in patients with decreased cardiorespiratory fitness. This may constitute another possible mechanism explaining, at least partly, our findings. Studies including near infrared spectroscopy or 31phosphorus-nuclear magnetic resonance (31P-NMR) spectroscopy, or muscle biopsies will help in investigating possible muscle abnormalities in patients suffering from OSA.

Conclusion

The results of our study indicate that exercise capacity and early kinetics of HRR and of V_{O_2} recovery are impaired in patients suffering from OSA, and that the magnitude of this impairment correlates with disease severity. These findings reflect an autonomic dysfunction and an abnormal O_2 delivery to the peripheral skeletal muscles and/or impaired oxygen extraction. Cardiopulmonary exercise testing remains a simple, noninvasive method to evaluate pathophysiological disorders involved in OSA syndrome.

Acknowledgment

The authors would like to thank Sotirios Gyftopoulos for his significant technical support.

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Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20707