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# Dose–response relationship between CPAP compliance and measures of sleep apnea severity

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**Abstract**

**Background**: Obstructive sleep apnea is a prevalent condition with serious medical and psychosocial consequences. Nasal continuous positive airway pressure (CPAP) is the treatment of choice and has been shown to reduce the frequency of nocturnal respiratory events, improve sleep architecture, and decrease daytime sleepiness. However, little is known about the dose–response relationship between CPAP compliance and measures of sleep apnea severity. This study examined the relationship between level of CPAP compliance and change in polysomnographic measures of sleep apnea severity.

**Methods**: Twenty-three CPAP-naive OSA patients were studied. None had other major medical illnesses or were receiving antihypertensive medication. Sleep apnea variables were measured at baseline and after 1 week of treatment. Objective CPAP compliance was measured nightly and was defined as the average number of hours of use per night.

**Results**: Higher rates of CPAP compliance were linearly associated with significant reductions in the respiratory disturbance index ($R = 0.49$, $P = 0.017$), the oxygen desaturation index ($R = 0.48$, $P = 0.029$), and the arousal index ($R = 0.51$, $P = 0.016$).

**Conclusions**: These data suggest that increased CPAP compliance is linearly associated with reductions in sleep apnea severity such that greater reductions in apnea were seen with increased CPAP use. It should be noted that all patients were reasonably compliant (i.e. >4 h CPAP use/night) and that even within this range of reasonable compliance, there was a significant benefit with more as opposed to less compliance. These findings offer support to the current recommendation that CPAP be used during the total time in bed to optimize treatment of polysomnographic measures of sleep apnea. 

*Keywords*: Sleep apnea; Continuous positive airway pressure; Compliance; Dose–response; Treatment

## 1. Introduction

Obstructive sleep apnea (OSA) is a disorder characterized by repeated complete cessations and/or reductions of breathing during sleep [1]. The clinical effectiveness of CPAP [2] in treating OSA is well documented. Continuous positive airway pressure (CPAP) has been shown to reduce daytime sleepiness [3], reduce oxyhemoglobin desaturations [4], reduce heart rate and pulmonary pressure [5], improve cognitive performance [6], and increase health-related quality of life [7]. In addition, compliance with CPAP treatment has been shown to result in a significant reduction in physician claims and hospital stays [8].

The heart of any CPAP prescription is a titration pressure by time exposure. This matter of 'time' is problematic because: (a) so few patients use CPAP religiously all the night through, and (b) the literature is unclear about whether the benefits from CPAP exposure are linear or whether they occur only after a certain threshold number of hours. Unfortunately, compliance with CPAP is poor to the extent that any use greater than 4 h per night is operationally defined as 'good' compliance [9]. We wondered if the benefit of CPAP would be evident even without the admittedly restricted range of 'good compliance'.

Despite the multitude of studies done to date, relatively little is known about the dose–response relationship between CPAP compliance and sleep apnea severity, and consequently the minimum threshold compliance level for improving outcomes has not been established. The current recommendation is for patients to use CPAP continuously while asleep, including naps [10,11]. The recommendation is based on full and partial night CPAP withdrawal studies that have examined the effects of CPAP discontinuation. However, the withdrawal studies that have been performed to date have shown mixed results (see Table 1). Following 2–3 months of treatment, patients off of CPAP for 1 night had a significant worsening of apnea severity and daytime

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Table 1
Summary of studies examining the effects of CPAP withdrawal

| Author | Sample | Length of withdrawal | Results |
|---|---|---|---|
| Kribbs et al. [3] | 15 OSA pts (mean RDI = 56.6 at baseline) used CPAP for 2.5 months; objective mean use = 5.5 h/night | 1 night | Apnea worsened from tx (RDI = 2.5) to withdrawal (RDI = 36.8). MSLT levels also significantly worsened from tx (5.8 min) to withdrawal (2.8 min) |
| Sforza and Lugaresi [12] | 30 OSA pts used CPAP for 1 year; subjective compliance = 6.2 h/night | 1 night | Apnea worsened from tx (RDI = 1.3) to withdrawal (RDI = 61.1). MSLT levels worsened from baseline (9.8 min) to withdrawal (5.3 min), but no change was reported in subjective alertness |
| Collop et al. [13] | 12 men with OSA used CPAP for 6 weeks; objective compliance = 7.0 h/night | 1 night | No worsening of any measure of sleep apnea severity |
| Hers et al. [14] | 27 OSA pts used CPAP for 2–3 nights at low pressure (5 cm $H_2O$) for habituation | 1/2 night | Improvements seen in desaturations index (34.9–10.4) and movement arousal index (29.2–9.1); RDI not reported |

sleepiness [3]. Similarly, a study with a 1-year treatment period found that apnea severity and daytime sleepiness worsened after 1 night off of CPAP [12]. In contrast, no change in apnea level was seen following 1 night without CPAP after treatment for 6 weeks [13]. More recently, using a split-night procedure, Hers and coworkers found that reduced apnea levels did not change when subjects crossed-over from CPAP in the first half of the night to none on the second half [14]. The authors suggest that a carry over effect occurs that may explain why a large number of OSA patients apply CPAP for only part of the night or not every night.

Another way of investigating the dose–response relationship between CPAP compliance and sleep apnea severity is to examine the relationship between the change in sleep apnea and compliance level over a defined period of time. To our knowledge, only one randomized, controlled CPAP trial to date has reported on the relationship between compliance and measures of sleep apnea severity. In a sample of patients with mild sleep apnea, defined by a respiratory disturbance index (RDI) between 5 and 15, Engleman and coworkers found that higher compliance was associated with higher initial RDI and microarousal indices [15]. Though the authors speculate that those patients with more symptoms may use the machine to a greater extent, the implications of this study are unclear for those with moderate to severe sleep apnea.

The current study reports on the effect of CPAP compliance on sleep apnea severity in a sample of patients with moderate to severe sleep apnea. We previously reported that CPAP was effective in lowering the RDI and the number of arousals, and in raising the sleep arterial oxygen saturation ($SaO_2$), relative to a placebo group [16]. The purpose of this paper is to expand on those findings by examining the relationship between CPAP compliance and measures of sleep apnea severity. It was hypothesized that increased CPAP compliance would be linearly associated with greater reductions in sleep apnea severity, e.g. lower RDI, fewer arousals, and improved nocturnal oxygen saturation levels.

## 2. Methods

### 2.1. Participants

Twenty-three CPAP naive OSA subjects were studied at the University of California, San Diego (UCSD) Clinical Research Center (CRC). They ranged in age from 32 to 60 years and their weight was between 1.0 and 1.7 times ideal body weight (see Table 2). Subjects were excluded if they were receiving medications known to affect their sleep or if they had congestive heart failure, symptomatic obstructive pulmonary, coronary, or cerebrovascular disease, history of life-threatening arrhythmias, cardiomyopathy,

Table 2
Sample characteristics (mean ± SD; range)

| Characteristics | Baseline | Final | Change |
|---|---|---|---|
| Women/men (*n*) | 7/16 | – | – |
| Age (years) | 47.1 ± 8.4 (32–60) | – | – |
| BMI ($kg/m^2$) | 32.6 ± 5.0 (20.0–40.4) | – | – |
| RDI | 54.2 ± 25.5 (14.4–95.1) | 3.1 ± 3.7 (0–16.8) | −51.1 ± 24.5 (−12.9 to −93.3) |
| ODI | 46.5 ± 29.1 (4.2–94.1) | 2.5 ± 4.2 (0.2–18.8) | −44.0 ± 28.0 (−3.4 to −89.3) |
| Arousal index | 53.4 ± 25.8 (15.9–92.0) | 14.3 ± 9.2 (3.7–36.4) | −40.0 ± 28.1 (19.6 to −83.6) |
| CPAP | 10.2 ± 2.1 (6–14) | – | – |
| Compliance | – | 5.8 ± 0.86 (4.4–7.7) | – |

history of psychosis, narcolepsy, or were currently abusing alcohol or drugs. All participants gave informed consent to the protocol, which was approved by the UCSD Institutional Review Board.

### 2.2. Design

Potential OSA participants were pre-screened with an unattended overnight home sleep study (Nightwatch; Respironics Inc.; Pittsburgh, PA, USA). Subjects with an RDI (total number of apneas and hypopneas per hour of sleep) ≥20 were admitted to the CRC for confirmatory overnight polysomnography (PSG) sleep recording (first night of admission).

On the second night of the admission, qualifying subjects had CPAP pressure titrated to a level that reduced the RDI to less than 5. PSG was repeated with CPAP on the third night of the admission (after 1 night of partial treatment). Patients were discharged home for 1 week of continued CPAP treatment. The research staff was in frequent contact with the patients to answer questions about mask placement and to encourage compliance with the therapy. The subjects were readmitted to the CRC to undergo a fourth sleep study (with CPAP at the same initial pressure level) on the last day of the protocol (i.e. 1 week later).

### 2.3. Apparatus

The CPAP units (Horizon, model 7353D; DeVilbiss; Somerset, PA, USA) had a hidden compliance clock that measured the amount of time that the CPAP units were powered on. Compliance was defined as the average number of hours the machine was powered on per night over the course of the protocol. Compliance was measured on each of the protocol nights it was used.

### 2.4. Sleep recordings

Sleep in the CRC was recorded using a polysomnograph (Model 4412P; Nihon Koden; Irvine, CA, USA) that recorded central and occipital Electroencephalogram (EEG) derivations (C3, C4, O1, O2), bilateral electrooculogram (LOC and ROC), submental and anterior tibialis electromyogram (EMG), electrocardiogram (ECG), nasal/oral airflow using a thermistor, respiratory effort using chest and abdominal inductance belts, and finger pulse oximetry. Apneas were defined as decrements in airflow of ≥90% from baseline for a period of ≥10 s. Hypopneas were defined as decrements in airflow of ≥50% but ≤90% from baseline for a period of ≥10 s. The RDI was defined as the number of apneas plus hypopneas per hour of sleep.

$SaO_2$ was monitored using a pulse oximeter (Biox 3740; Ohmeda; Louisville, CO, USA) and was analyzed using computer software (Profox; Escondido, CA, USA) [17]. The oxygen desaturation index (ODI) was defined as the number of desaturations ≥4% per hour of sleep. Sleep records were scored according to the Rechtschaffen and Kales criteria [18].

The definition of an arousal from sleep was based on the criteria published in the 1992 American Sleep Disorders Association Report on EEG arousals [19] with some modifications. An arousal was defined as a shift in EEG frequency to alpha or theta ≥1.5 s but <15 s in duration whether or not it was associated with a rise in chin EMG amplitude, a rise in leg EMG activity, or both. An arousal could be scored only after 10 s of continuous sleep in the same or contiguous sleep epoch. A minimum of 10 s of intervening sleep was necessary to score a second arousal. Shifts in EEG frequency were scored from either or both of the EEG derivations (occipital or central). The abrupt appearance of a burst of K-complexes was scored as an arousal only if it was accompanied by an obvious shift in background EEG frequency. The total arousal index (ARI) was defined as the number of arousals per hour of sleep.

### 2.5. CPAP titration

The patients underwent standard CPAP titration with the use of a Devilbis CPAP machine with a comfortably fitting mask. Pressure in the mask started at 2 cm $H_2O$ and was increased by 2 cm $H_2O$ increments to abolish apneic episodes until a pressure of 8–10 cm $H_2O$ was reached. Further pressure titration was then done in increments of 1 cm $H_2O$ on the basis of the presence of apneas, hypopneas, or snoring associated with arousals. The titration was considered complete when most respiratory events were controlled with CPAP while the patients were in the supine position and either in the second or third rapid eye movement sleep period, or until a pressure of 20 cm $H_2O$ had been reached. All patients had their apnea treated within this pressure range.

### 2.6. Statistical analysis

Pearson correlation coefficient was used to examine the relationship between variables. Bivariate scatterplots are provided and include the line of best fit. Change variables were calculated by subtracting time 1 (sleep recording on night 1, the first full PSG recording) from time 2 (sleep recording on night 10 of protocol, after 1 week of treatment), such that large negative values indicate greater reductions in the variable of interest. All data analyses were performed using SPSS for Windows (v.9.0) [20].

## 3. Results

Our patient sample was composed of moderately obese individuals with moderate to severe sleep apnea. Table 2 shows the sample characteristics. Each subject was successfully titrated to an RDI <5. All patients complied well during the 1-week of treatment, with every CPAP utilization ranging from 4.4 to 7.7 h per night. We then calculated the relationship between these varying amounts of good

compliance with respiratory disturbance index (RDI), ARI, and ODI.

### 3.1. Change in respiratory disturbance index

Regression analyses found that $R$ was significantly different from 0 ($R = 0.492$; $F(1, 21) = 6.69$; $P = 0.017$), such that greater reductions in RDI were seen with increased CPAP use. The 95% confidence interval for the regression coefficient ($B = -13.95$, $t = -2.587$, $P = 0.017$) for the CPAP group did not include 0 (range: $-25.15$ to $-2.7$), confirming the statistical test. Fig. 1 shows the scatterplot including the line of best fit.

### 3.2. Change in oxygen desaturation index

Regression analyses found that $R$ was significantly different from 0 ($R = 0.477$; $F(1, 19) = 5.61$; $P = 0.029$), such that greater reductions in ODI were seen with increased CPAP use. The 95% confidence interval for the regression coefficient ($B = -15.81$, $t = -2.368$, $P = 0.029$) for the CPAP group did not include 0 (range: $-29.78$ to $-1.84$), confirming the statistical test. Fig. 2 shows the scatterplot including the line of best fit.

### 3.3. Change in arousal index

Regression analyses found that $R$ was significantly different from 0 ($R = 0.507$; $F(1, 20) = 6.927$; $P = 0.016$), such that greater reductions in ARI were seen with increased CPAP use. The 95% confidence interval for the regression coefficient ($B = -16.61$, $t = -2.632$, $P = 0.016$) for the CPAP group did not include 0 (range: $-29.78$ to $-3.45$), confirming the statistical test. Fig. 3 shows the scatterplot including the line of best fit.

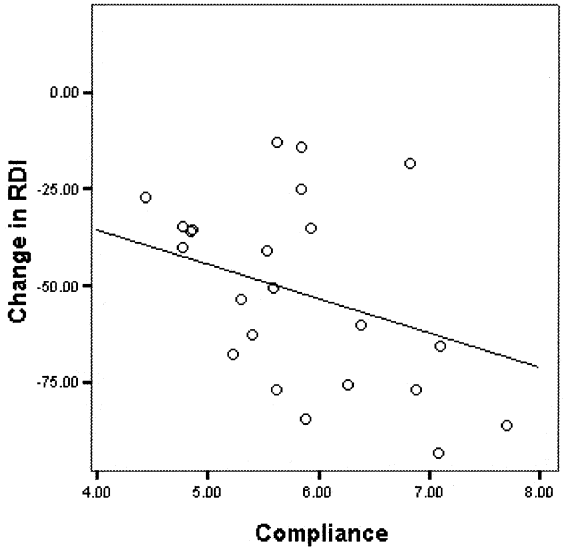


Fig. 1. Scatterplot of change in RDI by compliance. Scatterplot of the change in RDI (from sleep recordings done after 7 nights of CPAP to the pre-treatment night) compared to compliance (defined as the average number of hours used per night). Note that for change in RDI a greater negative number means greater reduction in RDI level. The line of best fit is defined as Change in RDI = 29.87 + (−13.94)* compliance.

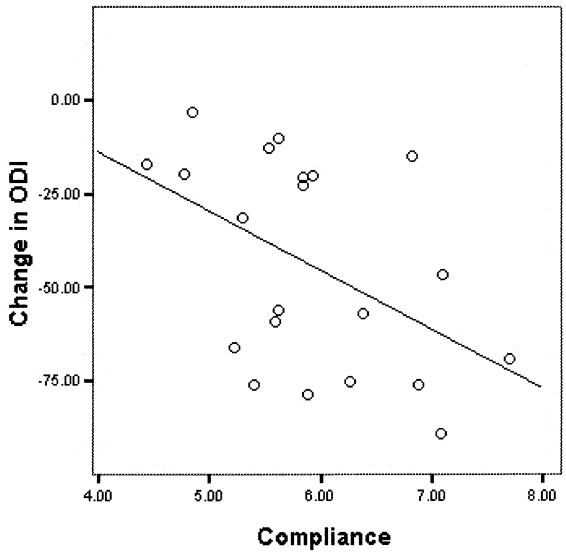


Fig. 2. Scatterplot of change in ODI by compliance. Scatterplot of the change in ODI (from sleep recordings done after 7 nights of CPAP use to the pre-treatment night) compared to compliance (defined as the average number of hours used per night). Note that for change in ODI a greater negative number means greater reduction in ODI level. The line of best fit is defined as Change in ODI = 49.25 + (−15.81)* compliance.

## 4. Discussion

No studies from randomized, controlled clinical trials of moderate to severe CPAP have reported on the relationship

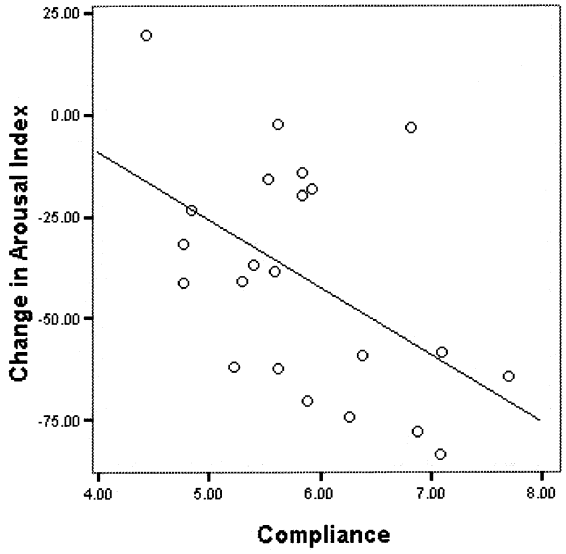


Fig. 3. Scatterplot of change in ARI by compliance. Scatterplot of the change in ARI (from sleep recordings done after 7 nights of CPAP use to the pre-treatment night) compared to compliance (defined as the average number of hours used per night). Note that for change in ARI a greater negative number means greater reduction in ARI level. The line of best fit is defined as Change in ARI = 57.2 + (−16.61)* compliance.

between CPAP compliance and measures of apnea severity. The results from this study have shown that higher rates of CPAP compliance were linearly associated with significant reductions in the number of respiratory disturbances per hour of sleep, the number of oxygen desaturations per hour of sleep, and the number of arousals per hour of sleep. These data offer preliminary support for the current recommendation that CPAP be used during the total time in bed to reduce polysomnographic measures of sleep apnea severity. Studies examining the relationship between amount of CPAP use and important sleep apnea symptoms will help evaluate the support for this recommendation.

Studies examining the effect of CPAP on sleep apnea to date have explored the effects of treatment withdrawal and group differences of CPAP on various measures of sleep apnea severity. The data from the present study offer an alternative way of evaluating the effect of CPAP on sleep apnea by focusing on the level of compliance as an independent variable. Effective CPAP dosing is based not only on both an appropriately titrated CPAP pressure, but amount of use, or compliance, as well. CPAP withdrawal studies have provided results on the effect of no treatment (i.e. no amount of CPAP use) on apnea measures after a defined period of continuous use. The data from the present study are able to address the effect of a range of CPAP use on sleep apnea over a 1-week period of time in first-time CPAP users. A better understanding of the effects of various levels of CPAP compliance is important so that accurate recommendations may be provided to patients. By their usage patterns, patients appear to be telling us that 4–5 h of use per night is 'enough'; sleep professionals recommend significantly more use per night and our data suggest that clear benefits are achieved by more complete compliance.

The results of the present study are based on subjects with moderate to severe sleep apnea who were compliant with CPAP. It should be noted that compliance in our study reflected a range of 4.4–7.7 h per night. It may be that the strength of the relationship between compliance and sleep apnea is affected by the inclusion of higher and lower ranges of compliance. It remains to be seen if these linear results generalize to patients who use CPAP less than 4 h or more than 8 h.

The mean compliance rate of 5.8 h per night in this study is higher than that reported in other studies performed in the USA [9,21]. One reason that may account for the relatively high compliance in this study was that compliance was calculated over the 10 nights that CPAP was used, including the nights of in-hospital monitoring. It is not unusual for participants to comply more when under observation, both when in the hospital setting and when part of a research study. However, no difference in the results would have been obtained had compliance been measured with just the at-home treatment. Compliance measured at home for 7 days (mean $= 5.6 \pm 1.1$) was highly associated with compliance for the 10-day study protocol (mean $= 5.8 \pm 0.86$; $r = 0.993$, $P < 0.0001$).

One potential limitation of the current study is that CPAP compliance was measured by the amount of time the machine was powered on, and not by time at prescribed pressure. However, three separate studies have shown that these two measures of compliance correlate in the 0.90 range in three separate studies [9,21,22]. Measuring the time that the machine is powered on appears to be an acceptable alternative to measuring the time at prescribed pressure.

Our study examined changes in sleep apnea after the first 1-week of CPAP treatment. We have recently commenced a similar trial that will study the impact of CPAP over a 2-week period of time, which may be able to address a broader range of compliance levels. Further, studies that systematically examine the effects of various CPAP compliance levels on measures of sleep apnea severity and important outcomes need to be done to better understand the gap between actual and recommended CPAP use.

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