The use of cardiopulmonary exercise testing in identifying the presence of obstructive sleep apnea syndrome in patients with compatible symptomatology

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Abstract

The aim of this study was to investigate the relationship between cardiopulmonary exercise testing (CPET) and the presence of obstructive sleep apnea syndrome (OSAS) in order to provide an innovative tool to identify patients with OSAS. A prospective nested case control design was adopted. A consecutive population of male volunteers referred to a Sleep Unit was subjected to nocturnal polysomnography, full lung function testing and maximal CPET. A stepwise linear discriminant function analysis (DFA) was applied to construct a model which could identify individuals with moderate-to-severe OSAS from healthy controls. The total of 30 volunteers formed the OSAS and 24 the non-OSAS groups. Demographic and somatometric parameters were similar between groups. Patients presented with lower Expiratory Reserve Volume (ERV: 106.7±28.3 vs. 123.9±22.1, p<0.001), Leg Fatigue$_{\text{Borg scale}}$ (3.9±1.1 vs. 6.1±1.4, p<0.001), VO_{2peak}(25.0±5.9 vs. 32.9±7.2 ml/kg^{-1}/min^{-1}, p<0.001), peak breathing frequency (31.0±5.8 vs. 35.5±7.3 1/min^{-1}, p<0.001) and peak heart rate (151.1±17.7 vs. 171.2±12.6 beats/min^{-1}, p<0.001) compared to controls, but higher peak end-tidal CO_2 ($P_{ET}CO_{2peak}$:38.6±4.2 vs. 35.0±4.9 mmHg, p=0.043) and peak systolic (SBP:188.3±21.9 vs. 173.1±17.9 mmHg, p=0.009) and diastolic (DBP: 91.3±8.2 vs. 85.4±8.2 mmHg, p=0.011) blood pressure. Stepwise DFA indicated that ERV$_{\text{\% of predicted}}$ (0.372), $P_{ET}CO_{2peak}$ (-0.376), $SpO_{2resting}$ (0.0667), Leg Fatigue $_{\text{Borg scale}}$ (0.564), HR_{peak} (0.530) and DBP_{peak} (-0.543) could separate the two groups, with an overall predictive accuracy of 96.3%. Selected CPET parameters (ERV$_{\text{\% of predicted}}$, $P_{ET}CO_{2peak}$, $SpO_{2resting}$,

HR_{peak}, DBP_{peak} and Leg $Fatigue_{Borg\ Scale}$) are independently associated with OSAS presence and could discriminate patients with and without this disorder.

Keywords: cardiopulmonary exercise testing, obstructive sleep apnea syndrome

Abbreviations

AHI = apnea-hypopnea index; BMI = body mass index; CPET = cardio-pulmonary exercise testing; DBP = diastolic blood pressure; DI = oxygen desaturation index during sleep; ERV = expiratory reserve volume; ESS = Epworth Sleepiness Scale; FEV_1 = forced expiratory volume in 1^{st} s; FVC = forced vital capacity; f_β = breath frequency; HR = heart rate; $MinSaO_2$ = minimum oxygen saturation during sleep; MVV = maximum voluntary volume; O_2pulse = ratio between oxygen uptake and heart rate; OSAS = obstructive sleep apnea syndrome; PEF = peak expiratory force; $P_{ET}CO_2$ = end-tidal carbon dioxide pressure; $P_{ET}O_2$ = end-tidal oxygen pressure; RER = respiratory exchange ratio; SBP = systolic blood pressure; SpO_2 = blood oxygen saturation with pulse oximetry; VCO_2 = carbon dioxide output; V_E = minute ventilation; VO_2 = oxygen uptake

Introduction

Obstructive sleep apnea syndrome (OSAS) is a common condition affecting 5-to-10% of the general population (Punjabi, 2008). It is characterized by recurrent upper airway collapse during sleep resulting in frequent arousals and sleep fragmentation. The pathophysiological consequences of the syndrome are several, including intermittent nocturnal hypoxia, large negative inspiratory deflection of intrathoracic pressure, hypercapnia, and increased systemic inflammation (Chiang et al., 2006).

Cardiopulmonary exercise testing (CPET) is a non-invasive technique which provides an objective quantitative assessment of metabolic, pulmonary and cardiovascular responses during exercise (Boutou et al., 2014). Available data indicate that CPET could be utilised to stratify the cardiovascular risk among patients with OSAS (Mansukhani et al., 2013), in a similar manner to coronary artery disease patients. Patients with OSAS have reduced VO_{2peak}, while they present with chronotropic incompetence and abnormal exercise blood pressure responses (Aron et al., 2009). Left heart disease (Lin et al., 2006), chronic sympathetic over-activation and endothelial dysfunction (Aron et al., 2009) are potential explanations, along with impaired muscle metabolism, possibly due to long-term exposure to conditions of hypoxia (Bonanni et al., 2004).

The aim of this study was to investigate whether the parameters of CPET can identify the presence of obstructive sleep apnea syndrome, and identify independent predictors in a cohort of patients evaluated for sleep disordered breathing in order to provide a supplemental tool to identify

patients with OSAS. We hypothesized that the patients with OSAS present a distinct cardiopulmonary pattern during exercise and the apnea-hypopnea index (AHI) could differentiate the patients with (AHI >15 events/h^{-1}) and without (AHI <5 events/h^{-1}) OSAS.

Methods

Study population

All males who were consecutively referred to the Sleep Units (University Hospital, Larissa, Greece) for suspected OSAS (Figure 1) between July 2017 and June 2018 (Table 1) constituted the initial study cohort. Inclusion criteria were age between 30-to-60 years and BMI<40 kg/m^2. Exclusion criteria were BMI≥40 kg/m^2, diabetes mellitus, heart failure, chronic obstructive pulmonary disease and/or other respiratory illness, peripheral vascular disease (that would limit exercise capacity), myocardial infarction within the previous month, severe uncontrolled arrhythmia and medicated arrhythmia, severe and uncontrolled hypertension, severe aortic stenosis, renal failure, anemia, mental illness and any form of musculoskeletal disability which could impair maximum exercise capacity. The study was approved by the Institutional Ethics Committee and informed consents were obtained from all participants (No. of Ethical Committee: 21/09-01-2017, University of Thessaly).

Insert Figure 1 here

Study protocol

A prospective nested case-control study was performed. Baseline and two other visits were piloted. During baseline visit detailed medical history, anthropometric data, physical examination and Epworth Sleep Scale (ESS), (Johns, 1991) were recorded. During the first visit all participants underwent night polysomnography (PSG) and subsequently subjects who were diagnosed with OSAS constituted the patients΄group, while subjects without OSAS or other forms of sleep-disordered breathing, constituted the control group.

During the second visit (within 48-hours from the first one) all participants were subjected to Doppler echocardiography (for exclusion of heart failure and/or severe valvular disorder) (Zamorano et al., 2011), lung function measurements (Miller et al., 2005) and performed maximal CPET (Wasserman et al., 2004).

Polysomnography

PSG included electroencephalography, electrooculography, submental electromyography, anteriortibialis electromyography, nasal cannula airflow signal using a nasal cannula/pressure transducer system, oral thermistor, electrocardiography, and body position. Sleep was scored manually according to the criteria of Rechtschaffen and Kales (1968). Respiratory efforts were monitored with abdominal and thoracic bands. Arterial SaO_2 was measured using SpO_2. Apnea was defined as complete cessation of airflow for at least 10s in duration. Hypopnea was defined as one of the following three: 1) >50% reduction in airflow, 2) <50% reduction in airflow associated with a

desaturation of>3%, or 3) a moderate reduction in airflow with associated arousal by electroencephalography. Apneas were classified as obstructive, central, or mixed according to the presence or absence of respiratory efforts. Patients with predominant obstructive sleep apneas and AHI≥5/h^{-1} were diagnosed with the OSAS.

Spirometry and lung volumes measurements

All participants underwent standard spirometry and lung volume measurements, in line with ATS/ERS guidelines (Miller et al., 2005). Maximal flow-volume loops were conducted for each subject with sitting position using MasterScreen-CPX pneumotachograph (VIASYS HealthCare, Germany). For each pulmonary function test, three maximal flow-volume loops were obtained to determine FVC and FEV_1; the largest one was retained to calculate the ratio of FEV_1 to FVC (FEV_1/FVC). Thoracic gas volume at FRC level, ERV, inspiratory capacity (IC) and vital capacity (VC) were measured, while subjects made gentle pants against the shutter at a rate of <1/s. The mean of three technically acceptable FRC measurements was used to calculate total lung capacity (TLC) as FRC+IC and residual volume as TLC-VC.

Maximum CPET

An electronic cycle ergometer (Ergoselect 100, Germany) MasterScreen-CPX was used for all respiratory and cardiac parameters (VIASYS HealthCare, Germany). Prior to testing all participants were familiarized with the cycle ergometer via a 2 min resting; for a 3 min unloaded cycling which also served as warm-up; after the end of the maximal test they performed a 5 min unloaded cycling for recovery purposes. The work rate increment calculated using the Wasserman et al. (2004) formula:

$$\text{Work Rate/min}^{-1}_{(\text{ramp})} = (VO_{2peak} - VO_{2unloaded}) / 100$$

$$VO_{2peak} = (Height_{(cm)} - Age_{(yrs)}) \times 20;\ VO_{2unloaded} = 150 + (6 \times Weight_{(kg)})$$

During testing, patients were instructed to keep a steady speed of 60-65 rpm throughout both the unloaded and exercising phase. Each trial was terminated when the participant reached symptom-limited maximum exercise, which was confirmed by the presence of RER >1.10, HR≥80% of predicted HR_{max}, and/or plateau of oxygen consumption with increasing work load (ATS/ACCP, 2003). A 12-lead ECG was also employed for HR monitoring, while SpO_2 was continuously measured using (MasterScreen, Germany). Blood pressure was recorded at rest and every 2-min during exercise and recovery phases using manual cuff manometry (Mac, Japan).

Statistical analyses

Univariate Analyses

All analyses were conducted using SPSS 19.0 (IBM Corporation, San Diego, CA). The Kolmogorov-Smirnov test was utilized to assess data normality. Univariate group comparisons were conducted using either the Independent Samples Student's T-test, for continuous variables or the

Chi-square test for qualitative variables. A level of p value <0.05 was considered statistically significant for all analyses.

Multivariate Analyses

The stepwise linear discriminant (LD) model was applied to our data, in order to produce a LD function. By definition, this resulting function may be subsequently used to classify new cases. The discriminant formula for a population of [1, 2..., n] subjects, with [1, 2..., i] canonical standardized discriminant function coefficients is described below,

$$D_j = k_1 m_{n1} + k_2 m_{n2} ... + k_i m_{ni}$$

where: "j" is the number of discriminant functions extracted, with jЄ[1, *c*-1]; "D_j" is the discriminant function score for the *j*th discriminant function; "k_i" is the canonical standardized discriminant function coefficient; "m_{ni}" is the predictor variable value for the *i*th subject and the nth discriminant function coefficients. The interpretation of the D score was performed using each group's centroids. Since the groups were two, the cut score was calculated half-way the 2 centroids as*: Cut score = (group 1 centroid-group 2 centroid) / 2*. The Wilk's lambda test was used to determine the derived DFA model's goodness of fit. A 2x2 confusion matrix was furthermore used to determine the function's predictive accuracy, whereas the cross-validated predictive accuracy was estimated via the "leave-one-out" classification process (Burns & Burns, 2009). The statistical significance was set at p <0.05.

Results

Out of the 245 individuals who were assessed for eligibility, 54 were selected; 30 patients with OSAS and 24 controls (Figure 1). Univariate group comparison regarding demographic and anthropometric characteristics, lung function measurements and polysomnography variables are presented in Table 1.

Insert Table 1 here

Univariate group comparison regarding CPET parameters is presented in Table 2. During unloaded pedaling, OSAS patients presented with lower $VO_{2unloaded}$ (3.5±0.9 vs. 4.6±1.6 ml/min^{-1}/kg^{-1}; p=0.023), $VCO_{2unloaded}$ (2.7±0.8 vs. 3.3±1.2 ml/min^{-1}/kg^{-1}; p=0.049), $f_{\beta unloaded}$ (12.8±1.8 vs. 14.7±4.1 breaths/min^{-1}; p=0.024) and $SpO_{2unloaded}$ (97.4±0.9 vs. 98.3±0.7 %; p<0.001) values and higher $P_{ET}CO_{2unloaded}$ (34.9±3.5 vs. 32.1±3.9 mmHg; p=0.006) values compared to controls. Further differences were noted between the groups at peak exercise. Patients with OSAS had lower VO_{2peak} (25.0±5.9 vs. 32.9±7.2 ml/min^{-1}/kg^{-1}; p<0.001), VCO_{2peak} (27.5±7.1 vs. 36.6±9.0 ml/min/kg; p<0.001), V_{Epeak} (78.6±17.3 vs. 97.6±26.1 L/min; p=0.003), $f_{\beta peak}$ (31.0±5.8 vs. 35.5±7.3 breaths/min^{-1}, p<0.001), $P_{ET}O_{2peak}$ (112.5±4.6 vs. 116.5±4.8 mmHg; p=0.003) and HR_{peak} (151.1±17.7 vs. 171.2±12.6 beats/min^{-}

[1];p<0.000), while they revealed higher DBP_{peak} (91.3±8.2 vs. 85.4±8.2 mmHg; p=0.011), SBP_{peak} (188.3±21.9 vs. 173.1±17.9 mmHg; p=0.009) and $P_{ET}CO_{2peak}$ (38.6±4.2 vs. 35.0±4.9 mmHg; p=0.043), compared to the control group. However, leg fatigue was significantly more intense among controls compared to OSAS patients (6.1±1.4 vs. 3.9±1.1, p<0.001), although dyspnea severity was similar between the groups (Borg dyspnea 3.2±1.9 vs. 2.7±1.5, p=0.308).

Insert Table 2 here

Multivariate analysis was subsequently performed via the application of a linear DFA model for two groups (OSAS and non-OSAS group). Table 3 presents the canonical discriminant function coefficients used to create the discriminant model:

$D\ score_{(patients\ with\ and\ without\ OSAS)} = 0.564 \times Leg\ Fatigue_{Borg\ Scale} + 0.530 \times HR_{peak} + 0.667 \times SpO_{2resting} - 0.543 \times DBP_{peak} + 0.372 \times ERV_{\%\ of\ predicted} - 0.376 \times P_{ET}CO_{2peak}$.

Insert Table 3 here

Centroid for the non-OSAS controls was 2.139 and -1.711 for the OSA patients, giving a cut-score of 2.139-1.711 / 2 = 0.214. Therefore, a D score higher than 0.214 was associated with the absence of OSAS, while a D-score below than 0.214 was linked with the presence of OSAS. The overall predictive accuracy of the model in correctly classifying cases was 96.3%, with a sensitivity of 95.8% and a sensitivity of 96.7%.

Discussion

The aim of this study was to investigate the whether exercise performance during maximum CPET could provide discriminative information which could facilitate the identification of OSAS presence in subjects with compatible symptomatology. Our main finding was that selected parameters obtained during CPET (i.e., $ERV_{\%\ of\ predicted}$, $P_{ET}CO_{2peak}$, $SpO_{2resting}$, $Leg\ Fatigue_{Borg\ Scale}$, HR_{peak} and DBP_{peak}) may serve as reliable predictors for OSAS.

We found that patients with OSAS revealed significantly reduced actual ERV which is consistent with Hoffstein et al. (1984), who demonstrated that the cross sectional area of the pharyngeal airway decreases as lung volume decreases from FRC to residual volume suggesting the contribution of lung volumes (FRC or EELV) in the pathogenesis of OSAS. Appelberg et al. (2000) also found a significant correlation between ERV and both nocturnal apnoea and desaturation frequency, explained by the closure of peripheral airways especially in the lower dependent regions of the lung which may lead to an increased residual volume and to a decreased ERV. Further, Abdeyrim et al. (2015) demonstrated that FRC and ERV were decreased in pre-obese and obese patients with OSAS

independently from BMI and that OSAS had a negative impact on lung volume possibly due to the abnormally increased lung elasticity recoil pressure in OSAS patients.

According to our data, patients with OSAS had higher unloaded $P_{ET}CO_2$, lower unloaded SpO_2, and lower unloaded breathing frequency, while at the peak of exercise they had higher $P_{ET}CO_{2peak}$ as well as lower $f_{\beta peak}$ and V_{Epeak} than the control group. OSAS is characterized by recurrent upper airway collapse during sleep which may cause CO_2 retention and therefore respiratory acidosis, resulting in compensatory renal retention of bicarbonate ions and excretion of hydrogen ions. The upper airway is not obstructed when the patient is awake and thus arterial PCO_2may then return to normal levels. The existing elevated bicarbonate levels may causeblunting of the respiratory center response, leading to decreased breathing frequency, and also metabolic alkalosis (Malley, 2005), resulting in compensatory respiratory acidosis through to reduced daily ventilation. Moreover, the blunted respiratory drive cannot compensate the increased respiratory load imposed during exercise, meaning that OSAS patients cannot eliminate the extra amount of CO_2 produced during exercise (Hargens et al., 2009). Another explanation might be that due to the chronic blunting of the respiratory drive, the increase in breathing frequency is relatively low and therefore not enough for the elimination of the extra CO_2 produced during exercise, resulting in the increased levels of $PaCO_2$ and $P_{ET}CO_2$ (Dempsey, 2004). Furthermore, according to Bijaoui et al. (2002) lung resistance and elastance increase significantly during obstructed breathing, suggesting that OSAS may lead to transient abnormalities in the recruitment of lung units and the gas exchanging capacity of the lungs resulting in V/Q mismatching. The increased $P_{ET}CO_2$ and the lower SpO_2 levels, like the ones measured in our OSAS cohort, may, thus, be an end product of a complex conglomerate, influenced by factors such as severity of sleep apnea, daytime PaO_2, blunted respiratory drive, respiratory mechanics and respiratory muscle fatigue (Kawata et al., 2007).

Our results showed significantly lower difference in leg fatigue, and lower values in patients with OSAS, compared to controls (3.9±1.1 vs. 6.1±1.4). Leg muscle weakness and leg effort are different sensations, but they are recorded as a leg fatigue, and can limit maximum exercise during CPET (el-Manshawi et al., 1986). The intensity of leg effort is very subjective (Lin et al., 2006) and the average individual tolerates a greater degree of discomfort (very severe) compared to most patients, who tolerate only a little discomfort before stopping exercise (Chennaoui et al., 2015). Previous studies have demonstrated decreased maximum exercise capacity in OSA patients because of intolerance to exercise and susceptibility to leg fatigue (Aguillard et al., 1998). Since leg fatigue can reflect an impairment of muscle metabolism (Vanuxem et al., 1997) these symptoms are probably associated with decreased peripheral oxygen uptake among OSAS patients, with increased maximal lactate concentration and delayed lactate elimination of exercising muscles. The impairment in oxidative metabolism might be explained by the occurrence of mitochondrial abnormalities in

skeletal myofibres and could explain, in part, the increased production of reactive oxygen species exhibited in the neutrophils of OSAS patients (Bonanni et al., 2004).

Previous reports have suggested altered hemodynamic response to exercise in OSAS (Malley, 2005; Abdeyrim et al., 2015), while when OSAS is combined with obesity the hemodynamic response to exercise is further impaired (lower VO_{2peak}, and lower HR response), as compared to simple obesity (Przybyłowski et al., 2007). In general, the present study supports these observations. The prevalence of chronotropic incompetence was much lower than reported by Grote et al. (2000). Moreover, in our study, age-adjusted HR_{peak} in severe OSAS was significantly lower compared with mild to moderate OSAS (91.2±9.7 vs. 94.3±10.9%), providing further evidence for blunted chronotropic response to graded exercise, which is consistent with other reports (Aguillard et al., 1998; Appelberg et al., 2000). The reasons for decreased chronotropic response to exercise in OSAS patients are not clear. It is suggested that the main causative factor is impaired cardiovascular autonomic function resulting from structural down regulation of cardiac β-receptors and/or altered baroreflex set-point (Somers et al., 1993). Increased SBP_{peak} and DBP_{peak} were also noted among OSAS patients, compared to controls a finding which might be related to sympathetic induced vasoconstriction, endothelial dysfunction, or a blunted response to beta-2 receptor stimulation, mechanisms that have been shown to be active in patients with sleep disordered breathing (Somers et al., 1993; Mansukhani et al., 2013).

Limitations

All data were prospectively collected and analyzed, so recall bias have been minimized. Moreover, all exercise tests were supervised and interpreted by the same team of ergophysiologists, thus minimizing diversities often encountered in studies with multicenter protocol. A limitations of this study might be the studied were all male and the lack of arterial blood gases measurements. $P_{ET}CO_2$ has been used to indirectly estimate arterial CO_2 pressure ($PaCO_2$), in patients with lung disease. Nevertheless, the $P_{ET}CO_2$ can differ from $PaCO_2$ because of ventilation-perfusion (VA/Q) mismatching, and changes in $P_{ET}CO_2$ may be seen with corresponding increase, decrease, or no change in $PaCO_2$ depending on what happens to VA/Q mismatching (Abdeyrim et al., 2015). Nevertheless, the exclusion of patients with obstructive or other respiratory disorders has minimized this diversity. Furthermore, obtaining arterial blood gases during CPET demands the placement of a radial arterial catheter, an invasive technique which we wished to avoid, trying to minimize participants' discomfort.

Conclusions

In this prospective, nested case-control study we identified that one lung function parameter ($ERV_{\%\ of\ predicted}$) and several CPET parameters ($P_{ET}CO_{2peak}$, $SpO_{2resting}$, Leg $Fatigue_{Borg\ Scale}$, HR_{peak}, and DBP_{peak}) are discriminative of the presence of OSAS with an accuracy of 96.3% in a subject population

with compatible symptomatology. Nocturnal PSG is certainly the gold standard for the diagnosis of OSAS and for its differential diagnosis of other forms of sleep disordered breathing. Although CPET cannot replace nocturnal PSG, it may be useful-when it is available-for initial evaluation of subjects with compatible symptomatology, in order to prioritize those where OSAS diagnosis is most likely. However, depending on the health insurance system of each country, it is an expensive examination which demands the hospitalization for at least one night and could be sometimes limited by the availability of beds and other resources. Larger, prospective studies are needed in order to further investigate whether CPET could have a supplemental role not only in the identification but also in the physical evaluation of subjects with sleep disordered breathing.

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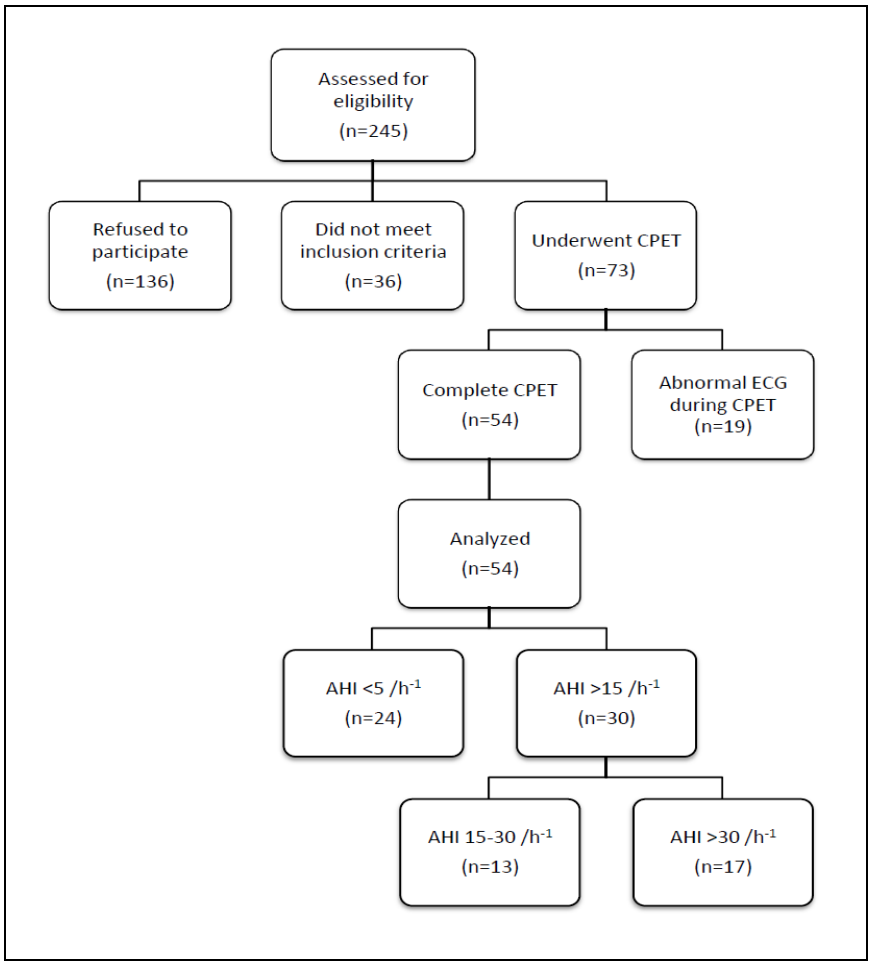

Figure 1. Study flow diagram.

Table 1. Univariate analysis between demographic, respiratory and sleep apnea characteristics. Continuous variables are presented as mean ± standard deviation.

	OSAS group (n=30)	**Control group (n=24)**	***P* value**
Age, yrs	45.2 ± 10.0	41.0 ± 8.7	0.116
BMI, kg/m^2	31.3±4.3	29.7 ± 2.7	0.135
FEV_1, %	104.5 ± 22.1	109.5 ± 11.9	0.320
FVC, %	106.1 ± 23.7	109.1 ± 14.1	0.586
FEV_1/FVC, %	80.9 ± 9.3	100.7 ± 6.1	0.282
ERV, %	106.7 ± 28.3	123.9 ± 22.1	<0.001
PEF, %	111.8 ± 14.1	103.3 ± 13.3	0.166
AHI, events/h^{-1}	44.9 ± 26.0	3.1± 0.8	<0.001
Apnea, events/h^{-1}	23.2 ± 24.2	1.7 ± 1.8	0.001
Hypopnea, events/h^{-1}	23.3±14.6	6.1±2.5	<0.001
ESS	9.0±4.4	8.9±3.3	0.939
DI, %	44.0±30.3	7.4±6.1	<0.001
$MinSaO_2$, %	78.5±10.7	89.6±3.2	<0.001
Sleep Duration, min^{-1}	316.4±55.2	299.8 ±50.2	0.261

AHI = apnea-hypopnea index; BMI = body mass index; DI = desaturation index during sleep; ERV = expiratory reserve volume; ESS = Epworth Sleepiness Scale; FEV_1 = forced expiratory volume in 1sts; FVC = forced vital capacity; PEF = peak expiratory force; $MinSaO_2$ = minimum oxygen saturation during sleep.

Table 2. Cardiopulmonary exercise testing results. Continuous variables are presented as mean ± standard deviation.

	OSAS group (n=30)	Control group (n=24)	*P* value
Intensity of leg fatigue	3.9 ± 1.1	6.1 ± 1.4	<0.001
Intensity of dysnea	3.2 ± 1.9	2.7 ± 1.5	0.308
Watts, ($J \bullet s^{-1}$)	174.8±44.5	189.8±50.1	0.004
$VO_{2unloaded}$, $ml/min^{-1}/kg^{-1}$	3.5 ± 0.9	4.6 ± 1.6	0.023
$VCO_{2unloaded}$, $ml/min^{-1}/kg^{-1}$	2.7 ± 0.8	3.3 ± 1.2	0.049
$V_{Eunloaded}$, L/min^{-1}	10.8 ± 2.5	10.8 ± 3.6	0.925
Tidal $Volume_{unloaded}$, L	0.7 ± 0.2	0.8 ± 0.3	0.401
$f_{\beta unloaded}$,$1/min^{-1}$	12.8 ± 1.8	14.7 ± 4.1	0.024
$P_{ET}CO_{2unloaded}$, mmHg	34.9 ± 3.5	32.1 ± 3.9	0.006
$P_{ET}O_{2unloaded}$, mmHg	109.3 ± 5.7	108.6 ± 5.6	0.621
$SpO_{2unloaded}$,%	97.4 ± 0.9	98.3 ± 0.7	<0.001
$O_2pulse_{unloaded}$, $ml \bullet min^{-1}/bpm^{-1}$	4.3 ± 1.2	4.09 ± 1.5	0.587
$SBP_{unloaded}$, mmHg	111.7 ± 7.3	112.7 ± 10.8	0.685
$DBP_{unloaded}$, mmHg	75.7 ± 7.5	76.2 ± 8.7	0.833
VO_{2peak}, $ml/min^{-1}/kg^{-1}$	25.0 ± 5.9	32.9 ± 7.2	<0.001
VCO_{2peak}, $ml/min^{-1}/kg^{-1}$	27.5 ± 7.1	36.6 ± 9.0	<0.001
RER	1.10 ± 0.1	1.11 ± 0.8	0.494
V_{Epeak}, L/min^{-1}	78.6 ± 17.3	97.6 ± 26.1	0.003
Tidal $Volume_{peak}$, L	2.5 ± 0.7	2.8 ± 0.8	0.259
$f_{\beta Peak}$, $1/min^{-1}$	31.0 ± 5.8	35.5 ± 7.3	<0.001
$P_{ET}CO_{2peak}$, mmHg	38.6 ± 4.2	35.0 ± 4.9	0.043
$P_{ET}O_{2peak}$, mmHg	112.5 ± 4.6	116.5 ± 4.8	0.003
V_E/MVV_{peak}	60.4 ± 16.9	67.6 ± 17.7	0.132
SpO_{2peak},%	97.1 ± 1.5	97.7 ± 0.9	0.106
O_2pulse_{peak}, $ml \bullet min^{-1}/bpm^{-1}$	15.7 ± 2.6	13.0 ± 2.5	0.803
HR_{peak}, bpm^{-1}	151.1 ± 17.7	171.2 ± 12.6	<0.001
SBP_{peak}, mmHg	188.3 ± 21.9	173.1 ± 17.9	0.009
DBP_{peak}, mmHg	91.3 ± 8.2	85.4 ± 8.2	0.011

DBP = diastolic blood pressure; f_β = breath frequency; HR = heart rate; MVV = maximum voluntary volume; O_2pulse = ratio between oxygen uptake and heart rate; $P_{ET}CO_2$ = end-tidal carbon dioxide pressure; $P_{ET}O_2$ = end-tidal oxygen pressure; RER = respiratory exchange ratio; SBP = systolic blood pressure; SpO_2 = blood oxygen saturation with pulse oximetry; VCO_2 = carbon dioxide output, V_E = minute ventilation; VO_2 = oxygen uptake.

Table 3. Discriminant function coefficients

Variable	Coefficient
ERV, % of predicted	0.372
$P_{ET}CO_{2peak}$, mmHg	-0.376
$SpO_{2resting}$ %	0.667
Leg Fatigue, Borg Scale	0.564
HR_{peak}, bpm^{-1}	0.530
DBP_{peak}, mmHg	-0.543

ERV = expiratory reserve volume; DBP = diastolic blood pressure; HR = heart rate; $P_{ET}CO_2$ = end-tidal carbon dioxide pressure; SpO_2 = blood oxygen saturation with pulse oximetry.