Obstructive sleep apnea (OSA) is a common clinical disorder in adult population. Repeated episodes of airway closure with resultant decrease in intrathoracic pressure and sympathetic nervous system activation may cause severe complications including cardiovascular system. Continuous positive airway pressure (CPAP) ventilation remains the best treatment option and has been shown to prevent the deterioration of health status. Cardiopulmonary exercise tests (CPETs) are used for detecting exercise tolerance mechanisms and reasons for intolerance. CPET provides information about cardiopulmonary system, oxygen transport system, muscular system, and metabolic activity of tissues that interact in exercise. The aim of this study was to evaluate the impact of OSA and CPAP treatment on cardiovascular, pulmonary, and oxidative metabolism during exercise.

PATIENTS AND METHODS
This prospective study was conducted between May 2010 and July 2011. The ethics committee approval was obtained. The study population consisted of patients diagnosed as OSA, and these patients were admitted to the Gaziantep University Sleep Clinic. Patients with obstructive or restrictive pulmonary disorder, cardiac failure, acute coronary syndrome, or inability to cycle due to orthopedic problems were excluded. Ninety consecutive patients who required CPAP for OSA treat-
ment and were older than 18 years were included.

Body mass index (BMI) was calculated as kg/m². Epworth sleepiness scale scores were calculated for each subject. Polysonomographic data was recorded with Viasys Sleep Screen (Viasys Healthcare, Germany). Sleep studies were evaluated according to American Academy of Sleep Medicine guidelines by the same doctor (MU). OSA was classified as mild (apnea-hypopnea index [AHI] ≥5-15), moderate (AHI=15-30), and severe (AHI≥30).

CPAP titration was performed with full-night polysomnographic recordings. Patients were informed about the use of CPAP. Control was conducted after 4 weeks. Patients with more than 4 hours of daily CPAP usage were evaluated as CPAP compliant; other patients were evaluated as the CPAP noncompliant group.

Bicycle ergometry was performed during diagnostic workup and at control visit. Exercise protocol and reference values were based on American Thoracic Society/American College of Chest Physicians guidelines. CPET was performed using Vmax Spectra 229 model (Viasys, USA) ergospirometry device. Spirometry and MVV values were obtained before CPET. The exercise consisted of symptom-limited, ramp workload protocol programmed to reach maximum in 10 minutes. The pedal rate was aimed to remain constant at 60 to 70 cycles/min during the procedure. Blood pressures were obtained using a standard sphygmomanometer in 2-minute intervals. Oxygen consumption (VO2), carbon dioxide production (VCO2), anaerobic threshold (AT), heart rate (HR), oxygen saturation, end-tidal O2 and CO2 (PetO2, PetCO2), tidal volume, respiratory rate, and minute ventilation (VE) were recorded.

Data was analyzed with SPSS, version 11.5 (SPSS, Chicago, IL, USA). Repeated measures of ANOVA, student t test, chi-square test, and Pearson correlation test were used as appropriate. Data was shown as mean (SD). P≤.05 was necessary for statistical significance.

RESULTS

Flow chart for the study group was shown in Figure 1. Sixty-five patients were included in the final analysis (57 males, 8 females). The mean age was 45.3 (10.6) years, AH1 38.0 (23.2), and BMI 31.7 (4.9) kg/m². Demographic and clinic characteristics of the study population are shown in Table 1.

The mean age was higher among the CPAP compliant group (P=.006); therefore, age was adjusted for comparisons between groups. CPAP compliant group had more co-morbidities also (P=.004), which were hypertension 39.4%, diabetes 6.1%, coronary artery disease 6.1%, hypercholesterolemia 3%, and other 18.2%. Hypertension was present in 12.5%, diabetes in 3.1%, and hypertension and diabetes in 9.4% in the CPAP noncompliant group.

Difference was not detected in mean AH1 values with respect to CPAP compliance (P=.348). Subgroup analysis with respect to OSA severity was performed. The CPAP compliant group consisted of 9.1% (n=3) mild OSA, 24.2% (n=8) moderate OSA, and 66.7% (n=22) severe OSA patients, whereas the noncompliant group had 21.9% (n=7) mild, 31.2% (n=10) moderate, and 46.9% (n=15) severe sleep apneics. Compliance was detected higher among patients with higher AH1 (P=.025, r=0.39), but gender did not affect compliance.

Control visits were performed at 42.1 (16.0) and 35.5 (8.8) days in CPAP compliant and noncompliant groups, respectively (P=.594). CPAP usage was reported as 6.2 (0.9) hours per night in the CPAP compliant group. Cardiopulmonary exercise data with respect to CPAP compliance is shown in Table 2.

WR% increased from 84.0 (16.3) to 85.0 (14.6) in the CPAP compliant group. Decrease in WR% was detected in the CPAP noncompliant group from 79.6 (17.9) to 77.1 (17.8) (P=.041) (Figure 2).

The peak VO2 uptake did not change in the CPAP compliant group (n=33) (22.5 [6.6] mL/[min.kg] vs 21.3 [5.3] mL/[min.kg]; P=.111), but decreased from 21.3 (5.7) mL/[min.kg] to 19.9 (5.4) mL/[min.kg] (P=.05) in the CPAP noncompliant group.

AT was detected as 1.0 (0.3) l/min in the initial admission and 0.9 (0.2) l/min in the control visit in the CPAP compliant group (P=.106). AT for the noncompliant group decreased from 1.0 (0.3) l/min in the first and 0.9 (0.2) l/min in the second visit (P=.036). AT as a ratio of the predicted maximum oxygen uptake also decreased significantly in the noncompliant group (from 38.7 [12.7%] to 34.3 [9.2%], P=.028) whereas the difference between the 2 measurements in the CPAP compliant group was not significant (from 43.8 [14.2%] to 41.1 [9.7%], P=.162).

VE/VCO2 at AT decreased from 28.4 (3.2) to 27.4 (2.6) in the CPAP compliant group, whereas this was found to increase from 27.4 (2.5) to 27.8 (2.7) in the CPAP noncompliant group (P=.033) (Figure 3).

Smoking history was not found to be related to exercise parameters among groups. Comparisons between the subgroup of patients with BMI normal+overweight and obese+morbid obese with respect to exercise parameters did not reach statistical significance.

DISCUSSION

In this study, we observed that workload, VO2, and AT decreased in OSA patients without treatment com-
pared to patients using CPAP treatment. VE/VCO₂ at ATP value decreased in the CPAP compliant group compared to the noncompliant group. Exercise parameters in the CPAP noncompliant group declined over time although they were younger and co-morbidities were fewer. However, exercise parameters in the CPAP compliant group were preserved during the same period. We considered that the treatment was effective in these patients despite co-morbidity and higher age.

Patients with OSA may exhibit respiratory problems as a result of higher BMI. Obesity causes a decrease in functional residual capacity due to impaired expiratory reserve volume and respiratory system compliance. Increased BMI necessitates higher metabolic energy during muscular exercise that causes increased oxygen consumption and CO₂ production. Nevertheless, changes in exercise response cannot be solely attributed to obesity because both study groups exhibited similar BMI. Furthermore, studies also display a multitude of abnormalities detected by CPET in OSA patients.

VO₂max, HR recovery, and chronotropic exercise reserve were lower in a study consisting of moderate-to-severe OSA patients without cardiac co-morbidity. Lin et al found a lower right ventricular ejection fraction, VO₂max, VO₂ max/kg, ATP, workload, and O₂ pulse values in 20 moderate-to-severe OSA patients compared to controls. We detected lower VO₂max/kg and VO₂max/kg (%) values in our study group compared to predicted values.

Obese subjects with BMI >35 kg/m² were included in a study by Vanhecke and coworkers, and patients with OSA (n=42) had a significantly lower oxygen uptake (17.6 mL/[min.kg]) than controls (n=50, 21.1 mL/[min.kg]). Increased HR and systolic and diastolic blood pressure were detected at rest, exercise, and recovery period in OSA patients as well. However, in another study including subjects with BMI lower than 25 mg/m², VO₂max, ATP, respiratory exchange ratio, blood pressure, and HR were not different between OSA and controls. OSA may not cause decreased functional capacity in lean patients; however, obesity may contribute to the decrease in cardiovascular capacity. We could not evaluate the effect of obesity on exercise parameters in detail because of the insufficient number of patients with normal weight (n=4).

In a study evaluating 23 normotensive, overweight OSA patients and 9 healthy subjects, OSA patients had a lower exercise HR and higher diastolic blood pressure, and a delayed systolic blood pressure recovery. Although 26% had hypertension in our study population, all patients showed exaggerated blood pressure response during exercise.

CPAP treatment has been shown to have favorable effects on exercise and functional parameters in patients with OSA. Schlosser et al. found that VO₂max/kg increased from 15.3 (4.8) mL/[min.kg] to 18.5 (6.9) mL/[min.kg] after at least 6 months of CPAP treatment in 17 subjects with OSA compared to 8 subjects noncompliant to CPAP. In another study consisting of 20 moderate and severe OSA patients, lower respiratory

### Table 1. Demographic and clinical characteristics of patient population (n=65).

|                        | CPAP compliant (n=33) | CPAP noncompliant (n=32) | P  |
|------------------------|-----------------------|--------------------------|----|
| Age (mean [SD])        | 48.76 (9.2)           | 41.72 (10.9)             | .006|
| Gender                 |                       |                          |    |
| Male                   | 28 (84.8%)            | 29 (90.6%)               | .479|
| Female                 | 5 (15.2%)             | 3 (9.4%)                 |    |
| Smoking history        |                       |                          |    |
| No                     | 9                     | 9                        | .902|
| Yes                    | 12                    | 10                       |    |
| Ex-smoker              | 12                    | 13                       |    |
| AHI (mean [SD])        | 40.7 (19.6)           | 35.2 (26.4)              | .348|
| BMI (mean [SD])        | 31.3 (13.8)           | 32.2 (5.8)               | .445|
| Comorbidity (%)        | 73                    | 37                       | .004|
| ESS (mean [SD])        | 10.8 (5.2)            | 11.5 (4.9)               | .555|
| FEV₁ (%) (mean [SD])   | 108.3 (16.1)          | 99.2 (11.7)              | .011|
| FVC (%) (mean [SD])    | 113.0 (15.2)          | 106.0 (10.6)             | .034|

AHI: Apnea-hypopnea index; BMI: body mass index; CPAP: continuous positive airway pressure; ESS: Epworth sleepiness scale; FVC: forced vital capacity; SD: standard deviation.
Table 2. Cardiopulmonary exercise test findings with respect to CPAP compliance.

|                     | CPAP compliant (n=33) (mean [SD]) | CPAP noncompliant (n=32) (mean [SD]) |
|---------------------|-----------------------------------|--------------------------------------|
|                     | First CPET                        | Control CPET                         | First CPET                        | Control CPET |
| VO₂ max (mL/min)    | 1979.8 (622.2)                    | 1871.2 (459.9)                       | 1957.2 (435.6)                    | 1839.2 (419.6) |
| VO₂ max (%)         | 87.4 (21.8)                       | 83.7 (18.6)                          | 78.3 (18.3)                       | 73.2 (16.1)  |
| VO₂ max/kg          | 22.5 (6.6)                        | 21.3 (5.3)                           | 21.3 (5.7)                        | 19.9 (5.4)   |
| VO₂ max/kg (%)      | 68.8 (18.8)                       | 65.9 (16.4)                          | 59.1 (16.5)                       | 55.0 (13.7)  |
| VO₂ (mL/min)        | 2610.2 (777.6)                    | 2541.3 (624.5)                       | 2577.5 (602.6)                    | 2461.7 (597.6) |
| Work load (watt)    | 137.6 (35.1)                      | 138.8 (33.0)                         | 148.0 (32.5)                      | 143.9 (33.9) |
| Work load (%)       | 84.0 (16.3)                       | 85.0 (14.6)                          | 78.6 (17.9)                       | 77.1 (17.7)  |
| AT (l/min)          | 1.0 (0.3)                         | 0.9 (0.2)                            | 1.0 (0.3)                         | 0.9 (0.2)    |
| AT (%pred max VO₂)  | 43.8 (14.2)                       | 41.1 (9.7)                           | 38.7 (12.7)                       | 34.3 (9.2)   |
| HR (pulse/min)      | 158.8 (16.0)                      | 154.7 (19.5)                         | 161.1 (18.2)                      | 156.3 (17.3) |
| HR (%)              | 89.0 (7.8)                        | 86.8 (9.9)                           | 88.2 (8.2)                        | 85.4 (7.7)   |
| O₂ pulse (mL/pulse) | 12.4 (3.4)                        | 12.3 (2.9)                           | 12.0 (3.0)                        | 11.3 (2.5)   |
| O₂ pulse (%)        | 98.6 (23.9)                       | 98.7 (21.7)                          | 88.6 (26.1)                       | 86.6 (21.8)  |
| HRR                 | 19.8 (13.7)                       | 23.7 (17.5)                          | 21.6 (14.5)                       | 26.3 (13.4)  |
| VE max (l/min)      | 86.7 (28.4)                       | 80.3 (22.3)                          | 81.1 (21.5)                       | 76.3 (18.0)  |
| VE max (%)          | 74.0 (20.9)                       | 71.0 (16.8)                          | 66.8 (16.0)                       | 64.3 (13.5)  |
| TV (%)              | 1.9 (0.5)                         | 1.8 (0.4)                            | 1.8 (0.5)                         | 1.8 (0.5)    |
| RR                  | 79.4 (15.2)                       | 83.7 (21.0)                          | 75.2 (16.7)                       | 74.2 (16.9)  |
| PetCO₂              | 5.0 (0.5)                         | 5.1 (0.5)                            | 5.2 (0.4)                         | 5.2 (0.4)    |
| PetO₂               | 13.8 (0.6)                        | 13.6 (0.7)                           | 13.2 (0.6)                        | 13.1 (0.6)   |
| VE/VO₂ AT           | 31.0 (5.2)                        | 30.2 (3.5)                           | 29.9 (2.7)                        | 30.5 (3.2)   |
| VE/VO₂ AT           | 28.4 (3.2)                        | 27.4 (2.6)                           | 27.4 (2.5)                        | 27.8 (2.7)   |

*P* values for first and control CPET comparisons. CPAP: Continuous positive airway pressure ventilation; AT: anaerobic threshold; HR: heart rate; HRR: heart rate reserve; RR: respiratory rate; TV: tidal volume; VE: ventilation.

Reserve and higher AT and O₂ pulse were detected after two months of CPAP treatment. Right ventricle ejection fraction, VO₂ max, VO₂ max/kg, and workload values were increased, whereas the decrease in VE/VCO₂ did not reach statistical significance. We showed a significant increase in workload and decrease in VE/VCO₂ despite the shorter period of CPAP treatment. AT, VO₂ max/kg, and VO₂ max/kg (%) values were preserved with CPAP; however, longer periods may be necessary for cardiac, vascular, and pulmonary adaptation after treatment. VO₂ max/kg and HR remained unchanged after 2 to 3 weeks of CPAP treatment in OSA patients. Alonso-Fernández et al showed higher systolic and mean nocturnal blood pressure, higher nocturnal catecholamine levels, lower cardiac output, and stroke volume response to exercise in consecutive 31 sleep apneics compared to controls. After 3 months of CPAP treatment and sham CPAP crossover, all indices of cardiac function response during exercise, including cardiac output and stroke volume, improved significantly with CPAP. We detected decrease in AT VE/VCO₂ values in the CPAP compliant group than in the CPAP noncompliant group. VO₂ max, VCO₂, and VE/VO₂ remained unchanged. Hargens et al. found that VO₂ max was similar but VE, VE/VCO₂, and VE/VO₂ increased in OSA patients compared to controls using bicycle ergometer. They explained this effect by re-
peated hypoxia episodes causing increased ventilatory response to exercise by increasing the release of endothelin-1 that in turn intensified chemoreflex sensitivity. There are a few mechanisms to explain an increased ventilatory requirement for a given CO₂ production: increased dead space and ineffective ventilation, early lactic acidosis, and abnormal activity of chemoreflex receptors. The elevated VE/VCO₂ slope was also associated with leptin levels. Lower VE/VCO₂ in patients using CPAP may reflect a decrease of chemo-
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