Effects of Short-Term CPAP Withdrawal on Neurobehavioral Performance in Patients With Obstructive Sleep Apnea

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Study Objective: Changes in sleep parameters and neurobehavioral functioning were systematically investigated after an acute (1 night) and short-term (7 nights) period of withdrawal from continuous positive airway pressure (CPAP) treatment and 1 subsequent night of CPAP reintroduction in patients with obstructive sleep apnea.

Design: Repeated-measurement within-subject design.

Setting: Sleep laboratory, university teaching hospital.

Participants: Twenty participants receiving optimal CPAP therapy for ≥ 12 months.

Interventions: CPAP withdrawal.

Measurements and Results: Polysomnograms were performed on Night 0 (with CPAP), Night 1 and Night 7 (without CPAP) and Night 8_R (with CPAP). Acute CPAP withdrawal resulted in the recurrence of sleep-disordered breathing with sleep disruption, hypoxemia, and increased subjective sleepiness. Short-term CPAP withdrawal exacerbated hypoxemia, increased subjective and objective sleepiness and poor mood ratings. Neurobehavioral functioning assessed using the Psychomotor Vigilance Task was impaired following Night 7 and associated with hypoxemia and changes in morning levels of tumor necrosis factor-alpha. However, other neurobehavioral measures were not affected. Autonomic arousals measured via respiratory-related reductions in finger blood volume by peripheral arterial tonometry decreased from Night 1 to Night 7. On Night 8_R, reintroduction of CPAP treatment eliminated most airway obstruction, maintained oxygenation, and reversed daytime sleepiness and some vigilance decrements.

Conclusion: Despite recurrence of sleep-disordered breathing with increased sleepiness and impaired vigilance, most neurobehavioral variables were unaffected by CPAP withdrawal. The reduction in vigilance appeared to be associated with worsened hypoxemia and changed levels of tumor necrosis factor-alpha. Resumption of CPAP treatment had immediate benefits on sleep consolidation and subjective sleepiness.

Keywords: OSA, CPAP, cognitive function, neurobehavioral performance, autonomic activity

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INTRODUCTION

TREATMENT WITH CONTINUOUS POSITIVE AIRWAY PRESSURE (CPAP) CAN EFFECTIVELY MAINTAIN UPPER-AIRWAY PATENCY, ELIMINATE NOCTURNAL oxygen desaturation, and restore sleep quality.1,2 Regular CPAP use reduces symptoms of sleepiness and reverses some neurobehavioral dysfunction associated with obstructive sleep apnea (OSA),2,3 but compliance with this treatment is often poor and quite variable.3 Patients with OSA frequently withdraw from CPAP therapy for short periods because of side effects such as mask-related problems, nasal irritation,4 or long-distance travel.5 The effects of intermittent CPAP use on sleep and subsequent neurobehavioral function have not been systematically examined.

It has been demonstrated that 1 night of CPAP withdrawal results in a return of sleep-disordered breathing (SDB)6–14; however, the resultant increase in sleep apnea has been variable. Two of these studies6,15 also reported an increased sleep propensity with no effects on subjective sleepiness or daytime vigilance (Psychomotor Vigilance Task [PVT]).15,16 In these studies, following 412 and 7 nights of CPAP withdrawal,13 SDB returned to prediagnostic levels. It is difficult to infer from these results the time course over which both the severity and daytime performance decrement redevelop with recurrent OSA.

Given the potential for neurobehavioral deficits to accumulate across 1 week of sleep restriction16,17 and the impact on work performance, occupational safety, and risk of motor vehicle accidents, it is important to determine the neurobehavioral effects of more than 1 night of CPAP withdrawal. In addition, the effect of reintroducing CPAP treatment following CPAP withdrawal on performance and physiologic variables is not well understood. Using a model of short-term CPAP withdrawal, changes in neurobehavioral function can be assessed with concurrent changes in sleep and breathing that reflect those occurring with intermittent CPAP use. Furthermore, it may be important to assess additional nonconventional measures of sleep disturbance, for example autonomic arousals measured using peripheral arterial tonometry (PAT).18,19 Measuring such novel parameters may provide insight into the effects of CPAP withdrawal on daytime function in patients with OSA. Apart from these parameters, changes in neuro-immunologic factors such as tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) may mediate increased sleepiness in individuals with OSA.20

Disclosure Statement

This was not an industry supported study. Dr. Rogers has received research support from Cephalon Inc. Dr. Seale has received research support from GlaxoSmithKline, Astra Zeneca, Altana, Amgen, Pfizer, and Accrux; has received honoraria from Astra Zeneca, Boehringer Ingelheim, and Altana Pharma; has served on advisory boards for Boehringer Ingelheim, GlaxoSmithKline, and Altana; and has acted as a consultant to Novartis. Dr. Grunstein has received research support from Sanofi-Aventis, Cypress Biosciences, GlaxoSmithKline, Neurocrine, ResMed, Respiromics, Abbots Pharmaceuticals, and Cephalon, Inc. Drs. Yang, Phillips, and Melehan have indicated no conflicts of interest.

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The aim of the present study was to systematically assess acute (1 night) and short-term (7 nights) changes in sleep, breathing, and neurobehavioral functioning during CPAP withdrawal in patients with OSA receiving optimal, long-term CPAP treatment.

PARTICIPANTS AND METHODS

Participants

Twenty participants (19 men, 1 woman; mean age ± SD = 54 ± 13 years; mean body mass index [BMI], 36 ± 6 kg/m²) with moderate to severe OSA (respiratory disturbance index [RDI] ≥ 15) and a minimum of 12 months of CPAP treatment participated in this study. Participants responded to advertisements seeking good CPAP users (> 4 hours per night) for research in sleep centers or a patient support-group newsletter. The Ethics Review Committees of the Central Sydney Area Health Services and the University of Sydney, Australia approved this study (Protocol number X01-0135). Participants were excluded if they had residual apnea-hypopnea index >10 on Autoset® (ResMed, Sydney, NSW, Australia), any significant comorbidities, alcohol consumption (> 40 g alcohol daily), or concurrent treatment on psychotropic drugs or if they were shift workers. Participants had previously undergone diagnostic sleep studies (n=19) or diagnostic oximetry (n=1) at a number of sleep investigation centers. Mean RDI obtained from study reports at original diagnostic polysomnography (PSG), was 47 ± 27 per hour (range 15-120 per hour) and mean minimum oxygen desaturation (min SaO₂) was 68 %± 16% for 19 subjects. The BMI at original diagnosis was 34 ± 6 kg/m² for 18 subjects (p = .008 vs BMI at study commencement). Median treatment time was 4.0 ± 3.5 years (interquartile range) (range 1.5-13 years) with mean CPAP pressure at 12 ± 2.4 cm H₂O.

Study Design

Following a clinical interview, study participants were given an Autoset® CPAP machine, set at their prescribed fixed pressure. Treatment compliance and efficacy were assessed for at least 7 to 14 nights prior to study procedures. Eligible participants then came into the sleep laboratory for baseline assessment (Night 0). They completed an Epworth sleepiness scale (ESS) followed by a PSG recording with CPAP treatment. On the following night (Night 1), participants were withdrawn from CPAP therapy and underwent a second in-lab PSG. During nights 2 to 6, participants slept at home without CPAP treatment. During the period of withdrawal, participants were cautioned against long-distance driving or operating heavy machinery, and regular phone contact was maintained with the investigators. On Night 7, participants returned to the laboratory and completed a modified ESS followed by a third PSG without CPAP. On the final study night (Night 8_R), CPAP was reintroduced, starting at each participant’s prescribed pressure. After the first 7 subjects, it was noted that during Night 8_R, CPAP pressures had to be adjusted to completely control all upper-airway obstructions; therefore, pressure were titrated when required for subsequent subjects (n=8). CPAP pressure was titrated manually to eliminate any apneas, hypopneas, or obvious flow limitations. Time in bed was maintained between 10:00 PM to 11:30 PM and 6:00 AM for all 4 PSG nights.

Nocturnal PSG

Overnight PSG (E-series, Compumedics, Melbourne, Victoria Australia) was performed using standard techniques, with sleep stages, electroencephalogram (EEG) arousals (American Sleep Disorders Association), and respiratory events based on American Academy of Sleep Medicine-recommended criteria. Specifi- cally, an apnea was defined as complete cessation of nasal pressure-transducer signal for ≥ 10 seconds. A hypopnea was defined as a discernable reduction from baseline in nasal pressure-transducer signal amplitude for ≥ 10 seconds associated with either an oxygen desaturation of ≥ 3% or an EEG arousal.

Peripheral Arterial Tonometry

On Night 1 and Night 7 of CPAP withdrawal, participants had PAT (PAT-200™, Itamar-Medical Ltd, Caesarea, Israel) to specifically examine changes in finger sympathetic tone associated with recurrent apneas. Visually scored PAT events were defined as a transient reduction (> 20%) in pulse wave amplitude for ≥ 5 seconds relative to baseline. Baseline refers to the mean amplitude of pulse waves in the 10 seconds preceding the onset of the event. Only respiratory-related PAT attenuations were measured to ascertain autonomic responses to an obstructive event that may not be accompanied by a cortical EEG arousal and to exclude other types of arousal such as leg movements. The numbers of PAT-attenuated events per hour of sleep time was derived. PAT was not recorded in the first 5 participants because equipment was not available, and data from 3 participants were excluded due to technical problems, so data from 12 participants were analyzed.

Neurobehavioral Performance

Neurobehavioral Assessment Battery (University of Pennsylvania, Philadelphia) was administered at 8:00 AM, following Night 0, Night 1, Night 7, and Night 8_R. Performance was assessed using the PVT, serial additional and subtraction task (SAST), digit symbol substitution task (DSST), and probed memory recall (PRM). These performance tasks assessed attention and cognitive throughput, which is a measurement of accuracy or speed, reflecting the number of correct responses per unit of time and memory. The primary outcome variable used from the PVT was the reciprocal of reaction time (1/RT). Subjects rated their sleepiness and mood by questionnaires including the Karolinska Sleepiness Scale (KSS), Profile of Mood States (POMS), and visual analogue scale (VAS). Simulated driving performance was assessed immediately following each neurobehavioral testing (data to be submitted separately).

Data from subject #1 were excluded from analysis on the PVT as an extreme outlier (greater than 2 SD from the group mean). Data from subject number #2 for the DSST could not be analyzed due to a computer problem during data collection.

Sleepiness

Oxford Sleep Resistance Test was used to assess objective daytime sleepiness. This test was administered at 11:00 AM and 4:00 PM following each sleep study. Mean sleep latency was derived for each day. An ESS was administered at baseline to evaluate the subject’s global sleepiness level before CPAP withdrawal. On Night 7, a statement: “In the past week (since stopping CPAP therapy...)” was added to the instructions of the modified ESS.
Cytokine Assessment

Fasting venous blood samples were collected following each sleep study and centrifuged, with serum stored at -80°C for subsequent analysis. Acute phase inflammatory cytokines, TNF-α, and IL-6 levels were determined by high-sensitivity enzyme-linked immunosassay (ELISA, R and D Systems, Minneapolis, MN, catalogue #HSTA00C for TNF-α and HS600B for IL-6). The samples were analyzed in duplicate with an intrarun precision of 7% for both assays. The lower limit of detection for TNF-α was 0.12 pg/mL and for IL-6 was 0.039 pg/mL.

Statistical Analysis

Data were analyzed using SPSS (V12.01, SPSS, Inc., Chicago, IL), with mean ± SD or median ± interquartile ranges (IQR) reported. The normality assumption was assessed using the Shapiro-Wilk test. Repeated-measures analysis of variance (ANOVA) was used to examine changes in normally distributed PSG data, neurobehavioral performance variables, cytokines, and measures of sleepiness and mood. PAT indexes and ESS scores were assessed using paired t-tests. Non-normally distributed PSG, neurobehavioral, sleepiness, and mood variables were analyzed using Wilcoxon signed rank test. The Sharpened Bonferroni procedure was applied to correct for multiple comparisons.

Effect sizes were calculated (quoted as ‘d’ in Results) to assess the relative magnitude of observed differences on and off CPAP treatment. Effect size is interpreted using criteria described by Cohen: 0.2 represents a small relevant difference, 0.5 a moderate difference, and differences of 0.8 or higher are interpreted as a large difference.

Spearman rank correlation coefficient was used to examine the absolute change (from baseline) in PVT, KSS, and measures of sleep-disordered breathing (RDI), arousal index, (AI), the frequency of oxygen desaturations greater than 4% (SaO₂ ≥ 4%), sleep time with oxygen saturation below 90% (SaO₂ < 90%), and cytokines. Pearson correlation coefficient was used to examine (1) the influence of BMI on changes in PVT performance from Night 0 to Night 7 and (2) the concordance between cortical EEG arousals and autonomic PAT arousals on Night 1 and Night 7. Given the large number of correlations analyzed, adjusted values (significance level p ≤ .025 and trend p ≤ .05) were used to reduce Type I error. Two-tailed partial correlation was used to determine whether “age” influenced performance and sleep and breathing parameters. Where “age” was an effect modifier, younger participants (≤ 54 years) and older participants (over 54) were analyzed separately.

RESULTS

CPAP Compliance During the Screening Phase

Median CPAP treatment use (n=17) during the screening period, assessed using the Autoset T® CPAP machines, was 99.0% ± 0.0%, with mean mask-on time of 6.5 ± 0.9 hours per night. Optimal treatment efficacy was confirmed by an mean apnea-hypopnea index of 4.7 ± 3.1 per hour and mean mask leak at 0.35 ± 0.19 L per minute, which was considered minimal. The first 3 participants had routine polysomnographic CPAP review studies 1 month prior to their participation in the present protocol without evidence of residual sleep apnea and, subsequently, were not screened using an Autoset T® CPAP machine.

PSG variables from the 4 sleep studies are summarized in Table 1. Compared with Night 0, on Night 1, there was a significant increase in RDI, AI, and indexes of oxygen desaturations and a reduction in slow-wave sleep (SWS) and rapid eye movement (REM) sleep (all p values < .01). Changes in sleep architecture are illustrated in Figure 1.

Compared with Night 1, on Night 7, apnea-hypopnea duration lengthened with concomitant worsening of hypoxemia (min SaO₂, SaO₂ ≥ 4%, and SaO₂ < 90%, Table 1). Despite the worsened hypoxic nadir on Night 7, these levels were not as severe as those recorded at the original diagnosis (refer to Figure 2). Worsening of hypoxemia between Night 1 and Night 7 was not related to time spent in supine position during sleep (p > .05). There was no change in other variables such as RDI or AI.

One night of sleep with reintroduction of CPAP treatment following CPAP withdrawal (Night 8_R), eliminated most of the SDB and maintained oxygen levels similar to baseline levels (all p values > .05). For 8 participants, CPAP pressure was retitrated by an additional 1.1 ± 0.5 cm H₂O to completely abolish all upper-airway obstructive events on Night 8_R compared with Night 0. SWS and REM sleep increased, and there was a shorter latency to REM sleep compared with Night 0, Night 1, and Night 7 (all p values < .004).

Peripheral Arterial Tonometry

The PAT arousal index correlated closely with cortical EEG arousal index on both Night 1 (r = 0.721, p = .008) and Night 7 (r = 0.682, p = .015). However, the total number of PAT attenuations per hour of sleep decreased (p = .003) after 7 nights of CPAP withdrawal compared with the first night of treatment.
Table 1—Polysomnographic Variables at Baseline and Night 1 and Night 7 of CPAP Withdrawal Followed by a Recovery Night of Sleep With CPAP Treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>N0 Mean ± SD</th>
<th>N1 Mean ± SD</th>
<th>N7 Mean ± SD</th>
<th>N8_R Mean ± SD</th>
<th>N0-N1 Significance (p &lt; .05)</th>
<th>N0-N7 Significance (p &lt; .05)</th>
<th>N0-N8_R Significance (p &lt; .05)</th>
<th>N1-N7 Significance (p &lt; .05)</th>
<th>N1-N8_R Significance (p &lt; .05)</th>
<th>N7-N8_R Significance (p &lt; .05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RDI</td>
<td>2.7 ± 4.2</td>
<td>50 ± 28</td>
<td>50 ± 26</td>
<td>6.2 ± 12</td>
<td>.000</td>
<td>.000</td>
<td>NS</td>
<td>NS</td>
<td>.000</td>
<td>NS</td>
</tr>
<tr>
<td>AHD, s</td>
<td>19 ± 6.8</td>
<td>22 ± 3.8</td>
<td>26 ± 4.4</td>
<td>17 ± 9.0</td>
<td>.000</td>
<td>.000</td>
<td>NS</td>
<td>NS</td>
<td>.000</td>
<td>NS</td>
</tr>
<tr>
<td>Min SaO2, %</td>
<td>92 ± 1.8</td>
<td>85 ± 12</td>
<td>81 ± 13</td>
<td>92 ± 4.0</td>
<td>NS (.065)</td>
<td>.002</td>
<td>NS</td>
<td>.001</td>
<td>.013b</td>
<td>.001</td>
</tr>
<tr>
<td>SaO2 &lt; 90%*</td>
<td>0.0 ± 0.0</td>
<td>0.9 ± 6.1</td>
<td>4.0 ± 14</td>
<td>0.0 ± 0.0</td>
<td>.000</td>
<td>.000</td>
<td>NS</td>
<td>NS</td>
<td>.000</td>
<td>NS</td>
</tr>
<tr>
<td>SaO2 ≥ 4%*</td>
<td>2.0 ± 5.2</td>
<td>101 ± 151</td>
<td>225 ± 263</td>
<td>3.5 ± 9.0</td>
<td>.000</td>
<td>.000</td>
<td>NS</td>
<td>NS</td>
<td>.000</td>
<td>NS</td>
</tr>
<tr>
<td>AI</td>
<td>14 ± 8.4</td>
<td>46 ± 24</td>
<td>46 ± 22</td>
<td>12 ± 8.5</td>
<td>.000</td>
<td>.000</td>
<td>NS</td>
<td>NS</td>
<td>.000</td>
<td>NS</td>
</tr>
<tr>
<td>SE, %</td>
<td>88 ± 10</td>
<td>80 ± 13</td>
<td>83 ± 13</td>
<td>90 ± 11</td>
<td>NS (.052)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>.019</td>
<td>.033b</td>
</tr>
<tr>
<td>TST, min</td>
<td>358 ± 46</td>
<td>337 ± 57</td>
<td>340 ± 54</td>
<td>364 ± 54</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>SL, min</td>
<td>8.8 ± 9.4</td>
<td>11 ± 7.9</td>
<td>6.5 ± 9.1</td>
<td>7 ± 10</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>.017 NS</td>
</tr>
<tr>
<td>REM Latency, min</td>
<td>104 ± 51</td>
<td>146 ± 97</td>
<td>112 ± 51</td>
<td>53 ± 22</td>
<td>NS</td>
<td>NS</td>
<td>.000 NS</td>
<td>NS</td>
<td>.001</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD or median (interquartile range) for normally and nonnormally distributed data, respectively. Repeated-measures analysis of variance with Sharpened Bonferroni correction for multiple comparisons or Wilcoxon signed rank test were applied.

CPAP refers to continuous positive airway pressure; N0, baseline with CPAP; N1 and Night 7 N7 and N8_R, recovery night of sleep with CPAP treatment; RDI, respiratory disturbance index; AHD, mean apnea-hypopnea duration; min SaO2, minimum oxygen desaturation; SaO2 ≥ 4%, the oxygen desaturations greater than 4%, SaO2 < 90%, percentage of total sleep time in oxygen saturation below 90%; AI, arousal index; SE, sleep efficiency; TST, total sleep time; SL, sleep latency; REM, rapid eye movement sleep; s, seconds.

Figure 2—Changes in minimum oxygen desaturation (SaO2_min) at original diagnosis, at baseline (N0), during continuous positive airway pressure (CPAP) withdrawal (Night 1 [N1] and Night 7 [N7]) and at CPAP resumption (Night 8 [N8_R]). Effective CPAP therapy maintained oxygen saturation within normal range on Night 0 and Night 8_R. One night without CPAP treatment resulted in a decrease in oxygen saturation, and this worsened with longer time off treatment on Night 7. Although oxygen saturation dropped with recurrence of OSA, the magnitude of this change was still less severe than at the original diagnosis. "*" Represent the outlier with value more than 1.5-3 times above or below the box value or interquartile range. "**" Represent the extreme value, which is more than three times above or below the interquartile range.

Figure 3—Changes in total peripheral autonomic tonometry (PAT) arousals at Night 1 and Night 7. Total number of respiratory-related PAT attenuations decreased from Night 1 and Night 7 without continuous positive airway pressure (CPAP). This chart includes data for 12 of the 20 participants.

Cytokine Assessment

There were no significant changes to TNF-α (Night 0, 1.69 ± 0.49 vs Night 7, 1.64 ± 0.39 NS) or IL-6 (Night 0, 1.18 ± 0.61 vs Night 7, 1.14 ± 0.55, NS) following CPAP withdrawal or after CPAP reintroduction.

Neurobehavioral Performance

Compared with Night 0, on Night 7, there was a trend (p = .06) toward slower response speed (1/RT) and greater performance variability between the individuals. This is illustrated in Figure 4 by the large IQR and error bars. Effect size for this decline in vigilance (1/RT) between Night 0 and Night 7 was d = 0.49. Obesity did not influence the decline in PVT performance from Night 0 to Night 7 (p = .56). Also after Night 7, cognitive throughput (DSST) improved compared with Night 0 (p = .02). After Night 8_R, response time for cognitive throughput was shorter and participants spent less working time per symbol presentation (re-
response rate) compared with Night 0, Night 1, and Night 7 (all p < .04).

Relative to Night 0, slower response speed from the PVT was associated with increased number of desaturations (SaO_2 ≥4%) on Night 1 (rho = -0.487, p = .029) and on Night 7 (rho = -0.525, p = .025). Slower 1/RT on Night 7 was also associated with changes in circulating TNF-α (rho = -0.628, p = .004). A subanalysis between the older (> 54 years) and younger (≤ 54 years) participants showed that slower 1/RT with CPAP withdrawal tended to occur in younger participants with raised TNF-α levels from Night 0 to Night 7 (rho = -0.714, p = .047). No association was found between 1/RT and TNF-α in the older-subject group. Other measures such as the frequency of sleep-disordered breathing (RDI), EEG-based arousal index (AI), and IL-6 did not show any significant relationship with PVT response time.

**Subjective Sleepiness and Mood**

Compared with Night 0, 1 night of CPAP withdrawal resulted in an immediate increase in subjective sleepiness (KSS, p = .02), increased feeling of being unrefreshed (VAS, p = .01), trends for increased fatigue (POMS p = .08), and reduced vigor (POMS, p = .05) (shown in Table 2). After Night 7, scores for sleepiness, fatigue, and feeling unrefreshed were further increased (Night 0 vs Night 7, all p values < .01). Vigor reached the lowest level after Night 7 (p = .02). Relative to Night 0, global sleepiness measured by ESS increased (p = .04) after 7 nights of CPAP withdrawal (see Table 2). The increases in ESS were moderately correlated with the increase in RDI (rho 0.480, p = .032) and SaO_2 ≥4% (rho 0.490, p = .039) from Night 0 to Night 7. One night of recovery sleep with CPAP therapy decreased subjective sleepiness (KSS), feelings of being unrefreshed, and fatigue (Night 7 vs Night 8_R, all p values < .04) to levels equivalent to those seen at baseline (Night 0 vs Night 8_R, all p values > .05).

**Objective Sleepiness**

Compared with Night 0, mean sleep latency assessed by the Oxford Sleep Resistance Test was not affected following Night 1 but was significantly reduced after Night 7 (p < .004, shown in Figure 5). Specifically, sleep latency at 11:00 AM and 4:00 PM significantly decreased after Night 7 (Night 0 vs Night 7, all p values < .03). Across the withdrawal period (Night 1 to Night 7), mean sleep latency decreased, but this was not statistically significant after adjustment for multiple comparisons (p = .026). After 1 night of reintroduction of CPAP treatment, the mean sleep latency improved compared with Night 7 (p < .008) and was not different to those observed at baseline level (Night 0 vs Night 8_R, p > .1).

**DISCUSSION**

We examined a range of physiologic and neurobehavioral parameters to characterize the effects of both immediate and 7 nights of CPAP withdrawal and 1 night reintroduction of CPAP treatment. Although there was clear recurrence of SDB following CPAP withdrawal, most objective performance tasks were unaffected by 1 night or 7 nights of CPAP withdrawal. Vigilance was

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**Table 2**—Subjective Sleepiness and Mood States at Baseline and Night 1 and Night 7 of CPAP Withdrawal Followed by a Recovery Night of Sleep With CPAP Treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>N0 Mean ± SD</th>
<th>N1 Mean ± SD</th>
<th>N7 Mean ± SD</th>
<th>N8_R Mean ± SD</th>
<th>Significance (p &lt; .05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESS*</td>
<td>6.5 ± 8.0</td>
<td>N/A</td>
<td>14 ± 11</td>
<td>N/A</td>
<td>N/A .004 N/A</td>
</tr>
<tr>
<td>KSS</td>
<td>3.5 ± 1.6</td>
<td>4.6 ± 1.9</td>
<td>5.7 ± 2.1</td>
<td>3.9 ± 1.9</td>
<td>N/A .02b .001 NS</td>
</tr>
<tr>
<td>VAS</td>
<td>14 ± 7.2</td>
<td>21 ± 12</td>
<td>20 ± 10</td>
<td>15 ± 10</td>
<td>NS .005 NS NS .004</td>
</tr>
<tr>
<td>POMS-V</td>
<td>16 ± 7.2</td>
<td>14 ± 7.6</td>
<td>12 ± 8.1</td>
<td>15 ± 8.1</td>
<td>.05b .024 NS NS .05b</td>
</tr>
<tr>
<td>POMS-F</td>
<td>4.0 ± 6.0</td>
<td>6.0 ± 5.5</td>
<td>8.0 ± 13</td>
<td>4.8 ± 7.0</td>
<td>NS (.07) .027 NS .05b</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD or median (interquartile range)* for normally and nonnormally distributed data, respectively. Repeated-measures analysis of variance with sharpened Bonferroni correction for multiple comparisons or Wilcoxon signed rank test was applied.

*Not statistically significant after sharpened Bonferroni adjustment.

CPAP refers to continuous positive airway pressure; baseline with CPAP [N0]; Night 1 [N1] and Night 7 [N7] and N8_R, recovery night of sleep with CPAP treatment; ESS, Epworth Sleepiness Scale; VAS, visual analogue scale; POMS_V, profile of mood states in vigor subscale; POMS_F, profile of mood states in fatigue subscale.

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**Figure 4**—Mean reciprocal reaction time (1/RT) at baseline (N0), following Night 1 (N1) and Night 7 (N7) of continuous positive airway pressure (CPAP) withdrawal, and after recovery sleep with CPAP treatment (N8_R). The speed of the Psychomotor Vigilance Test (PVT) responses increased with CPAP withdrawal. However, due to large interindividual differences, the data were not statistically significant despite slower response time after both Night 1 and Night 7 nights off CPAP. These data represent 19 participants. Data from Subject #1 were excluded from the analysis as an extreme outlier.
Figure 5—Changes in the Oxford Sleep Resistance Test (mean sleep latency) at baseline (N0), during of continuous positive airway pressure (CPAP) withdrawal Night 1 (N1) and Night 7 (N7), followed by recovery sleep with CPAP treatment (N8 R). Changes in sleep latencies were analyzed using Wilcoxon signed ranks test. There was a decrease in mean sleep latency (MSL) after 7 nights of CPAP withdrawal. One night of recovery sleep increased MSL compared with Night 7, and this increase was not different to the levels observed at baseline. **N0 vs N7, p ≤ .03; †N7 vs N8 R, p ≤ .004; #N1 vs N7, NS after correction, p = .026. SL refers to sleep latency.

Changes in PSG Variables

Previous studies have reported that sleep apnea recurs immediately with 1 night of CPAP withdrawal to levels generally less severe than those found at original diagnosis. In the present study, we observed an RDI similar to their original diagnostic report but with less-severe minimum oxygen desaturation following 1 night of CPAP withdrawal. This finding suggests that chemosensitivity to hypoxemia may have improved in these patients after long-term CPAP treatment. These changes were not due to significant weight loss because BMI at study participation increased compared with BMI at original diagnosis.

There are no previous reports comparing 1 night with 7 nights of CPAP withdrawal; therefore, we compared PSG variables between the first night and the seventh night of withdrawal. There were further changes to some PSG measures but not others. For example, certain parameters such as the magnitude of minimum oxygen desaturation, frequency of desaturation ≥ 4%, and sleep time with oxygen saturation < 90%, as well as mean apnea-hypopnea duration, worsened. In contrast, the frequency of SDB, standard EEG-based arousals from sleep, and the amount of Stage 2 and REM sleep did not change from the first to the seventh night of CPAP withdrawal. These findings suggest that extended re-exposure to SDB reduces an individual’s arousability to hypoxemia such that, on Night 7, cortical arousals occurred at a much lower oxygen-saturation level compared with Night 1. Although night-to-night variability in sleep apnea could explain these findings, they are more likely due to impaired arousal responses secondary to intermittent hypoxemia, sleep fragmentation, and worsening upper-airway edema. In addition, the slight increases in CPAP pressures observed during reintroduction of CPAP treatment supports the hypothesis that the upper airway becomes edematous with CPAP withdrawal, thereby contributing to narrowing of the upper airway.

Consistent with previous studies, CPAP withdrawal altered sleep organization manifested as reduced time in SWS and REM sleep and increased amounts of Stage 1 and 2 sleep. Interestingly, no further changes in sleep architecture were evident with short-term CPAP withdrawal despite worsened hypoxemia. This finding suggests that sleep fragmentation may have disrupted the progression of non-REM and REM sleep cycles on Night 1 and Night 7. When CPAP was reintroduced on Night 8, a SWS and REM sleep rebound phenomenon occurred replacing sleep time in lighter sleep (Stage 1 and 2). This finding is consistent with studies reporting increased SWS duration following total sleep deprivation or sleep restriction. It appears that reintroduction of CPAP treatment eliminated sleep fragmentation and maintained sleep continuity, thereby enhancing sleep time in recuperative sleep stages. SWS and REM rebound is also indicative of the accumulation of sleep pressure over the short-term withdrawal period.

Changes in PAT

One night off CPAP with recurrent apnea evoked the expected response in finger vascular tone. Interestingly, however, PAT-defined autonomic arousals decreased between the first and last night of CPAP withdrawal, but this was not accompanied by a reduction in American Sleep Disorders Association-defined cortical arousals. Although previous studies have reported a reasonable agreement between autonomic (PAT) and cortical (EEG) arousals, data from this current study indicates that there may be a differential response to recurrent OSA between the brainstem and cortex region with CPAP withdrawal. In this context, exposure to intermittent hypoxia has shown different hypoxic susceptibility in cortical and brainstem regions of rats, and this may explain the different adaptation to hypoxic stimuli. Therefore, we speculate that there may be a central adaptation response to recurrent asphyxia in the brainstem autonomic neurons (influencing PAT responses) that is not present in cortical regions (influencing EEG-based arousals).

Changes in Performance and Symptoms

Most performance tests were unaffected by CPAP withdrawal. Trends in slower response time on the PVT were accompanied by a wide variation in performance after Night 7, suggesting that there was intraindividual variability in the neurobehavioral response to CPAP withdrawal. This finding is consistent with the trait differences observed following sleep restriction in healthy volunteers. Intraindividual variability has been recognized in cross-sectional studies on neurobehavioral effects of sleep apnea. Even rodents exposed to intermittent hypoxia as a model of sleep apnea have...
variable neurobehavioral and neurobiologic responses that may be related to age differences. Interestingly, there was an association between slower reaction times and changes in TNF-α with CPAP withdrawal, particularly in younger participants. We speculate that individuals who have greater cytokine responses to recurrent hypoxemia and sleep fragmentation may be more vulnerable when withdrawing from CPAP treatment. In this context, TNF-α is elevated after 1 week of sleep restriction in healthy humans and is associated with increased sleepiness and impaired performance. Further studies specifically examining the effect of short-term CPAP withdrawal and cytokine responses on sleepiness and performance in younger participants with severe OSA need to be performed.

Previous work has shown that individuals may have difficulty in recognizing their worsening sleepiness levels with progressive sleep loss. In the current study, with sleep fragmentation secondary to CPAP withdrawal, participants consistently reported increased subjective sleepiness and fatigue and decreased vigor that were also reflected in objective measures of sleepiness after Night 7 off treatment.

It was clear that 1 night of sleep with CPAP treatment following 7 nights of CPAP withdrawal effectively reversed subjective sleepiness to levels comparable with those observed at baseline. From a treatment-compliance perspective, these data may provide a potential reason for partial CPAP use commonly seen in patients receiving this therapy. Following cessation and resumption of CPAP treatment, deterioration and improvement in subjective sleepiness was rapid. In contrast, decline in neurobehavioral functioning appeared to be gradual and was affected by other factors, such as hypoxemia or age. It is possible that 1 night of sleep with CPAP therapy may produce sufficient benefits on subjective symptoms and subsequent daytime functioning to allow intermittent CPAP use in patients receiving long-term CPAP therapy.

To minimize learning effect from repeated testing, we did not monitor participants’ sleep and performance during the week of CPAP withdrawal. Therefore, we cannot determine the rate of deterioration in PVT performance during this period. It is possible that learning effect may have obscured differences with short-term CPAP withdrawal for performance tasks such as the DSST, whereas the PVT has been shown to be unaffected by learning or individual aptitude. In addition, we did not assess the changes in sleepiness and performance after 1 week of effective CPAP therapy following CPAP withdrawal. However, we did measure performance following a recovery night with CPAP resumption, and the results indicate that there was effective control of SDB and reversal of subjective symptoms.

Participant selection bias may exist in this study. Individuals who are compliant CPAP users may be reluctant to volunteer for this type of research if they have previously experienced marked negative symptoms with CPAP withdrawal. In addition, we had a clear sex bias toward investigating male participants. However, the overall patient selection and characteristics were representative of our clinic population in age, BMI, and background. By carefully excluding patients with less-than-optimal CPAP compliance, we may have amplified the effect of increased subjective sleepiness after treatment withdrawal. We felt it was important to establish that improved self-reported sleepiness persisted after long-term CPAP treatment and that any changes in sleepiness were not influenced by incomplete control of SDB. Although subject numbers in this study were small, the sample size was based on previous research. A crossover design comparing on-CPAP and CPAP-withdrawal weeks may have had methodologic weakness, such as determining the length of the “washout” from CPAP withdrawal and high drop-out rates from the study. Larger subject numbers in future studies, using this CPAP-withdrawal paradigm, may help to clarify the relationship between CPAP withdrawal, sleep, and performance. In addition this research model may be helpful in the design of crossover research studies comparing CPAP with other OSA therapies.

CONCLUSION

Our findings demonstrate that, after long-term CPAP treatment, the return of SDB following acute CPAP withdrawal was immediate. However, we found that the decline in hypoxemia was a gradual process with short-term withdrawal that may be reflected by modification of autonomic and chemosensory responses to recurrent apnea. Although subjective and objective sleepiness increased and mood decreased, most objective performance measures did not change after 7 nights of CPAP withdrawal. Age, hypoxia, changes in TNF-α, and interindividual differences were all significant determinants that contributed to decline in vigilance. Most cognitive function does not appear to be affected by short-term CPAP withdrawal in patients receiving long-term therapy. This withdrawal paradigm may be useful as an experimental model to better characterize the effects of hypoxemia, sleep fragmentation, and cytokines on physiologic and neurobehavioral function in OSA.

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