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ORIGINAL INVESTIGATION

Effect of Nasal Continuous Positive Airway Pressure Therapy on the Functional Respiratory Parameters and Cardiopulmonary Exercise Test in Obstructive Sleep Apnea Syndrome

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Abstract

OBJECTIVES: Nasal continuous positive airway pressure (nCPAP) treatment is the gold standard treatment for obstructive sleep apnea syndrome (OSAS). In this study, we aimed to show that the pulmonary functions, exercise limitation on the cardiopulmonary exercise test (CPET), and the health-related quality of life can be improved after a short treatment period by nCPAP.

MATERIALS AND METHODS: Our case group with severe obstructive sleep apnea (OSA) performed incremental CPET before and after 8 weeks of nCPAP treatment. All the subjects also underwent physical examination, body composition analysis, simple spirometric measurements, maximal inspiratory pressure (PImax)-maximal expiratory pressure (PEmax), and lung volume tests before and after nCPAP treatment.

RESULTS: Thirty-one patients (4 female, 27 male) completed the study. The mean age of the patients was 53.41 ± 1.46 years. Sixteen had at least one comorbidity. In addition, 17 of the subjects were ex-smokers. After nCPAP treatment for 8 weeks, higher PImax-PEmax ($p< 0.05$), peak oxygen uptake ($p= 0.001$), workpeak ($p= 0.000$), maximal heart rates ($p= 0.000$), and short form-36 scores ($p< 0.05$) were observed. nCPAP treatment helped control the blood pressure ($p= 0.005$). There was no significant change in body composition analysis, spirometric parameters, and lung volumes.

CONCLUSION: In a short time period, nCPAP can improve exercise capacity, respiratory muscle strength, and the health-related quality of life scores and help control blood pressure.

KEY WORDS: Obstructive sleep apnea syndrome, cardiopulmonary exercise test, nasal continuous positive airway pressure, peak oxygen uptake, short form 36

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INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is characterized by total (apnea) or partial (hypopnea) repetitive upper airway obstruction resulting in oxygen desaturation, an awakening of sleep, loud snoring, and increased daytime sleepiness [1,2]. Sympathetic activation, vascular endothelial dysfunction, metabolic disorders, oxidative stress related to cyclic intermittent hypoxia, and inflammation may lead to cardiovascular diseases existing in OSAS [3,4]. Several studies have shown that OSA and chronic heart failure, hypertension, and obesity are linked to each other [5,6]. Pulmonary functions of OSAS have been explored in recent years [7-9]. The most commonly known spirometric findings in OSAS are that forced expiratory flow at 50%/forced inspiratory flow at 50% (FEF_{50}/FIF_{50}) > 1 and a saw-tooth pattern in the flow-volume curve [7-10]. Overweight OSA patients may have abnormal lung function values because of their weight. These include decreases in total lung capacity (TLC) and functional residual capacity (FRC) due to mainly a decrease in the expiratory reserve volume (ERV) and a decrease in the compliance of the respiratory system [11,12]. High body mass effects metabolic energy during exercise, resulting in ventilatory stress. Daytime hypersomnolence, low daily activity, and tissue hypoxemia impairs muscle function, which affects exercise fitness. It has been shown that the exercise limitation is related to the severity of sleep disorders independent of body habitus [12]. Decreases in cardiovascular mortality and non-fatal cardiovascular events have been shown in long-term follow-up studies of OSA patients under continuous positive airway pressure (CPAP) treatment [13].

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A meta-analysis about the CPAP effects on the quality of life in OSAS showed little impact of CPAP on the general quality of life when compared with control treatment. This meta-analysis also showed that generic quality of life instruments might not find the considerable changes in OSAS. CPAP did not improve general quality of life scores but improved physical domains and vitality [14].

Cardiopulmonary exercise testing (CPET) is used to differentiate the etiology of exercise limitation as follows: cardiac, pulmonary, or resulting from muscle dysfunction [15-19]. Previous studies evaluating exercise limitation in OSA have shown improvements in cardiac dysfunction and CPET performance after 8 weeks of nasal CPAP (nCPAP) treatment [20].

Nasal continuous positive airway pressure treatment effects on CPET in OSAS have been studied with only 20 patients in one study [20]. The aim of our study was to support the improvement in exercise limitation in OSA patients after a short-term nCPAP treatment period. We tried to determine whether pulmonary functions and health-related quality of life can also be improved after 60 days of nCPAP treatment using a larger study group.

MATERIALS AND METHODS

Subjects

Study protocols and written informed consents of the patients were approved by the institutional review committee on clinical research of the Dokuz Eylül University Faculty of Medicine, Turkey. Patients selected from those whose polysomnography reports were compatible with moderate or severe OSAS and who underwent nCPAP titration study prior to enrolment. The inclusion criteria for this study included patients who were non-smokers or ex-smokers for at least 12 months. Medical conditions that would affect pulmonary function tests and make exercise dangerous, such as chronic obstructive pulmonary disease, asthma, lung cancer, bronchiectasis, angina pectoris, congestive heart failure, poorly controlled diabetes mellitus, or other metabolic diseases, recent upper respiratory surgery, acute infection within 6 weeks prior to the study, morbid obesity, and anemia served as exclusion criteria. We also added neurological, psychological, and cooperation problems that would affect good participation to the exclusion criteria.

Participants underwent physical examination, body composition analysis, pulmonary function testing, CPET, and completed the general health-related quality of life questionnaires before and after nCPAP therapy. Patients did not have any instruction on diet, exercise, or weight loss during this period.

Physical Examination

Cardiac and pulmonary examinations were performed at baseline, including manual blood pressure measurements taken at rest (Riester Minimus III 0124).

Short Form-36 (SF-36) Health Survey

The general health-related quality of life was evaluated using the SF-36 questionnaire. SF-36 has eight multi-item dimensions that have scores from 0 to 100: physical functioning, physical role (role limitations due to physical problems), vitality, social functioning, emotional role (role limitation due to emotional problems), body pain, general health, and mental health.

Body Composition Analysis

Body mass index (BMI), percent body fat (PBF), and waist-to-height ratio (WHR) were calculated by bioelectrical impedance analysis (BIA) [21]. The technology assigns the electrical impedance of body tissues, which provides an estimate of total body water (TBW) [21]. Using values of TBW derived from BIA, one can then estimate fat-free mass (FFM) and body fat (adiposity) [21]. The availability of BIA in general adults and obese adults has been shown by several studies [22-25]. In our study, we used a BIA device with eight tactile electrodes (InBody720, Biospace, GE Health Care, Madison, USA), which is not suitable for pregnant subjects and those with a prosthesis. All of the subjects were advised to fast for 2 h prior to the testing.

Pulmonary Function Tests

The study group performed pulmonary function tests to determine the lung functions. Spirometry and respiratory muscle strength mouth pressures were administered with a Sensor medics Vmax 22 machine (SensorMedics Inc., Anaheim, CA, USA) confirming to the ATS/ERS criteria [26,27]. Forced vital capacity (FVC), first second forced expiratory volume (FEV_1), FEV_1/FVC, forced expiratory flow at the 25% point to the 75% point of forced vital capacity (FEF_{25-75}), and forced expiratory flow at 50% (FEF_{50}) values were measured. Body plethysmography (Jaeger Master Screen Body Spirometry V 5.1.0, Germany) was used to measure the lung volume. Residual volume (RV), total lung capacity (TLC), RV/TLC, inspiratory capacity (IC), inspiratory reserve volume (IRV), and expiratory reserve volume (ERV) were recorded.

Exercise Testing

Exercise tests were performed by an electrically braked cycle ergometer (Ergoline GmbH via Sprint 150 P Master Screen Cpx Ergospirometry V 5.11.0). A physician monitored the electrocardiographic changes. Serious cardiac arrhythmias, hypotension, and electrocardiographic changes by maximal incremental cycle ergometry protocols were the defined criteria for stopping. This incremental cycle ergometry protocol consists of 3 min of rest, followed by 3 min of unloaded pedaling with incremental loading (3 w per 10 s) until reaching a maximal load [28]. Terminating criteria for exercise testing were the patient reaching volitional exhaustion or the physician terminating the test. We evaluated the pre-test and post-test dyspnea severity and leg tiredness with a modified Borg scale.

Statistical Analysis

Statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) ver. 15 software package. We used the Wilcoxon signed rank test to compare the pre- and post-treatment data of the study group. All the values were calculated as the mean ± standard

deviation. We used the Kruskal–Wallis test to determine the correlation between the changes in BMI and changes in the CPET parameters. This was a per protocol analysis, and those subjects who completed the test were added in the analysis.

RESULTS

Forty patients consented to the study, of whom 31 completed all the baseline and follow-up testing. The subjects were contacted by telephone every 2 weeks to determine compliance and to identify problems with CPAP therapy use. CPAP therapy for an average of 4 h a night for at least 70% of the nights was considered as CPAP compliance. We checked the effective CPAP treatment with smart cards in patients' CPAP machines after 8 weeks. Nine patients did not meet the criteria for compliance due to removing the CPAP early in the night. When patients first started using the CPAP, they established their pattern of compliance within the first week of treatment.

Characteristics of the Subjects

There were 31 subjects (4 females and 27 males), with a mean age of 53.4 ± 1.4 years. Sixteen of the patients had hypertension and/or diabetes mellitus. In addition, 17 of the patients were ex-smokers, and the ex-smokers' mean package year was 18.05 ± 2.46. The mean AHI of the subjects was 54.25 ± 3.65, the lowest oxygen saturation was 75.29 ± 1.74, and the oxygen desaturation index was 47.26 ± 3.70 per hour. The mean CPAP pressure was 7.93 ± 0.34. Most of the study population (90%) was composed of patients with a BMI higher than 25 kg/m^2 but lower than 40 kg/m^2.

Physical Examination and Body Composition Analysis

These are summarized in Table 1. None of the patients had pathological diagnosis during the 8 weeks of nCPAP treatment. The mean systolic and diastolic blood pressures decreased after nCPAP treatment. There were no significant changes in neck circumference, BMI, PBF, or WHR after nCPAP treatment.

Quality of Life

In our study group, nCPAP treatment led to significant improvements in the SF-36 health survey. Patients undergoing 8 weeks of nCPAP treatment scored better in physical function, physical problems, general health, energy vitality, social functioning, emotional problems, mental health, physical component summary, and mental component summaries (Table 2). There was no significant change in body pain (Table 2).

Table 1. Physical examination and body composition analysis

	Before CPAP	After CPAP	p
Mean systolic BP	122.26 ± 1.2	118.39 ± 1.3	0.005
Mean diastolic BP	78.70 ± 0.6	76.12 ± 1.1	0.021
Neck circumference	39.53 ± 0.5	39.50 ± 0.5	0.317
BMI	31.43 ± 0.8	31.74 ± 0.7	0.090
PBF	32.50 ± 1.3	33.40 ± 1.3	0.051
WHR	0.97 ± 0.01	0.92 ± 0.04	0.061

Data are presented as mean ± SD. Wilcoxon signed rank test was used. BP: blood pressure; BMI: body mass index; PBF: body fat percentage; WHR: waist-to-hip ratio.

Pulmonary Function Tests and Lung Volumes

After the nCPAP treatment, there were no significant changes in all of the pulmonary function tests and lung volumes except FEV_1 (%). PI max and PI max values were better after treatment (Table 3).

Table 2. Quality of life

	Before CPAP	After CPAP	p
Body pain	76.4 ± 5.1	84.3 ± 3.6	0.145
General health	54.2 ± 3.3	71.3 ± 3.1	0.000
Energy vitality	54.7 ± 4.5	78.1 ± 2.8	0.000
Social functioning	54.2 ± 3.3	71.3 ± 3.0	0.000
Emotional problems	49.4 ± 7.6	79.9 ± 6.7	0.000
Mental health	66.7 ± 2.9	77.4 ± 2.6	0.000
PCS	45.9 ± 1.5	51.8 ± 1.3	0.004
MCS	43.2 ± 1.8	53.8 ± 1.2	0.008
Physical function	77.6 ± 3.8	86.8 ± 3.8	0.001
Physical problems	51.7 ± 7.8	93.3 ± 4.1	0.000

Data are presented as mean ± SD. Wilcoxon signed rank test was used. PCS: physical component summary; MCS: mental component summary.

Table 3. Spirometric measurements

	Before CPAP	After CPAP	p
FVC (% pred.)	96.1 ± 2.5	94.6 ± 2.6	0.294
FEV_1 (% pred.)	99.9 ± 2.5	97.2 ± 2.5	0.017
FEV_1 / FVC	84.3 ± 0.8	83.1 ± 0.9	0.157
PEF (% pred.)	99.8 ± 3.4	98.2 ± 3.1	0.468
FEF_{50} (% pred.)	99.9 ± 4.2	94.7 ± 4.4	0.112
FEF_{25-75} (% pred.)	88.3 ± 3.9	91.8 ± 4.5	0.491
FEF_{50}/FIF_{50}	1.5 ± 0.1	1.3 ± 0.1	0.176
PI max	74.6 ± 5.1	82.0 ± 5.9	0.011
PE max	98.2 ± 5.7	109.3 ± 6.7	0.009
RV (% pred.)	109.4 ± 5.5	103.1 ± 4.6	0.710
TLC (% pred.)	96.4 ± 2.4	93.0 ± 2.4	0.252
IC (% pred.)	94.7 ± 4.5	96.5 ± 4.3	0.389
ERV (% pred.)	87.8 ± 10.9	79.1 ± 8.5	0.272

Data are presented as mean ± SD. Wilcoxon signed rank test was used. FVC: forced vital capacity; FEV_1: forced expiratory volume; PEF: peak expiratory flow; FEF_{50}: forced expiratory flow at 50%; FEF_{25-75}: forced expiratory flow at 25-75%; FIF_{50}: forced inspiratory flow at 50%; PI max: maximal inspiratory pressure; PE max: maximal expiratory pressure; RV: residual volume; TLC: total lung volume; IC: inspiratory capacity; ERV: expiratory reserve volume.

Table 4. Cardiopulmonary exercise test (CPET) results

	Before CPAP	After CPAP	p
VO_2 peak (%)	61.0 ± 2.2	68.6 ± 2.2	0.001
Workpeak (W)	109.6 ± 4.5	126.5 ± 4.5	0.000
Maximal hearth rate	129.5 ± 3.0	136.2 ± 3.0	0.000
Hearth rate reserve	36.4 ± 2.6	29.6 ± 2.4	0.000
SpO_2 (%)	96.7 ± 0.2	97.3 ± 0.1	0.003
O_2 pulse (%)	69.2 ± 2.6	76.5 ± 2.9	0.019
VE max (L/dk)	53.1 ± 2.4	63.4 ± 2.9	0.000
Breathing reserve (%)	52.1 ± 2.2	41.8 ± 2.2	0.000

Data are presented as mean ± SD. Wilcoxon signed rank test was used. VO_2 peak: peak oxygen uptake; SpO_2: blood oxygen level O_2; pulse: pulse oximetry; VE max: maximal pulmonary ventilation.

Exercise Tests

Dyspnea and leg fatigue severity of patients was lower after the 8 weeks of nCPAP treatment. Significant improvements in VO_2 peak, maximal work peak, maximal heart rate, oxygen saturation (SpO_2), oxygen (O_2) pulse, maximal minute ventilation (VE max), and correlation of a decrease in heart rate reserve with the increase in the maximal heart rate were noted on exercise testing after nCPAP treatment (Table 4).

DISCUSSION

In our study, severe OSA patients had lower VO_2 peak, workpeak, maximal heart rate, and oxygen pulse, all of which improved after a short time with nCPAP treatment period. There was no significant improvement in the respiratory parameters, but the quality of life scores were significantly better after treatment.

During the treatment period, study patients did not receive any instruction on diet, exercise, or weight loss. Patients' anthropometric measurements after the treatment period did not change significantly. Therefore, improvements may be related to nCPAP treatment. We found that nCPAP treatment helped control arterial blood pressure and improved the inspiratory and expiratory muscle functions and quality of life scores.

Ozturk et al. [15] showed that moderate-to-severe OSA patients had limited exercise capacity. They determined that this exercise limitation seemed to originate from cardiovascular reasons and/or peripheral vascular impairment. Aguillard et al. [22] had to end their moderate and severe OSA patients' CPET because of tiredness. They said that the subjective tiredness was not correlated with OSA severity. Daytime hypersomnolence may be a reason for exercise limitation in OSA patients.

In our study, all the patients tolerated CPET without any serious complications such as ischemia or arrhythmias in the echocardiogram. They stopped exercising at submaximal ventilation. The reasons for stopping CPET were dyspnea and leg muscle tiredness.

Our patients had a small but significant improvement in their blood pressure; similar findings were reported by Lin et al. [20]. In both studies, patients' exercise responses after nCPAP treatment were better without any significant differences in age, BMI, or exercise habits. These changes seem to be related with only nCPAP treatment. In our study, we found significant increases in maximal heart rate and SpO_2. The increases in maximal heart rate and breathing reserve may show that the patients did better exercise after nCPAP treatment. Increases in VE max may be related with the increase in workpeak. The increase in SpO_2 after nCPAP treatment supports the improvement in exercise capacity. The potential reason for this is the sleep recovery because sleep restores cellular functions in the brain and the muscles [29,30]. The rise in tissue oxygenation may be the reason for the higher SpO_2.

Kaneko et al. [31] showed that CPAP treatment helped control systolic blood pressure and increased the left ventricular ejection fraction. Doherty et al. [32] found that long-term CPAP treatment decreased the cardiovascular mortality without any effect of age, BMI, smoking, alcohol, or OSA severity. In our study, the improvements in O_2 pulse, maximal heart rate, and arterial blood pressure may show the cardiovascular recovery in OSA patients. There was no significant difference in exercise capacities between obese and non-obese patients before nCPAP treatment. This may support the idea that obesity does not have an important effect on exercise limitation in OSA patients.

Inspiratory muscles of OSA patients are under more negative intrathoracic pressure compared with healthy subjects [33]. Aran et al. [34] showed that the respiratory muscle force and resistance were lower with night-time CPAP treatment in OSA patients. Barreiro et al. [35] noted that night-time inspiratory muscle resistance and continuous hypoxia-reoxygenation circle may increase the oxidative stress in respiratory muscles, and CPAP treatment may recover this respiratory muscle dysfunction. In our study group, inspiratory and expiratory muscle strength improved significantly after 8 weeks of nCPAP treatment. Recovery of respiratory muscle resistance and oxidative stress in muscles after CPAP treatment may be the reason. Bonay et al. [36] showed there was no change in TLC and RV in OSA patients without obstructive pulmonary disease in their study when they observed pulmonary functions before and after nCPAP treatment in OSA patients with and without obstructive pulmonary disease. In accordance with the literature, there was no significant difference in lung volumes (TLC, RV, IC, ERV) in our study after the treatment.

There was no change in spirometric measurements except FEV_1, but this was not clinically important or meaningful. Our patients did not have any different treatment that could influence their spirometric parameters. The reason for FEV_1 loss in our study patients is not clear. Bonay et al. [36] noted a loss of FEV_1 and FEF_{25-75} in OSA patients without obstructive lung disease after 16.8 ± 8 months of nCPAP treatment. Chaouat et al. [37] detected a decrease in FEV_1 after nCPAP treatment (64 ± 6 months) related to a high smoking history

(77%). Bonay et al. [36] noted that CPAP may irritate airway epithelia and induce airway inflammation. In addition, long-term nCPAP may act as a mechanical alteration of the nasal mucosa and creates a change in small airway resistance via the nasobronchial reflex. In our study, we did not think the mechanical effect of CPAP was the cause for the FEV_1 loss because of the short-term follow-up period. Our patients used their CPAPs in cold winter days, and most of the machines did not have any heater plate. Cold air inhalation might cause bronchoconstriction and increase mucus secretion.

A meta-analysis about the effect on the quality of life of CPAP in OSAS showed little impact of CPAP on the general quality of life when comparing CPAP with a control treatment. This meta-analysis also showed that generic quality of life instruments might not be suitable for detecting changes in the quality of life in OSA patients and that CPAP did not improve the general quality of life scores but did improve the physical domains and vitality. In our study, we found significant improvements in physical function, physical problems, energy/vitality, social functioning, emotional problems, mental health, physical component summary, and mental component summary scores after nCPAP treatment. SF-36 may be useful for discriminating patients with and without OSAS and may be sensitive to treatment-induced changes [14].

Our study is limited by the small sample size and lack of a control polysomnography after nCPAP treatment. Because of the known effects of smoking on the respiratory system, active smokers and those who have recently quit smoking were excluded. Morbidly obese OSA patients were not included in our study because they could not finish exercise testing. These are the reasons for our small sample size. However, our study numbers were greater than in other similar studies. Our patients could not undergo control polysomnography because some of them did not want to spend one more night in the hospital. In further studies, it will be better to perform control polysomnography after an nCPAP treatment period to show the change in desaturation time or percentage during sleep. If the desaturation period is shorter after treatment, this will help to explain the recovery of tissue oxygenation and exercise capacity.

In conclusion, nCPAP treatment is effective in reducing exercise limitation, can help control blood pressure, and improves respiratory muscle strength. nCPAP can also improve the quality of life scores in OSA patients without any uncontrolled comorbidities.

Ethics Committee Approval: Institutional review committee on non-invasive clinical research of the Dokuz Eylül University School of Medicine (22.09.2010).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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REFERENCES

1. American Academy of Sleep Medicine, International Classification of Sleep Disorders, version 2: Diagnostic Coding Manual, 2005.
2. McNicholas WT, Bonsignore MR; Management Committee of EU COST ACTION B26. Sleep apnea as an independent risk factor for cardiovascular disease: current evidence, basic mechanisms and research priorities. Eur Respir J 2007;29:156-78. [CrossRef]
3. Caples SM, Gami AS, Somers VK. Obstructive sleep apnea. Ann Intern Med 2005;142:187-97. [CrossRef]
4. Parish JM, Somers VK. Obstructive sleep apnea and cardiovascular disease. Mayo Clin Proc 2004;79:1036-46. [CrossRef]
5. Levinson PD, McGarvey ST, Carlisle CC, et al. Adiposity and cardiovascular risk factors in men with obstructive sleep apnea. Chest 1993;103:1336-42. [CrossRef]
6. Zerah-Lancner F, Lofaso F, Coste A, et al. Pulmonary function in obese snorers with or without sleep apnea syndrome. Am J Respir Crit Care Med 1997;156:522-7. [CrossRef]
7. Ozturk L, Metin G, Cuhadaroglu C, et al. FEF(25-75)/FVC Measurements and extrathoracic airway obstruction in obstructive sleep apnea patients. Sleep Breath 2005;9:33-8. [CrossRef]
8. Hoffstein V, Wright S, Zamel N. Flow volume curves in snoring patients with and without obstructive sleep apnea. Am Rev Respir Dis 1989;139:957-60. [CrossRef]
9. Rauscher H, Popp W, Zwick H. Flow-volume curves in obstructive sleep apnea and snoring. Lung 1990;168:209-14. [CrossRef]
10. Ray CS, Sue DY, Bray G, et al. Effect of obesity on respiratory function. Am Rev Respir Dis 1983;128:501-6. [CrossRef]
11. Jones RL, Nzekwu MM. The effects of body mass index on lung volumes. Chest 2006;130:827-33. [CrossRef]
12. Peppard PE, Young T. Exercise and sleep-disordered breathing: an association independent of body habitus. Sleep 2004;27:480-4.
13. Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long term cardiovascular outcomes in men with obstructive sleep apnea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. Lancet 2005;365:1046-53. [CrossRef]
14. Jing J, Huang T, Cui W, Shen H. Effect on quality of life of continuous positive airway pressure in patients with obstructive sleep apnea syndrome: a meta-analysis. Lung 2008;186:131-44. [CrossRef]
15. Oztürk LM, Metin G, Cuhadaroglu C, et al. Cardiopulmonary responces to exercise in moderate-to-severe obstructive sleep apnea. Tuberk Toraks 2005;53:10-9.
16. Lin CC, Hsieh WY, Chou CS, Liaw SF. Cardiopulmonary exercise testing in obstructive sleep apnea syndrome. Respir Physiol Neurobiol 2006;150:27-34. [CrossRef]
17. Sengul YS, Ozalevli S, Oztura I, et al. The effect of exercise on obstructive sleep apnea: a randomized and controlled trial. Sleep Breath 2011;15:49-56. [CrossRef]
18. Przybyłowski T, Bielicki P, Kumor M, et al. Exercise capacity in patients with obstructive sleep apnea syndrome. J Physiol Pharmacol 2007;58(Suppl 5):563-74.

19. Hargens TA, Guill SG, Aron A, et al. Altered ventilatory responses to exercise testing in young adult men with obstructive sleep apnea. Respir Med 2009;103:1063-9. **[CrossRef]**
20. Lin CC, Lin CK, Wu KM, Chou CS. Effect of treatment by nasal CPAP on cardiopulmonary exercise test in obstructive sleep apnea syndrome. Lung 2004;182:199-212. **[CrossRef]**
21. Baumgartner RN, Chumlea WC, Roche AF. Bioelectric impedance for body composition. Exerc Sport Sci 1990;18:193-224.
22. Aguillard RN, Riedel BW, Lichstein KL, et al. Daytime functioning in obstructive sleep apnea patients: exercise tolerance, subjective fatigue, and sleepiness. Appl Phychophysiol Biofeedback 1998;23:207-17.
23. Segal KR, Van Loan M, Fitzgerald PI, et al. Lean body mass estimation by bioelectrical impedance analysis: a four-site cross-validation study. Am J Clin Nutr 1988;47:7-14.
24. Gray DS, Bray GA, Gemayel N, Kaplan K. Effect of obesity on bioelectrical impedance. Am J Clin Nutr 1989;50:255-60.
25. Tanaka K, Kim H, Nakanishi T, Amagi H. Multi-frequency impedance method for the assessment of body composition in Japanese adults. J Exercise Sports Physiol 1999;6:37-45.
26. American Thoracic Society. Standardization of Spirometry, 1994 update. Am J Respir Crit Care Med 1995;152:1107-36. **[CrossRef]**
27. Black LF, Hyatt RE. Maximal respiratory pressures: normal values and relationship to age and sex. Am Rev Respir Dis 1969;99:696-702.
28. American Thoracic Society; American College of Chest Physicians. ATS/ACCP statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med 2003;167:211-77. **[CrossRef]**
29. Vondra K, Brodan V, Bass A, et al. Effects of sleep deprivation on the activity of selected metabolic enzymes in skeletal muscle. Eur J Appl Physiol Occup Physiol 1981;47:41-6. **[CrossRef]**
30. White DP, Douglas NJ, Pickett CF, et al. Sleep deprivation and the control of ventilation. Am Rev Respir Dis 1983;128:984-6.
31. Kaneko Y, Floras JS, Usui K, et al. Cardiovascular effects of continuous positive airway pressure in patients with heart failure and obstructive sleep apnea. N Engl J Med 2003;348:1233-41. **[CrossRef]**
32. Doherty LS, Kiely JL, Swan V, Mc Nicholas WT. Long-term effcets of nasal continuous positive airway pressure therapy on cardiovascular outcomes in sleep apnea syndrome. Chest 2005;127:2076-84. **[CrossRef]**
33. Wilcox PG, Pare PD, Road JD, Fleetham JA. Respiratory muscle function during obstructive sleep apnea. Am Rev Respir Dis 1990;142:533-9. **[CrossRef]**
34. Aran X, Felez MA, Gea J, et al. Respiratory muscle force and resistance in patients with SAHS. The effect of using night time CPAP. Arch Bronconeumol 1999;35:440-5.
35. Barreiro E, Nowinski A, Gea J, Sliwinski P. Oxidative stres in the external intercostal muscles of patients with obstructive sleep apnea. Thorax 2007;62:1095-101. **[CrossRef]**
36. Bonay M, Nitenberg A, Maillard D. Should flow-volume loop be monitored in sleep apnea patients treated with continuous positive airway pressure? Respir Med 2003;97:830-4. **[CrossRef]**
37. Chaouat A, Weitzenblum E, Kessler R, et al. Five-year effects of nasal continuous positive airway pressure in obstructive sleep apnoea syndrome. Eur Respir J 1997;10:2578-82. **[CrossRef]**