Effect of Continuous Positive Airway Pressure Versus Supplemental Oxygen on Sleep Quality in Obstructive Sleep Apnea: A Placebo-CPAP–Controlled Study

José S. Loredo, MD; Sonia Ancoli-Israel, PhD; Eui-Joong Kim, MD; Weon Jeong Lim, MD; Joel E. Dimsdale, MD

1Department of Medicine and the 2Department of Psychiatry, University of California, San Diego, CA; 3Department of Psychiatry, Eulji University, Daejeon, Korea; 4Department of Psychiatry, Ewha Womans University, Seoul, Korea

Study Objective: We investigated the short-term effectiveness of continuous positive airway pressure (CPAP) and oxygen in improving sleep quality in patients with obstructive sleep apnea (OSA).

Design: Randomized, double-blind, placebo-controlled, parallel study.

Setting: General Clinical Research Center at a university hospital.

Patients: Seventy-six patients with untreated OSA.

Interventions: Patients were randomly assigned to 1 of 3 treatments (CPAP, placebo-CPAP, or nocturnal oxygen at 3 L per minute) for 2 weeks. Sleep quality was assessed at baseline and after 1 and 14 days of therapy. Repeated-measures analysis of variance was used to evaluate treatment and time effects, and their interaction.

Measurements and Results: Sixty-three patients completed the protocol. When compared with placebo-CPAP and nocturnal oxygen, CPAP increased rapid eye movement (REM) sleep and significantly reduced stage 1 sleep and the number of stage shifts (p ≤ .003). CPAP improved, to within normal limits, the apnea-hypopnea index, total arousal index, and mean oxyhemoglobin saturation (p ≤ .001). The effects of CPAP were apparent during the first night of therapy. Oxygen improved only mean nocturnal saturation (p = .009). CPAP had no significant effect on stage 2 sleep or slow-wave sleep.

Conclusions: CPAP was associated with an improvement in sleep quality in patients with OSA by consolidating sleep, reducing stage 1 sleep, and improving REM sleep. CPAP was effective in correcting the respiratory and arousal abnormalities of OSA. The effectiveness of supplemental oxygen was limited to oxyhemoglobin desaturation.

Keywords: Continuous positive airway pressure, obstructive sleep apnea, sleep quality, oxygen, placebo-CPAP.

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INTRODUCTION

CONTINUOUS POSITIVE AIRWAY PRESSURE (CPAP) IS CONSIDERED TO BE THE MOST EFFECTIVE AND THE PREFERRED THERAPY FOR OBSTRUCTIVE SLEEP APNEA (OSA). In placebo-controlled and uncontrolled studies, CPAP has been shown to correct the elevated apnea-hypopnea index (AHI) and the transient desaturations associated with respiratory events during sleep.1-4 In uncontrolled studies, CPAP has also been shown to improve daytime sleepiness,5 mood,6 cognitive function,7 quality of life,8 and cardiovascular function in patients with OSA.9 In 1 controlled study of subtherapeutic CPAP, CPAP was effective in reducing excessive daytime somnolence and improving self-reported well-being.10 However, the effects of CPAP in improving sleep quality in OSA have been less consistent.1,12 Patients with OS generally have poor sleep quality, characterized by short sleep latency, increased stage 1 sleep, decreased rapid eye movement (REM) sleep and slow-wave sleep (SWS), poor sleep efficiency, and frequent sleep fragmentation caused by transient arousals. We were surprised to find that only 2 randomized placebo-controlled trials have evaluated the effectiveness of CPAP in improving sleep quality. We previously reported that, in patients with severe OSA, a 1-week trial of CPAP was not different from placebo-CPAP (CPAP at a subtherapeutic pressure) in improving sleep architecture, except for improvement in arousal index.1 More recently, McArdle and Douglas reported improvements in stage 1 sleep, SWS, and the arousal index after 4 weeks on CPAP but no improvement in REM sleep in a randomized cross-over study utilizing an oral capsule as placebo.12 In 1997, in a systematic review of the sleep literature, the effectiveness of CPAP as a treatment for OSA was called into question because of the dearth of studies using adequate placebo-CPAP controls.13 This review highlights the need for rigorously controlled studies, which are still all too few in the field of sleep medicine. We therefore designed a study to further evaluate the effects of CPAP on sleep quality in patients with OSA, comparing it with a placebo-CPAP that delivered virtually no CPAP pressure.

The effect of supplemental oxygen on sleep architecture in patients with OSA has not been rigorously studied against CPAP or placebo-CPAP controls. In some patients with OSA who cannot tolerate CPAP and are not candidates for a surgical procedure, supplemental oxygen therapy has been used in an attempt to reverse the harmful effects of the transient hypoxemia during sleep.14,15 Nocturnal supplemental oxygen has been suggested by some as an alternative therapy in the patient with OSA who is not somnolent or not compliant with CPAP.15,16 Most studies evaluating supplemental oxygen in OSA have included only a few patients, had mixed results, and used nasal canulas to deliver oxygen, and few have evaluated the effect of supplemental oxygen on sleep architecture in OSA.15-18 To our knowledge, the combination of placebo-CPAP with oxygen, to allow for a more-precise and needed comparison with CPAP therapy, has not been reported.

The aim of this study was to evaluate the effectiveness of CPAP or supplemental oxygen, delivered via placebo-CPAP set-up, on sleep quality in patients with OSA in a randomized double-blind placebo-CPAP–controlled trial after 1 day and after 2 weeks of treatment.

Disclosure Statement
This was not an industry supported study. Dr. Ancoli-Israel has participated in speaking engagements supported by Takeda, Sepracor, Neurocrine/Pfizer, and Sanofi-Aventis; and is a consultant for Neurocrine/Pfizer. Drs. Loredo, Kim, Lim, and Dimsdale have indicated no financial conflicts of interest.

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Address correspondence to: Dr. José S. Loredo, UCSD Medical Center Dept. of Medicine, 200 West Arbor Drive, San Diego, CA 92103-0804; Tel: (619) 543-5593; Fax: (619) 543-7519; E-mail: jloredo@ucsd.edu

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METHODS

Subjects

All subjects gave informed consent, which was approved by the University of California San Diego Institutional Review Board. Seventy-six adult subjects suspected of having OSA were studied at the University of California San Diego General Clinical Research Center Gillin Laboratory of Sleep and Chronobiology (GCRC LSC) between 2000 and 2004. Subjects suspected of having OSA were recruited from the community and from local sleep laboratories by advertisement. Screening criteria included a history of chronic loud snoring with or without excessive daytime somnolence, aged 30 to 65 years, and weight between 1.0 and 2.0 times the ideal body weight, as determined from Metropolitan Life tables. Inclusion criteria also included having an AHI ≥ 15. Subjects were excluded if they were receiving medications known to affect sleep; if they had congestive heart failure, symptomatic obstructive pulmonary, coronary or cerebral vascular disease, a history of life-threatening arrhythmias, cardiomyopathy, a history of psychosis, narcolepsy, current alcohol or drug abuse; if they had previous surgery for the treatment of OSA; or if they had a periodic limb movement index (number of leg kicks per hour of sleep) ≥ 15 on baseline polysomnography (PSG). In the study interval, 413 subjects were screened for this study, 337 were ineligible, and 76 agreed to participate. Subjects received a modest honorarium for their participation.

Experimental Design

Subjects who potentially had OSA were prescreened with an unattended overnight home sleep study using the Stardust (Respirronics, Inc., Marietta, GA) home sleep-recording system. Subjects who were suspected of having significant OSA based on the home recordings were evaluated for sleepiness with the ESS,20 and were admitted to the GCRC LSC for a confirmatory overnight full-PSG sleep recording. If the PSG recording revealed an AHI ≥ 15, the subject was admitted to the GCRC LSC for 2 additional nights. The same team of nighttime technicians and daytime technicians performed and scored the PSGs under the direction of the lead author.

On the second night of admission, qualifying subjects were randomly assigned in a double-blind fashion to receive traditional nasal CPAP, placebo-CPAP, or supplemental oxygen at 3 L per minute, delivered via placebo-CPAP set-up. The technicians who scored the sleep studies and the investigators were blinded to the randomization assignments.

Equipment for all treatment arms was similar, consisting of a CPAP generator, CPAP mask and tubing, heated humidifier (Fisher and Pykel HC100, Auckland New Zealand), and oxygen concentrator (Alliance, Healthdyne Technologies Model 505, Marietta, GA) that could be switched to produce room air with the flick of a hidden switch, as indicated. The supplemental gas was introduced into the CPAP system at the level of the humidifier.

Subjects randomly assigned to CPAP received active CPAP plus an oxygen concentrator that provided room air. Those assigned to placebo-CPAP received subtherapeutic CPAP (CPAP < 1 cm H2O at the mask) plus an oxygen concentrator that provided room air. Finally, those assigned to nocturnal supplemental oxygen received subtherapeutic CPAP plus an oxygen concentrator delivering oxygen at 3 L per minute. Supplemental oxygen with placebo-CPAP produced an FiO2 of 32% to 34% at the CPAP mask.

A modified version of the sham-CPAP system reported by Farre et al23 was used for the placebo-CPAP. A modified CPAP mask containing ten .25-inch drill holes to allow for adequate gas exchange with room air was used while the CPAP pressure was set at a constant 3 cm H2O. A pressure reducer, with a 3-mm orifice, was placed in the CPAP tubing between the CPAP unit and the modified CPAP mask. With this system, the pressure at the CPAP mask was 0.5 cm H2O at end expiration and 0 cm H2O during inspiration, and the patient was able to feel a gentle breeze at the nose. The noise level of real CPAP plus the oxygen concentrator was not perceptibly different than that of placebo-CPAP and oxygen concentrator.

In the CPAP-treated group, optimal effective nasal CPAP pressure to minimize sleep apnea was obtained by conventional manual overnight CPAP titration during monitoring with PSG, as has been previously described.1 The patient was fitted with an appropriate-size CPAP mask (Respirronics Profile Light). After generic orientation, the patient was allowed to fall asleep at a CPAP of 4 cm H2O. CPAP was increased in 1- to 2-cm H2O increments until the respiratory events and snoring were abolished. The titration was considered ended when most respiratory events were controlled while the patient was in the supine position and in the second or third REM sleep period, or until a CPAP of 20 cm H2O had been reached. If the AHI was > 10 per hour, the CPAP therapy was considered suboptimal, and the patient was discharged from the study (all subjects randomly assigned to CPAP had an effective titration, and none reached a CPAP of 20 cm H2O).

Subjects assigned to placebo-CPAP and supplemental oxygen were oriented to the mask and equipment in the same way as the CPAP group and underwent a mock titration.

PSG was repeated on the third night of admission as subjects slept with their assigned treatment. During this time, the patients had time to adjust to CPAP in an observed environment and had their questions answered. The next morning, subjects were discharged home and instructed to use their assigned treatment (CPAP, placebo CPAP, or supplemental oxygen) during sleep for 2 weeks. Research staff was in frequent telephone contact with subjects to answer questions and check and encourage compliance with the therapy. All CPAP units (Aria LX CPAP System, Respironics Inc., Murrysville, PA) had a hidden compliance clock.

After 2 weeks of treatment, the subjects were readmitted to the GCRC LSC to undergo a fourth overnight PSG with their assigned treatment. The ESS was repeated. To verify the effectiveness of the blinding process, before discharge from the study, the subjects were asked what they thought their treatment assignment was.

Sleep Recordings and Sleep-Quality Variables

Sleep was recorded using the Grass Heritage, (model PSG36-2, West Warwick, RI) sleep-recording system, which recorded central and occipital electroencephalogram, bilateral electrooculogram, submental and tibialis anterior electromyogram, electrocardiogram, nasal airflow (nasal cannula and pressure transducer), oral airflow (thermistor), respiratory effort (chest and abdominal piezoelectric belts), and oxyhemoglobin saturation (SpO2).

Sleep staging was scored according to the criteria of Recht-
Arousal definition was based on the criteria published in the 1992 American Sleep Disorders Association report on electroencephalogram arousals. An arousal from sleep was described as a sudden rise in electroencephalographic frequency to alpha or theta for 3 seconds or longer but less than 15 seconds, whether or not associated with a rise in electromyographic activity, the abrupt appearance of K complexes or a burst of delta activity before an arousal was scored as part of the arousal only if accompanied by superimposed alpha electroencephalographic frequency. The total arousal index was calculated by dividing the total number of arousals by the total sleep time.

Apneas were defined as decrements in airflow of 90% or more from baseline for a period at least 10 seconds. Hypopneas were defined as decrements in airflow of at least 50% but less than 90% from baseline for a period at least 10 seconds. Airflow was measured using a pressure transducer and thermistor simultaneously. Apneas and hypopneas were differentiated based on the presence or absence of airflow below baseline.

Statistical Analysis

Eleven commonly measured variables from PSG were used to describe sleep quality (Table 2). The ESS score was evaluated as a secondary outcome. Data not normally distributed underwent natural log transformation before analysis. Differences between and within the 3 treatment groups over time were assessed using repeated-measures analysis of variance (2-way analysis of variance). Daily average treatment duration was included as a covariant to control for compliance. An α value of .05 was considered significant. Statistical analyses were performed using the SPSS statistical software packages (SPSS for Windows 11.0; SPSS Inc.; Chicago, IL).

RESULTS

Of the 76 subjects admitted for testing, 2 were excluded from the study due to medical illnesses, and 2 were excluded because of an AHI less than 15 per hour. Three subjects were removed from the study due to inability to sleep with or intolerance of CPAP equipment. One subject was excluded because of a periodic limb movement index during sleep > 15. Five subjects were removed from the analysis because they did not complete the study protocol. The final sample included 63 subjects with an AHI ≥ 15.

Baseline Measurements

Table 1 provides the subjects’ characteristics. The subjects were predominantly men (79%) and were obese, with an average

Table 1—Characteristics of Subjects by Treatment Group Prior to Randomization

<table>
<thead>
<tr>
<th>Variables</th>
<th>Placebo</th>
<th>CPAP</th>
<th>Supplemental O2</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>19</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>Men/women</td>
<td>16/3</td>
<td>18/4</td>
<td>16/6</td>
</tr>
<tr>
<td>Age, y</td>
<td>48.3 ± 11.2</td>
<td>48.2 ± 10.9</td>
<td>42.4 ± 8.6</td>
</tr>
<tr>
<td>(31–65)</td>
<td>(29 – 65)</td>
<td>(30 – 65)</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>31.8 ± 6.8</td>
<td>31.8 ± 5.5</td>
<td>32.0 ± 6.4</td>
</tr>
<tr>
<td>(23.4 – 50.2)</td>
<td>(23.1 – 44.0)</td>
<td>(23.4 – 52.0)</td>
<td></td>
</tr>
<tr>
<td>ESS score</td>
<td>12.3 ± 6.7</td>
<td>11.6 ± 4.9</td>
<td>12.8 ± 4.5</td>
</tr>
<tr>
<td>(0 – 23)</td>
<td>(2 – 22)</td>
<td>(0 – 21)</td>
<td></td>
</tr>
<tr>
<td>Mean BP, mm Hg</td>
<td>126.7 ± 16.6</td>
<td>134.8 ± 15.7</td>
<td>132.3 ± 13.3</td>
</tr>
<tr>
<td>Systolic</td>
<td>(102 – 161)</td>
<td>(111 – 163)</td>
<td>(113 – 162)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>77.2 ± 10.3</td>
<td>79.7 ± 8.8</td>
<td>78.8 ± 9.7</td>
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<tr>
<td>(57 – 96)</td>
<td>(61 – 96)</td>
<td>(64 – 105)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2—Baseline Sleep Characteristics by Treatment Group

<table>
<thead>
<tr>
<th>Variables</th>
<th>Placebo</th>
<th>CPAP</th>
<th>Supplemental O2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total sleep time, min</td>
<td>338.2 ± 38.7</td>
<td>347.8 ± 47.8</td>
<td>358.4 ± 53.6</td>
</tr>
<tr>
<td>Sleep efficiency, %</td>
<td>83.1 ± 7.2</td>
<td>80.7 ± 11.4</td>
<td>83.8 ± 11.3</td>
</tr>
<tr>
<td>Sleep latency, min</td>
<td>9.7 ± 6.9</td>
<td>7.7 ± 5.2</td>
<td>9.3 ± 14.5</td>
</tr>
<tr>
<td>Sleep stage, %</td>
<td>17.9 ± 11.4</td>
<td>19.5 ± 9.3</td>
<td>19.0 ± 12.4</td>
</tr>
<tr>
<td>Stage shifts/night, no.</td>
<td>194 ± 68</td>
<td>200 ± 75</td>
<td>206 ± 65</td>
</tr>
<tr>
<td>AHI, no./h</td>
<td>57.5 ± 32.1</td>
<td>65.9 ± 28.6</td>
<td>64.9 ± 33.7</td>
</tr>
<tr>
<td>Mean SpO₂, %</td>
<td>92.9 ± 4.4</td>
<td>93.2 ± 4.0</td>
<td>92.6 ± 5.0</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD. There was no statistically significant difference between treatment groups. CPAP refers to continuous positive airway pressure; SWS, slow wave sleep (stage 3 + stage 4 sleep); AHI, apnea hypopnea index; SpO₂, oxyhemoglobin saturation during total time in bed by pulse oximeter.
On average, subjects had a body mass index of 31.8 ± 6.1 kg/m². On average, subjects had significant excessive daytime somnolence at baseline, as reflected by the ESS score of 12.2 ± 5.4. There were no significant differences at baseline between groups in age, body mass index, ESS score, or screening blood pressure.

There were no significant differences in the baseline sleep-quality characteristics for the 3 treatment groups (Table 2). On average, the subjects had severe OSA with severe sleep fragmentation, as noted by severely elevated AHI and total arousal index.

### Compliance With Therapy

Compliance with the treatment assignment was similar for all treatment groups (6.61 ± 1.19 hours, 5.98 ± 1.27 hours, and 6.60 ± 1.19 hours for the CPAP, placebo-CPAP and oxygen groups, respectively). The mean effective titrated CPAP was 11.0 ± 3.7 cm H₂O (range 7-19 cm H₂O) for the CPAP-treated group. Approximately one third of the subjects on placebo or supplemental oxygen felt they were receiving CPAP or subjectively felt better. Approximately one third of the subjects had no opinion as to their therapy assignment, and one third were able to correctly guess their treatment assignment at completion of the study.

### Table 3—Changes in Percentages of SWS and Stage 2 sleep With CPAP, Supplemental Oxygen, and Placebo-CPAP

<table>
<thead>
<tr>
<th>Condition</th>
<th>Baseline</th>
<th>After 1 day</th>
<th>After 2 wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of SWS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>4.1 ± 5.1</td>
<td>5.9 ± 6.4</td>
<td>4.7 ± 5.8</td>
</tr>
<tr>
<td>CPAP</td>
<td>5.0 ± 6.9</td>
<td>11.5 ± 10.0</td>
<td>7.1 ± 6.2</td>
</tr>
<tr>
<td>Oxygen</td>
<td>7.3 ± 11.3</td>
<td>7.8 ± 9.2</td>
<td>6.9 ± 9.5</td>
</tr>
<tr>
<td>Percentage of Stage 2 sleep</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>62.7 ± 8.2</td>
<td>61.9 ± 10.1</td>
<td>62.2 ± 9.0</td>
</tr>
<tr>
<td>CPAP</td>
<td>61.3 ± 9.2</td>
<td>56.8 ± 10.8</td>
<td>61.1 ± 9.2</td>
</tr>
<tr>
<td>Oxygen</td>
<td>58.6 ± 12.1</td>
<td>59.0 ± 14.8</td>
<td>59.0 ± 14.4</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD. There was no statistically significant difference between treatment groups over time. CPAP refers to continuous positive airway pressure; SWS, slow-wave sleep.

Figure 1—Time plots of the effectiveness of continuous positive airway pressure (continuous positive airway pressure [CPAP], closed circles), supplemental oxygen (opened squares), and placebo-CPAP (opened circles), on correcting sleep architecture sleep-quality variables. Values represent mean ± standard error of the mean. (A) Percentage of stage 1 sleep (Stage 1 %) is improved to near normal by CPAP. (B) Percentage of stage rapid eye movement sleep (REM %) is improved to normal limits by CPAP. (C) Number of stage shifts per night is significantly reduced by CPAP. (D) Total arousal index (TAI) improved to within normal limits with CPAP. Supplemental oxygen at 3 L/min had no effects on sleep architecture. The effects of CPAP were apparent during the first night of therapy. *Denotes statistically significant change from placebo-CPAP.
Effect of Treatment on Sleep Architecture and Arousals

On repeated-measures analysis of variance, there was a significant group-by-time interaction for percentage of stage 1 sleep (p = .001), percentage of REM sleep (p < .001), total arousal index (p < .001), and number of sleep-stage shifts per night (p = .032). There were no group-by-time interactions for percentages of stage 2 sleep or SWS (Table 3), sleep latency, total sleep time, or sleep efficiency.

On posthoc analyses, CPAP, as compared with the placebo-CPAP or supplemental oxygen, significantly reduced the percentage of stage 1 sleep (p ≤ .006), number of stage shifts per night (p ≤ .004), total arousal index (p ≤ .001), and significantly increased the percentage of REM sleep (p ≤ .003), both after 1 and after 14 days of therapy (See Figure 1).

Effect of Treatment on Respiratory Parameters During Sleep

On repeated-measures analysis of variance, there was a significant group-by-time interaction for AHI (p < .001) and mean nocturnal SpO2 (p = .002). On posthoc analyses, CPAP, as compared with the placebo-CPAP or supplemental oxygen, significantly reduced AHI (p < .001) both after 1 and after 14 days of therapy. CPAP and supplemental oxygen significantly increased the mean nocturnal SpO2 (p ≤ .01) (See Figure 2).

Effect of Treatment on Daytime Somnolence

On repeated-measures analysis of variance, there was a borderline significant time effect on the ESS score before and after therapy (p = .076), suggesting that excessive daytime sleepiness decreased with time for all treatment groups. There was no significant treatment effect or time-by-treatment interaction on ESS. However, only the CPAP group had a mean ESS score that was less than 9 after 2 weeks of therapy (8.2 ± 4.4, 10.0 ± 4.5, 10.6 ± 6.4, for CPAP, placebo-CPAP, and oxygen, respectively).

DISCUSSION

The effects of CPAP or supplemental oxygen in improving sleep quality in OSA have not been rigorously tested against an adequate placebo-CPAP, as is required in an evidenced-based approach. The lack of rigorously controlled studies is a decided limitation for advancing the knowledge base in sleep medicine. In this study, we looked at the short-term changes in sleep architecture with CPAP and supplemental oxygen and present evidence that, in a randomized, prospective, placebo-CPAP-controlled, double-blind trial, CPAP was associated with an improvement in sleep quality by decreasing stage 1 sleep and stage shifts, increasing REM sleep, and reducing the total number of arousals. Surprisingly, CPAP had no effect on SWS, stage 2 sleep, or other sleep parameters, suggesting that CPAP was only partially effective in improving sleep architecture in our sample population of patients with OSA. As previously shown by controlled and uncontrolled studies, CPAP was completely effective in correcting AHI and mean nocturnal SpO2 in subjects with severe OSA (Figure 2). Supplemental oxygen, as a therapy for OSA, was only effective in correcting mean nocturnal SpO2 and had no significant effect on any other sleep variable (Figure 1 and 2).

CPAP is considered the most effective therapy for OSA. It is not unusual to encounter reported cases of remarkable improvements in excessive daytime sleepiness and well-being after just 1 night of CPAP. However, the strength of the evidence on the effectiveness of CPAP in correcting the physiologic derangements in sleep caused by OSA have been questioned. There is a general lack of well-designed and carefully controlled prospective studies to determine the true effectiveness of CPAP in improving sleep quality. In the current, study we used extreme care to ensure blinding and compliance with the treatment arms, allowing us to determine the effectiveness of both CPAP and supplemental oxygen in correcting sleep quality and respiratory physiology.

Effects of Treatment on Sleep Architecture and Arousals

Only the CPAP-treated group demonstrated significant improvements in sleep architecture and arousals. CPAP significantly reduced the percentage of stage 1 sleep and the number of sleep-stage shifts. CPAP also improved the percentage of REM sleep to
the normal range (Figure 1). These changes were noted after 1 day of therapy and were maintained at 2 weeks of therapy. The effect of CPAP on stage 1 and REM sleep appears to be the result of its effectiveness in correcting AHI and arousals. Apneic events are known to result in sleep fragmentation by increasing the number of arousals, which leads to greater proportions of stage 1 sleep and less REM sleep. We previously reported no significant improvement in sleep architecture after a 1-week CPAP trial compared with a subtherapeutic CPAP control (CPAP at 2 cm H2O), in a study with a design similar to the current one. It is unclear why we did not see improvements in sleep architecture with CPAP in our prior study. However, a possible explanation is that the subtherapeutic placebo-CPAP was not sufficiently subtherapeutic and, rather, had a significant therapeutic effect on sleep architecture. In the current study, the placebo-CPAP used provided less than 0.5 cm H2O of pressure at the nasal interface at end expiration and 0 cm H2O of pressure during inspiration.

McArdle and Douglas published the only other placebo-controlled trial in the literature that specifically studied the effectiveness of CPAP in correcting sleep architecture in OSA.12 They used an oral capsule-placebo versus CPAP for 1 month in a cross-over design. Similar to the current study, they found that CPAP reduced stage 1 sleep and the arousal index and had no effect on sleep efficiency. However, opposite to our findings, they found improvement in SWS and no improvement in REM sleep. These differences are not likely explained by duration of treatment trial, since, in the current study and in uncontrolled studies, CPAP was effective in improving REM sleep and various other measures of sleep architecture even after a single night of therapy. Compliance with CPAP was more than 6 hours per night in the current study, as compared with 4.5 hours per night in the McArdle and Douglas study. Greater total sleep time allowing for more REM-sleep cycles could explain the correction of the percentage of REM sleep in the current study. Conversely, a shorter total sleep time in the McArdle and Douglas study could have overestimated SWS, since it primarily occurs in the first third of the sleep period. Another factor that could be contributing to the differing results in SWS include the crossover design in the McArdle and Douglas study that may have provided greater statistical power than our parallel design with a similar sample size. Regrettably, placebo studies in this area are extremely rare, and inconsistencies across these few studies will only be resolved by further replication.

Stage 2 sleep is the most abundant stage during normal sleep, ranging from 45% to 55% of total sleep time in young adults. Stage 2 sleep has recuperative effects on alertness, mood, and performance. In patients with untreated OSA, stage 1 and stage 2 sleep rise in an apparent compensation for the reduction in REM sleep and SWS. Therefore, with the correction of apneas with CPAP, we expected a reduction in stage 2 sleep. The lack of reduction in stage 2 sleep in this study was probably related to the lack of improvement in SWS. However, in our CPAP and placebo groups (mean age, 48 years), percentages of SWS and stage 2 sleep before and after treatment were low but within their age-related normative values (Table 3). Therefore, it is possible that a significant change in SWS and stage 2 sleep with CPAP may only be seen in younger patients with OSA and may, thus, explain the lack of response to CPAP in our population. Further research with age stratification is needed to clarify this point. This study looked at sleep-architecture changes based on in-laboratory PSG measurements. Therefore, the low percentage of SWS noted in our population could have been due to a laboratory effect. It is possible that sleep-quality patterns may be different when the patients sleep in their own homes and beds.

Effect of Treatment on Daytime Somnolence

In the current study, the effect of CPAP in decreasing the ESS score over time was not statistically different from placebo-CPAP or supplemental oxygen. Our results differed from those of Monserrat et al and Jenkinson et al, both of whom used a subtherapeutic placebo-CPAP similar to ours. They reported improvement in daytime sleepiness and function with a 6- and 4-week course of CPAP, respectively. Our findings also differ from those of McArdle and Douglas, who reported improvement in ESS score after 6 to 12 months of CPAP therapy. The significant difference in design between these studies and ours is the longer duration of CPAP therapy. It is possible that the ESS score takes longer than 2 weeks of CPAP to improve or, conversely, that the beneficial effects of placebo-CPAP attenuate over time.

The Effect of Supplemental Oxygen

Supplemental oxygen therapy for OSA has been recommended for those who are not able to tolerate CPAP and who are not surgical candidates. Several small uncontrolled or nonblinded studies (n = 4-21) that used supplemental oxygen to treat OSA have mixed results in overnight oxygenation and AHI. In general, supplemental oxygen, given at a flow ranging from 2 L to 4 L per minute, improved nadir saturation and, in some cases, improved mean saturation. In 2 studies, transtracheal oxygen decreased AHI and, in one study, supplemental oxygen was reported to be more effective than CPAP in improving oxygenation and hypopneas.

In the current study, supplemental oxygen given at a fixed flow of 3 L per minute through a placebo-CPAP set-up was highly effective in correcting only mean nocturnal oxyhemoglobin saturation (Figure 2). Supplemental oxygen had no effect on the AHI, on the total arousal index, or on any other sleep-architecture variable (Figures 1 and 2). Our findings are consistent with the hypothesis that increased respiratory effort and not transient hypoxemia causes arousals in OSA. The best example of such phenomena is the upper airway resistance syndrome, a variant of OSA, in which the patient experiences classically with frequent arousals but no transient hypoxemia. Also, hypoxia is a poor arousal stimulus in humans, both in non-REM and REM sleep. We chose supplemental oxygen at 3 L per minute because this is a commonly used flow as initial therapy for a number of illnesses, including OSA. It is unclear if a greater flow of oxygen would have resulted in improvements in other sleep-quality parameters. The variability of the outcomes in prior reports is most likely due to small study-sample populations, widely different study protocols, and lack of adequate blinding or controls, making it difficult to compare with our current findings. The combination of supplemental oxygen with placebo-CPAP, instead of the usual nasal cannula utilized in other studies, allowed for a more rigorous comparison between CPAP and supplemental oxygen.

The specific role of oxyhemoglobin desaturation in the pathophysiology of OSA has not been well elucidated. It is unclear if drops in SpO2 have any pathologic additive or synergistic interactions with apneas or arousals. However, there is strong
effectively improved, to within normal range, the mean SpO₂ as to what they had received. In the current study, the compliance CPAP. Approximately one third of the participants had no opinion oxygen felt subjectively better or felt that they had received real one third of the subjects receiving placebo-CPAP or supplemental CPAP was well tolerated, and, on exit questioning, approximately patient using CPAP undergoes, minus the CPAP. The placebo- a placebo set-up would replicate the actual experience that the feel is critical for a true placebo-CPAP model. We felt that such experienced a gentle breeze from the CPAP mask, which we is for sympathetic nervous system activation and hypertension seen in OSA. In the current study, supplemental oxygen effectively improved, to within normal range, the mean SpO₂ without affecting the AHI or total arousal index (see Figures 1 and 2). Our data suggest that supplemental oxygen could be used as a tool to separate the individual pathophysiologic effects of hypoxemia from those of apneas and arousals in OSA. The effectiveness of supplemental oxygen alone in preventing OSA-related cardiovascular complications is not known.

**Weaknesses and Strengths of the Study**

In this study, we carefully controlled for CPAP by using a placebo-CPAP set-up that was well accepted by the patient and provided less than 0.5 cm H₂O of pressure at the nose. Patients using placebo-CPAP or placebo-CPAP plus oxygen supplementation experienced a gentle breeze from the CPAP mask, which we feel is critical for a true placebo-CPAP model. We felt that such a placebo set-up would replicate the actual experience that the patient using CPAP undergoes, minus the CPAP. The placebo-CPAP was well tolerated, and, on exit questioning, approximately one third of the subjects receiving placebo-CPAP or supplemental oxygen felt subjectively better or felt that they had received real CPAP. Approximately one third of the participants had no opinion as to what they had received. In the current study, the compliance with all treatment arms was excellent (6.4 ± 1.2 hours per night), increasing the level of confidence in our findings.

A potential weakness in the current study was the relatively short duration of therapy (2 weeks). CPAP can often take longer than 2 weeks for proper adjustment. However, we purposely worked closely with the patients to ensure compliance and troubleshoot any problems arising with the various component of CPAP, resulting in a high level of compliance.

We used a parallel design in this study, which can be viewed as less powerful than a crossover design, as had been used by McArdle and Douglas. However, a crossover design would not have been appropriate when using placebo-CPAP, since going from real CPAP to placebo would potentially be quite obvious to the patient.

In a study such as ours, it would have been interesting to explore the changes produced by CPAP or oxygen on hypopneas of various definitions, ie, with or without an associated oxyhemoglobin desaturation. However, our definition of hypopneas did not allow for such an analysis.

Another limitation in the study design was the use of a fixed flow of oxygen to correct OSA-induced desaturations. In retrospect, titration of the supplemental oxygen to achieve a certain predetermined level of SpO₂ during respiratory events would have been more appropriate, since the degree of desaturation will vary with obesity, REM sleep, and pulmonary function.

**CONCLUSIONS**

In conclusion, CPAP therapy, when compared with placebo-CPAP, was associated with a rapid improvement in sleep quality by decreasing sleep-stage shifts, reducing stage 1 sleep, and improving REM sleep, which persisted throughout a 2-week treatment trial. CPAP also improved, to within normal limits, the respiratory and arousal abnormalities characteristic of OSA patients. The effectiveness of supplemental oxygen as a therapy for OSA was restricted to oxyhemoglobin saturation during sleep.

**REFERENCES**


