Prevalence of Persistent Sleep Apnea in Patients Treated With Continuous Positive Airway Pressure

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Study Objective: There are limited data on the prevalence of persistent obstructive sleep apnea (OSA) in patients who are clinically asymptomatic with continuous positive airway pressure (CPAP). Our objectives were to estimate the prevalence of persistent OSA and to explore the parameters that may be capable of discriminating these patients.

Design: Prospective survey.

Setting: A tertiary-care sleep-disorders clinic.

Participants: Consecutive patients treated with single-pressure CPAP for at least 3 months were studied. All had undergone CPAP titrations and were compliant with treatment. They denied snoring or persistent excessive daytime somnolence. Of 114 who qualified, 101 were studied.

Interventions: Subjects underwent 16-channel polysomnography with electroencephalogram and pneumotachometer while using their CPAP.

Measurements and Results: Seventeen of 101subjects (17%) had an apnea-hypopnea index of over 10. Fifty-one had only split-night protocols for CPAP titration. There was no significant difference between participants with persistent OSA and those with an apnea-hypopnea index < 5 with regard to age, sex, time since diagnosis, reported snoring, change in weight, or quality of life (all p > .10). Mean current CPAP level was higher, with a mean ± SD 10.6 ± 2.8 versus 8.6 ± 2.3 cm H_2O (p = .002). Unresolved air leak related to CPAP was more frequent in the patients with persistent OSA. Morning headaches, nonrestorative sleep, and frequent central apneas on the CPAP titration were all associated with persistent OSA.

Conclusions: Persistent OSA is frequent in patients treated with CPAP. This is more frequent in patients with high body mass index, higher prescribed pressures, and unresolved mask leak.

Keywords: Sleep apnea syndromes, sleep apnea, polysomnography, therapy

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INTRODUCTION

OVER THE PAST 20 YEARS, POPULATION-BASED STUDIES HAVE DOCUMENTED THE PREVALENCE AND THE WIDE RANGE OF SEVERITY OF OBSTRUCTIVE SLEEP apnea (OSA).[1] Some of these studies have found that even mild OSA is associated with significant morbidity, including increased cardiovascular risk when the apnea-hypopnea index (AHI) is 5 or more. Evidence from well-designed cohort studies indicates that untreated OSA, regardless of symptoms, is independently associated with increased likelihood of hypertension, cardiac events, stroke, daytime sleepiness, motor vehicle accidents, and lower quality of life. The most commonly used treatment of patients with OSA is nasal continuous positive airway pressure therapy (CPAP).[2-4]

Many patients are prescribed CPAP for OSA and tolerate therapy well, while others remain on treatment despite side effects. Noncompliance with therapy is frequent.[5,6] The growing number of patients attending sleep disorders clinics create important logistical challenges for the follow-up of these patients.[7] The adequacy and comfort of mask fit and the appropriate selection of pressure level at the time of initial titration may have a major influence on treatment efficacy.[3] The usual outcome measures of treatment efficacy available to a clinician include improvements in snoring, daytime symptoms, and quality of life.[3,4,8] The impact on cardiovascular morbidity may be incomplete if OSA persists despite the lack of clinical symptoms. Untreated OSA is associated with an increased risk of cardiovascular disease at and after diagnosis.[9-12] To positively affect blood pressure, a target AHI on CPAP has been less than 5 per hour.[13,14] Yet, even in the well-controlled circumstances of a research-oriented sleep clinic or a randomized controlled trial of CPAP, the posttreatment AHI on CPAP may be higher.[15,16] One study, to our knowledge, has been made into the frequency of inadequate treatment of OSA by CPAP.[17] Furthermore, no study has specifically verified CPAP efficacy in patients treated for OSA. This question is important because practical alternatives now exist to conventional 1-pressure CPAP,[3,18] and effective follow-up strategies of this chronically treated population vary widely.

Our hypothesis for this study is that suboptimal treatment of OSA on CPAP is frequent despite being apparently adequate in the opinion of both patient and treating physician. To answer this question, we recruited 101 consecutive subjects and studied them using 16-channel polysomnography (PSG) in their homes on their usual CPAP treatment. Among the patients who had significant persistent OSA, we sought practical and clinical clues that may serve as predictors of persistent OSA. Some of the results of these studies have been previously reported in the form of an abstract.[19]

Disclosure Statement

This was an industry supported study supported by OSR Medical, a private home care company. The authors analyzed the data and wrote the paper. Dr. Kassissia acted as medical director for OSR Medical. Drs. Baltzan, Elkholi, Palayew, Dabrusin, and Wolkove have indicated no conflicts of interest.

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METHODS

Study Design

We studied consecutive patients treated with the same level of single-pressure CPAP for at least 3 consecutive months who had persistent resolution of their previous symptoms of OSA. All patients were recruited from routine follow-up visits to the specialized outpatient sleep clinic of Mount Sinai Hospital Center. Symptoms of OSA routinely asked by their treating physicians included persistent snoring, witnessed apnea, and persistent excessive daytime somnolence while using CPAP. If these symptoms were absent, the patients were referred to a study coordinator. Inclusion criteria verified by the coordinator were the PSG diagnosis of OSA and, if central apneas were scored, more obstructive rather than central apneas had to have been originally scored with a central apnea index of less than 5 per hour. Average CPAP compliance was verified as more than 4.50 hours per night. No patients with known severe cardiorespiratory disease or evidence of neurologic disease were accepted. Patients with variable-pressure CPAP, bilevel positive airway pressure therapy, or supplemental oxygen were excluded. Data from patients who met these inclusion criteria but who were not studied were tabulated prospectively. The study was approved by the Mount Sinai Hospital Ethics Committee.

Measurements

Each subject underwent a structured interview on symptoms of OSA. These included self-rated snoring, witnessed apnea, choking out of sleep, nonrestorative sleep, morning headaches, dry mouth in the morning (scale: All the time = 3; Some of the time = 2; Rarely = 1; Never = 0); daytime sleepiness (using the Epworth Sleepiness Scale); daytime concentration, general quality of life, vitality, and mood (Scale: Excellent = 4; Good = 3; Fair = 2; Poor = 1); usual number of nocturnal awakenings to urinate; and potential side effects of CPAP, including current mask leaks, mouth leaks, nasal symptoms, pain, and claustrophobia with the mask. Height and current weight were measured.

Home PSG was performed on all patients. This was set up in the home with a dedicated study team of registered inhalation therapists. Sleep staging was performed using standard electroencephalographic (EEG) leads (C4-A1/C3-A2, O1-A2/O2-A1); bilateral electrooculogram; chin and anterior tibialis electromyograms; airflow measured with a pneumotachometer in line with their usual CPAP mask and pressure with any heated humidity disconnected to avoid condensation-related decay in signal; thoracoabdominal movements by inductive plethysmography (Respitrace Systems, Respitrace Corp., Ardsley, NY); and arterial oxyhemoglobin saturation by finger pulse oximetry. All signals were acquired on a digital data-management system (Alice 4, Respironics). The CPAP devices at home were calibrated by the installing inhalation therapist who was blind to the original prescription. One certified EEG and PSG technologist scored the studies using standard criteria,[20,21] blind to the results of any other patient variables. A study was repeated if the raw data contained less than 3 hours of EEG sleep. A hypopnea was defined a priori as at least a 30% drop in airflow with coincident desaturation of at least 4% lasting at least 10 seconds, according to the standards of the American Academy of Sleep Medicine Clinical Practice Review Committee.[22]

Retitration of Patients with Persistent OSA on CPAP

All patients with clinically significant persistent OSA while sleeping with their usual CPAP (defined as an AHI more than 10 per hour) underwent subsequent titrations to determine the required pressure to treat their OSA, as mandated a priori by the study protocol.

Clinical CPAP Titrations

A formal policy and procedure manual is followed by the PSG technologists at Mount Sinai Hospital Center. They are taught to score sleep. Titration of CPAP is performed during full-night or split-night studies following written protocol since 1995; in short, the pressure is raised by 1-cm H_2O pressure increments to a maximum of 20 cm H_2O until all apneas, hypopneas, oximetry desaturations, snoring, evidence of inspiratory flow limitation, and respiratory-event related arousals are no longer evident during real-time monitoring. Patient set-up and mask fitting is allotted 30 minutes prior to lights out. If unacceptable leaks are detected by the technologist, mask fit is verified; more than 20 masks of various makes and sizes using nasal, oral, or oronasal interfaces are available at any time. Heated humidity is added to the circuit as required. If severe desaturations persist despite extinction of apneas and hypopneas, supplemental oxygen may be bled into the respiratory circuit at or near the mask. The PSG CPAP titrations are regularly reviewed and discussed with the technologists, the chief technologist, and the sleep clinic specialists at weekly meetings.

Some patients undergo non-PSG CPAP titrations. The most common is at home over 3 nights with an automatic CPAP device (Autoset, ResMed; Mallincrodt GK 418P, Tyco; REMstar Auto, Respironics). When a clear single-pressure CPAP estimate is made by this procedure, this may be considered a sufficient titration if accepted by the treating physician. Less commonly, patients with severe problems with panic or mask leaks, where at least 1 attempt in the sleep lab fails to obtain a valid titration, are admitted to the hospital for serial nights of supervision, mask adaptation, CPAP pressure readjustment, and nocturnal oximetry. These 2 methods of titration were found to be the sole method of titration in 11% of cases.

All previous PSG CPAP titrations were examined with predefined criteria; these quantified the total EEG sleep time, sleep latency, waking after sleep onset, sleep efficiency, and the amount of supine sleep and REM sleep recorded during titration, as well as the technician's comments and the highest CPAP achieved.

Statistical Analysis

Demographic data are summarized with descriptive statistics with standard deviations. All PSG scores of sleep-disordered breathing were categorized by a priori defined cutpoints of AHI: AHI of 15 or more, 14.9 to 10, 9.9 to 5.0, and less than 5 per hour of EEG sleep. Persistent obstructive sleep apnea-hypopnea was defined as an AHI of 10 or more events per hour of EEG sleep. This was analyzed in comparison with patients who demonstrated no evidence of OSA, defined as an AHI of less than 5 per hour. Confidence intervals for proportions were computed with the mid-p exact method.[23] Statistical significance was declared at a 2-sided p value of $< .05$. Likelihood ratios and 95% confidence intervals were calculated with regard to the presence of persistent

Table 1—Characteristics of the Study Population and Patients Eligible But Not Studied

	Study Population	Patients Not Studied
Number	101	13
Age, y	54.3 ± 12	58.1 ± 12
Men, no. (%)	75 (75)	9 (77)
Current BMI, kg/m^2	34.7 ± 11.0	36.6 ± 9.0
AHI at diagnosis, no./h	57.3 ± 45	52.2 ± 27
Current CPAP Level, cm H_2O	8.9 ± 2.4	11.8 ± 3.3
Months since starting CPAP	26.1 ± 17	23 ± 19
ESS score at inclusion	6.5 ± 4.2	6.1 ± 7.3

Data are presented as mean ± SD unless otherwise indicated. BMI refers to body mass index; AHI, apnea-hypopnea index; CPAP, continuous positive airway pressure; ESS, Epworth Sleepiness Scale.

Table 2—Frequency of Persistent Obstructive Sleep Apnea in 101 Consecutive Patients

AHI on CPAP, no./h	No. (95% CI)
5-9.9	12 (5.6-18)
10-14.9	7 (2.0-12)
> 15	10 (4.1-16)

OSA refers to obstructive sleep apnea; AHI, apnea-hypopnea index; CPAP, continuous positive airway pressure; CI, confidence interval.

obstructive sleep apnea-hypopnea.[24] Effect sizes were calculated with 95% confidence intervals to compare clinical indicators.[25,26]

RESULTS

Patient Population

The 101 patients who completed the consent, questionnaires, and PSG on their CPAP are described in Table 1. The patients studied had been using CPAP for a mean of over 2 years, with a range of 3.2 to 90.5 months. Those who were seen in the clinic yet were not included and who were eligible demonstrated no important difference as a group from those patients who were studied (Table 1). Of the 13 patients who were not studied, 2 lived too far away; 3 said they were too busy to comply; 4 refused to comply for unspecified reasons after consenting; 1 did not answer the door or telephone to allow PSG; 1 slept with a bed partner who interfered twice disabling the PSG, which was subsequently abandoned; 1 each frequently had small children or animals in their bed, which they feared may become entrapped in the wires. Problems with data acquisition, transfer, and artifact required repeating 10 studies, which were successful.

The Prevalence of Persistent Sleep Apnea-Hypopnea

Persistent sleep apnea-hypopnea was found to be frequent in this population (Table 2). The prevalence of an AHI of ≥ 10 per hour was 17% (95% confidence interval of 9.5%-24%). Patients with persistent sleep apnea when compared with patients with no residual sleep apnea on their CPAP were found to have similar amounts of EEG sleep time, time asleep supine, cortical arousals, and periodic limb movements (Table 3). The amount of rapid eye movement (REM) sleep demonstrated no difference with respect to the presence of persistent OSA (p = .42). The respiratory

Table 3—Polysomnographic Characteristics While Sleeping With CPAP

	No OSA	OSA	p value
No.	72	17	-
Time, min			
Total sleep	400 ± 82	363 ± 71	.089
Supine	190 ± 128	242 ± 154	.15
Snoring	2.4 ± 12.1	19.7 ± 36	.002
Index, no./h			
Central apnea	0.24 ± 0.53	0.76 ± 1.1	.001
Obstructive apnea	0.10 ± 0.28	1.3 ± 2.2	< .001
Mixed apnea	0.03 ± 0.59	0.13 ± 0.22	.006
Total apnea	0.38 ± 0.59	2.2 ± 2.4	< .001
Apnea-hypopnea	1.8 ± 1.4	18.0 ± 6.3	< .001
Arousal	13.9 ± 11.3	14.9 ± 9.0	.75
Periodic limb movements	14.4 ± 22.2	13.8 ± 16.0	.94
Oxygen desaturation	1.31 ± 1.36	15.9 ± 10.9	< .001
Minimum SaO_2, %	91.2 ± 2.6	83.4 ± 5.3	< .001
Time at < 90% SaO_2, %	1.2 ± 2.4	16.7 ± 22.2	< .001

Data are presented as mean ± SD unless otherwise indicated. No OSA (obstructive sleep apnea) is defined as an apnea-hypopnea index (AHI) < 5; OSA is an AHI of 10 or more. CPAP refers to continuous positive airway pressure; SaO_2, oxygen saturation.

Table 4—Prior Polysomnographic CPAP Titration Variables

	No OSA	OSA	p value
Titrations, no.	1.2 ± 0.4	1.6 ± 1.0	.003
Split night, if PSG, %	57	65	.19
Sleep-onset latency, min	20 ± 21	20 ± 18	.94
Total sleep time, h	3.6 ± 1.4	3.8 ± 1.1	.60
Sleep efficiency, %	77 ± 17	72 ± 16	.50
Supine sleep, h	2.5 ± 1.7	3.0 ± 1.5	.23
REM sleep, min	44 ± 30	58 ± 48	.151
Supine REM, min	43 ± 27	49 ± 24	.38
Mask problem noted by technician, no. (%)	8/56 (14)	8/17 (47)	.004
Highest pressure achieved, cm H_2O	9.5 ± 3.0	11 ± 3.6	.13
AHI on final pressure, no./h	9.0 ± 12	11.4 ± 6.9	.51
Higher CPAP pressure on subsequent titration, no. (%)	—	11 (65)	—

Data are presented as mean ± SD unless otherwise indicated. No OSA (obstructive sleep apnea) is defined as an apnea-hypopnea index (AHI) < 5; OSA is an AHI of 10 or more. The AHI from these titrations are scored according to AASM "Chicago criteria"; CPAP refers to continuous positive airway pressure; PSG, polysomnography; REM, rapid eye movement; SaO_2, oxygen saturation.

variables were different with regard to the number of obstructive apneas, hypopneas, and desaturation profiles.

Examination of CPAP Titrations of Patients with Persistent Apnea-Hypopnea

None of the patients with persistent sleep apnea had undergone only unattended automatic CPAP titrations in the home (11 patients). Split-night protocols were used for the majority of patients, with no significant relationship with regard to the persistence of OSA. The AHI on CPAP for patients with split-night protocols was 5.42 ± 7.80 per hour compared to participants with full-night attended PSG CPAP titrations where the AHI was 6.22

Table 5—Potential Predictors of Persistent Obstructive Sleep Apnea

	No OSA	OSA	p value
No.	72	17	-
Age, y	53 ± 12	56 ± 12	0.33
Men, no (%)	54 (79)	12 (71)	0.44
Months since starting CPAP, no.	26.1 ± 18	26.4 ± 19	0.94
Body mass index, kg/m^2			
Current	34.0 ± 8.4	41.6 ± 18.8	0.022
Initial	33.9 ± 8.4	42.1 ± 19.7	0.010
Change since prescription	0.15 ± 2.8	-0.52 ± 1.7	0.038
AHI at diagnosis ± hour-1	54 ± 41	74 ± 51	0.065
CPAP, cm H_2O			
Initial	8.1 ± 2.4	10.1 ± 2.8	0.0032
Current	8.6 ± 2.3	10.6 ± 2.8	0.0021
Difference	0.56 ± 1.6	0.53 ± 1.5	0.95
CPAP compliance, h/night	6.4 ± 1.3	5.2 ± 1.1	0.024

Data are presented as mean ± SD unless otherwise indicated. No OSA (obstructive sleep apnea) is defined as an apnea-hypopnea index (AHI) < 5; OSA is an AHI of 10 or more.

± 7.34 per hour (p = .69). Patients with persistent sleep apnea had, on average, undergone more CPAP titrations compared with patients without persistent sleep apnea (Table 4). There was no significant difference with regard to sleep-onset latency, sleep efficiency, total sleep time, REM sleep time, or supine sleep time. Difficulties with the CPAP mask interface (considerable leaks or patient discomfort) noted by the sleep technologist at the time of the CPAP titration were associated with subsequent persistent sleep apnea. The central apnea index during titration (but not the diagnostic study) was also related to the presence of persistent sleep apnea.

Characteristics Related to Persistent Sleep Apnea-Hypopnea

The demographic characteristic that was significantly related to persistent sleep apnea was body mass index. The absolute index was related to the presence of persistent sleep apnea, although interval weight loss was observed in the group with persistent sleep apnea. A higher prescription of CPAP (either original or current prescription) was related to the presence of persistent sleep apnea, although the change in CPAP pressure during the time interval since first prescription was not related to persistent sleep apnea. There was no relationship between the time since the first prescription of CPAP and the prevalence of persistent sleep apnea. Compliance was significantly better in the absence of persistent OSA (Table 5).

There was no difference in general mood, quality of life, and vitality in subjects with persistent sleep apnea (all p values > 0.2). The mean ± SD scores on the Epworth Sleepiness Scale in those without persistent sleep apnea were similar to those with persistent sleep apnea (6.1 ± 3.6 vs. 7.2 ± 5.4); p = .37). There was no relationship with the changes in the Epworth score since diagnosis, which were respectively -4.1 ± 6.0 and -3.9 ± 7.7 (p = .87). Most of the respiratory symptoms of OSA were infrequent and without any discriminatory value. Snoring was usually reported as present "rarely" if at all present and showed no correlation with measured minutes of snoring during home PSG (r = -0.14, p > .1). Symptoms of air leak, either by the mouth or around the mask, demonstrated an association with persistent sleep apnea; when these symptoms were taken together, they were strongly associated with persistent sleep apnea (p = .008). Morning headache (occurring at least some of the time) as well as nonrestorative sleep were significantly related to the presence of persistent sleep apnea on CPAP (Table 6).

Table 6—Potential Symptom-based Predictors of Persistent Obstructive Sleep Apnea

	No OSA	OSA	p value
Nose blocks	0.60 ± 0.92	0.76 ± 1.1	.53
Nose runs	0.45 ± 0.84	0.29 ± 0.67	.48
Sneezing with CPAP	0.42 ± 0.84	0.29 ± 0.69	.58
Mouth leaks	0.88 ± 1.0	1.47 ± 1.9	.041
Mask leaks	0.97 ± 1.0	1.53 ± 1.1	.047
Take off mask while sleeping	0.59 ± 0.81	0.94 ± 1.1	.14
Claustrophobia with mask	0.18 ± 0.52	0.24 ± 0.66	.69
Snoring	0.45 ± 0.66	0.62 ± 0.65	.42
Witnessed apnea	0.32 ± 0.59	0.50 ± 0.67	.36
Choking out of sleep	0.15 ± 0.40	0.33 ± 0.49	.14
Dry mouth in the morning	1.1 ± 1.0	1.3 ± 1.0	.65
Morning headache	0.32 ± 0.61	0.76 ± 0.97	.021
Nonrestorative sleep	0.87 ± 0.70	1.29 ± 0.77	.032
Sleepy in the daytime	0.91 ± 0.62	1.2 ± 0.61	.12
Difficulty concentrating	2.9 ± 1.0	3.1 ± 0.63	.32

Data are presented as mean ± SD unless otherwise indicated. No OSA (obstructive sleep apnea) is defined as an apnea-hypopnea index (AHI) < 5; OSA is an AHI of 10 or more. Scale: All the time = 3; Some of the time = 2; Rarely = 1; Never = 0. CPAP refers to continuous positive airway pressure.

Likelihood ratios for the significant categorical predictors of persistent sleep apnea were calculated. Most of these were weakly discriminatory when positive and not significantly discriminatory when negative, with the exception of morning headaches and the observation of the central apnea index of more than 5 on a PSG CPAP titration (Table 7). The comparison of the strength of the various clinical indicators in relation to persistent sleep apnea on CPAP is illustrated in the Figure. Oximetry alone, when using the oxygen desaturation index, demonstrated a sensitivity of 71% for an oxygen desaturation index of 10 or more, with a specificity of 99%. When an oxygen desaturation index of 5 or more was used, the sensitivity increased to 76% with similar specificity.

The Clinical Findings in the Presence of Persistent OSA

Patients with persistent sleep apnea-hypopnea on their CPAP were examined and underwent retitration of CPAP in the sleep laboratory. One patient without significant sleep apnea was found to be biochemically hypothyroid (AHI on CPAP of 5.1 per hour). Higher levels of CPAP were found to be effective in 11 of 17 patients (65%), with pressure differences ranging from 1 to 4 cm H_2O. Persistent mouth or mask leaks were a problem in the 6 subjects in whom higher effective pressures could not be determined. In these few remaining patients, 1 eventually was fitted with an oral appliance, which was subsequently found to be effective by PSG; 3 purchased substantially different masks from their current mask; 1 required similar pressure; and 1 was found to have new central sleep apnea (AHI on CPAP of 31 per hour) unresponsive to CPAP associated with a new diagnosis of moderate vascular ischemic white-matter changes by computed brain tomography. All but the last patient were clinically similar or more satisfied with the changes at last follow-up.

Table 7—Likelihood Ratios for Persistent Obstructive Sleep Apnea

Clinical Feature	Likelihood Ratio (95% confidence interval)	
	If Positive	If Negative
Morning headaches on CPAP at least some of the time	7.8 (1.6 to 39)	0.8 (0.6 to 1.0)
Nonrestorative sleep on CPAP at least some of the time	3.0 (1.4 to 6.2)	0.6 (0.4 to 1.0)
Mouth leak on CPAP at least some of the time	1.9 (1.2 to 3.2)	0.5 (0.3 to 1.0)
Mask problem noted on titration	3.0 (1.4 to 6.5)	0.6 (0.4 to 1.0)
Central Apnea Index > 5/h on lab titration	4.0 (1.3 to 12)	0.8 (0.6 to 1.0)

CPAP refers to continuous positive airway pressure.

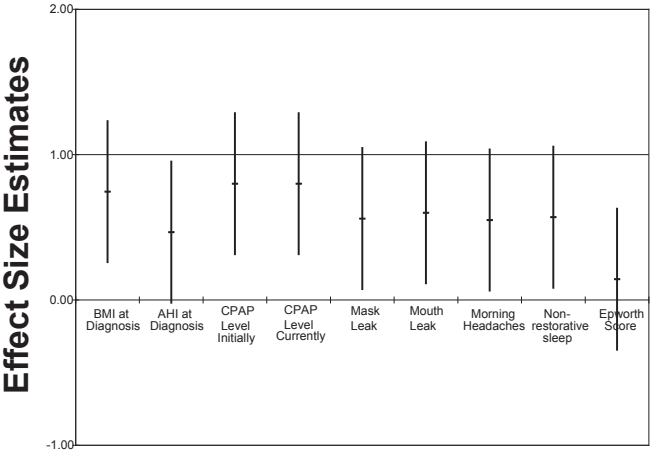

Figure 1—Effect Size of Clinical Predictors of Persistent Obstructive Sleep Apnea (OSA). Clinical predictors are charted with 95% confidence intervals. Effect sizes of a mean 0.5 or more are considered clinically meaningful, and are considered strong if 0.8 or higher. BMI refers to body mass index; AHI, apnea-hypopnea index; CPAP, continuous positive airway pressure.

DISCUSSION

We have shown that a significant number of patients apparently well treated for OSA with fixed-pressure CPAP have persistent OSA. In our study population, 17% of subjects had significant persistent OSA on CPAP (AHI of 10 per hour or more). This is in keeping with a previous study in which 13 of 40 patients had persistent OSA on CPAP after their titration, although that study noted that somnolence improved and the persistent OSA regressed within 2 months in the majority.[16] We found that patients with persistent OSA reported improved somnolence and did not report significantly more residual daytime somnolence or respiratory symptoms of OSA, which was likely a result of our selection process. They did complain more frequently of morning headaches, nonrestorative sleep, mouth leaks, or mask leaks. These patients generally had a higher body mass index, required higher pressures of CPAP, had undergone more CPAP titrations, and more frequently had central apneas on CPAP during the titrations.

Our review of the factors that may help clinicians predict when a patient may have persistent OSA on CPAP shows that these patients are likely needing higher pressures to treat their OSA. This was also associated with problems with mask fit, which was often noted during the original PSG titration and which was not resolved months or years later when they accepted to be studied in this research protocol. These patients did not have less EEG sleep or sleep continuity during titration and had similar amounts of supine and REM sleep. It was also found that they had no increase in cortical EEG arousals compared with those without residual OSA (Table 3); this may be due to characteristics of this subpopulation that does not always manifest EEG arousals at termination of a hypopnea and may explain why the subjects had no complaints of residual daytime somnolence. We did not find an association with split-night titration compared with all-night PSG titrations. Those with significant sleep apnea on CPAP actually had a tendency to lose weight since first prescription, likely related to their higher mean body mass index. Only 1 patient had a significant new diagnosis leading to likely new onset of central sleep apnea from subcortical ischemic vascular disease.

We chose a strict definition of hypopnea prior to beginning this study. This was based on the fact that the patients were selected because they were assessed to have adequately treated symptoms of daytime somnolence. The definition of hypopnea[22] is stable, with very reproducible scoring,[27] and has excellent evidence with regard to the resulting AHI as an independent risk factor for future cardiovascular disease.[11,12,28] We also chose to avoid hypopnea definitions based only on waveform or associated with EEG arousals because the significance of such usually milder events in patients with little or no daytime symptoms is unclear.

The limitations of our study included the absence of a valid formal quality-of-life assessment. The emphasis in planning this study was to determine the prevalence and predictors of persistent OSA on CPAP. We chose short simple questions that may be easily available to clinicians who follow their patients in a busy clinical practice. Our general screening regarding quality of life (an interviewer administrated assessment on a 4-point scale ranging from Exciellent to Poor) may not have sufficient discriminative value to exclude a significant difference in quality of life. The finding that patients with persistent OSA perceived more nonrestorative sleep suggests that quality of life may also be reduced. Further studies with valid disease-specific quality-of-life instruments are warranted to explore whether persistent OSA is associated with lower quality of life. Another limitation of our study is the various methods used by the clinicians to titrate CPAP. Yet, the overwhelming majority of the patients underwent at least 1 nocturnal PSG CPAP titration, with the majority of these undergoing a split-night protocol. This is likely similar to the majority of practices in North America,[29] with perhaps an institutional bias toward the use of split-night protocols. Yet, the split-night protocol was no more frequent among the patients with persistent OSA in our study. A final limitation is that our home PSG-monitoring technique was expensive, required a significant number of repeated studies and was not accepted by all potential participants.

We did not specifically assess any cardiovascular parameters in our patients for the purpose of this study. This was not the stated goal and would likely require separate studies of neurohumoral activation and detailed blood-pressure assessments. In our opinion, these cardiovascular aspects would be best investigated specifically in studies designed with sufficient power to appropriately quantify the intended outcomes.

We believe that the mask interface coupling the CPAP to the patient's upper airway is a critical factor in delivering adequate pressure to overcome OSA. Unresolved leaks around the mask

or out the mouth limit the effective pressure that can be delivered to or tolerated by the patient. The histories of many of the patients with persistent OSA in this study revealed several who had pursued treatment with several different interfaces through their home-care provider or during repeated PSG CPAP titrations. The resolution of persistent sleep apnea required multiple interventions, including changing of mask interface, higher pressures in some, and the abandonment of CPAP for the use of an effective oral appliance in 1 patient. If adequate attention is paid to patient education and mask fitting, many modes of CPAP titration may be considered adequate for the appropriate patient.[30-33]

The long-term impact of persistent OSA is not known. The studies of cardiovascular outcomes generally compare patients naturally without OSA to those with OSA or those who are treated (with or without persistent OSA) compared with those are untreated for whatever reason.[1,9-14,34,35] As a result, it is not clear that patients with persistent asymptomatic OSA are at risk of increased cardiovascular events or accidents. The best inference from the current evidence suggests that persistent OSA with significant oxyhemoglobin desaturation in sleep may cause similar neurohumoral disturbances, but to a lesser degree than in untreated OSA.[9,11,12, 28] This inference remains to be proven.

Periodic respiratory monitoring on CPAP and pressure readjustment may be warranted even in asymptomatic patients treated with single-pressure CPAP for OSA. We found oximetry examined alone was specific but insensitive to detecting residual sleep apnea. There is currently no ambulatory monitoring both validated against PSG and published regarding the detection of residual OSA on CPAP, although 1 method has been presented in abstract.[17] Such monitoring could be part of a coherent OSA management plan in order to seek physiologically optimal CPAP. Further troubleshooting of mask problems may be required for those patients with persistent OSA. The use of variable-pressure positive airway pressure devices may also provide a solution for some patients with interface leaks at higher pressures.

In conclusion, we found that significant persistent OSA was frequent in patients treated with single-pressure CPAP. Persistent OSA was associated with the requirement of higher CPAP pressures by patients with a higher mean body mass index. Mask or mouth leaks were more common. No one clinical feature appeared to be strongly predictive. During PSG titration, only the findings of frequent central apneas or unresolved mask problems were predictive of persistent OSA.

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REFERENCES

1. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. Am J Respir Crit Care Med 2002;165:1217-39.
2. Sullivan C E, Issa F G, Berthon-Jones M, Eves L. Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares. Lancet 1981. 1:862-865.
3. Beninati W, Sanders MH. Optimal continuous positive airway pressure for the treatment of obstructive sleep apnea/hypopnea. Sleep Med Rev 2001;5:7-23.
4. Patel SR, White DP, Malhotra A, Stanchina ML, Ayas NT. Continuous positive airway pressure therapy for treating sleepiness in a diverse population with obstructive sleep apnea: results of a meta-analysis. Arch Intern Med 2003;163:565-71.
5. Zozula R, Rosen R. Compliance with continuous positive airway pressure therapy: assessing and improving treatment outcomes. Curr Opin Pulm Med 2001;7:391-8.
6. Haniffa M, Lasserson TJ, Smith I. Interventions to improve compliance with continuous positive airway pressure for obstructive sleep apnoea. Cochrane Database Syst Rev 2004;CD003531.
7. McNicholas WT. Follow-up and outcomes of nasal CPAP therapy in patients with sleep apnea syndrome. Monaldi Arch Chest Dis 2001;56:535-9.
8. Engleman HM, Kingshott RN, Wraith PK, Mackay TW, Deary IJ, Douglas NJ. Randomized placebo-controlled crossover trial of continuous positive airway pressure for mild sleep Apnea/Hypopnea syndrome. Am J Respir Crit Care Med 1999;159:461-7.
9. Peker Y, Hedner J, Norum J, Kraiczi H, Carlson J. Increased incidence of cardiovascular disease in middle-aged men with obstructive sleep apnea: a 7-year follow-up. Am J Respir Crit Care Med 2002;166:159-65.
10. Peker Y, Hedner J, Johansson A, Bende M. Reduced hospitalization with cardiovascular and pulmonary disease in obstructive sleep apnea patients on nasal CPAP treatment. Sleep 1997;20:645-53.
11. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. N Engl J Med 2000;342:1378-84.
12. Nieto FJ, Young TB, Lind BK, et al, for the Sleep Heart Health Study. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. Sleep Heart Health Study. JAMA 2000;283:1829-36.
13. Hla KM, Skatrud JB, Finn L, Palta M, Young T. The effect of correction of sleep-disordered breathing on BP in untreated hypertension. Chest 2002;122:1125-32.
14. Pepperell JC, Ramdassingh-Dow S, Crosthwaite N, et al. Ambulatory blood pressure after therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised parallel trial. Lancet 2002;359:204-10.
15. Engleman HM, McDonald JP, Graham D, et al. Randomized crossover trial of two treatments for sleep apnea/hypopnea syndrome: continuous positive airway pressure and mandibular repositioning splint. Am J Respir Crit Care Med 2002;166:855-9.
16. Series F, Marc I, Cormier Y, La Forge J. Required levels of nasal continuous positive airway pressure during treatment of obstructive sleep apnoea. Eur Respir J 1994;7:1776-81.
17. Pittman SD, Pillar G, Berry R, Malhotra A, MacDonald MM, White DP. Follow-up assessment of CPAP efficacy in patients with obstructive sleep apnea using an ambulatory device based on peripheral arterial tonometry. Sleep 2005;28:A166.
18. Massie CA, McArdle N, Hart RW, et al. Comparison between automatic and fixed positive airway pressure therapy in the home. Am J Respir Crit Care Med 2003;167:20-3.
19. Baltzan M A, Kamel H, Kassissia I, Dabrusin R, Small D, Palayew M, Wolkove N. Predictors of asymptomatic sleep apnea-hypopnea in patients treated with continuous positive airway pressure (CPAP). Sleep 2004;27:A214.
20. Rechtschaffen A, Kales A, eds. A Manual of Standardized Terminology, Techniques, and Scoring System for Sleep Stages of Human Subjects. Washington, DC: National Institute of Health, Publication 204, U.S. Government Printing Office; 1968.
21. EEG arousals: scoring rules and examples: a preliminary report from the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association. Sleep 1992;15:173-84.
22. Meoli AL, Casey KR, Clark RW, et al. Hypopnea in sleep-disordered breathing in adults. Sleep 2001;24:469-70.
23. Edwardes MD de B. The evaluation of confidence sets with application to binomial intervals. Statistica Sinica 1998; 8:393-409.

24. Sackett DL, Haynes RB, Guyatt GH, Tugwell P. Clinical Epidemiology. A Basic Science for Clinical Medicine. 2nd ed. Boston: Little, Brown and Company; 1991:53-7.
25. Matthews JN, Altman DG. Statistics notes. Interaction 2: Compare effect sizes not p values. BMJ 1996;313:808.
26. Cohen J. Statistical Power Analysis for the Behavioural Sciences. 2nd ed. Hillsdale NJ: Lawrence Earlbaum Associates; 1988.
27. Whitney CW, Gottlieb DJ, Redline S, et al. Reliability of scoring respiratory disturbance indices and sleep staging. Sleep 1998:21:749-57.
28. Yaggi H K, Concato J, Kernan W N, Lichtman J H, Brass L M, Mohsenin V. Obstructive sleep apnea as a risk factor for stroke and death. N Engl J Med 2005;353:2034-41.
29. Flemons WW, Douglas NJ, Kuna ST, Rodenstein DO, Wheatley J. Access to diagnosis and treatment of patients with suspected sleep apnea. Am J Respir Crit Care Med 2004 169:668-72.
30. Masa JF, Jimenez A, Duran J, et al. Alternative methods of titrating continuous positive airway pressure: a large multicenter study. Am J Respir Crit Care Med 2004;170):1218-24.
31. Sanders MH, Kern NB, Costantino JP, et al. Adequacy of prescribing positive airway pressure therapy by mask for sleep apnea on the basis of a partial-night trial. Am Rev Respir Dis 1993;147:1169–74.
32. Yamashiro Y, Kryger MH. CPAP titration for sleep apnea using a split-night protocol. Chest 1995;107:62-6.
33. Gordon P, Sanders MH. Sleep. 7: positive airway pressure therapy for obstructive sleep apnoea/hypopnoea syndrome. Thorax 2005;60:68-75.
34. Caples SM, Gami AS, Somers VK. Obstructive sleep apnea. Ann Intern Med 2005;142:187-97.
35. Robinson GV, Stradling JR, Davies RJ. Sleep. 6: obstructive sleep apnoea/hypopnoea syndrome and hypertension. Thorax 2004;59:1089-94.