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SCIENTIFIC INVESTIGATIONS

Adherence Index: sleep depth and nocturnal hypoventilation predict long-term adherence with positive airway pressure therapy in severe obstructive sleep apnea

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Study Objectives: Treatment of obstructive sleep apnea with positive airway pressure (PAP) devices is limited by poor long-term adherence. Early identification of individual patients' probability of long-term PAP adherence would help in their management. We determined whether conventional polysomnogram (PSG) scoring and measures of sleep depth based on the odds ratio product would predict adherence with PAP therapy 12 months after it was started.

Methods: Patients with obstructive sleep apnea referred to an academic sleep center had split-night PSG, arterial blood gases, and a sleep questionnaire. Multiple linear regression analysis of conventional PSG scoring and the odds ratio product both during diagnostic PSG and PAP titration provided an "Adherence Index," which was correlated with PAP use 12 months later.

Results: Patients with obstructive sleep apnea (n = 236, apnea-hypopnea index 72.2 ± 34.1 events/h) were prescribed PAP therapy (82% received continuous PAP, 18% received bilevel PAP). Each patient's adherence with PAP therapy 12 months later was categorized as "never used," "quit using," "poor adherence," and "good adherence." PSG measures that were most strongly correlated with PAP adherence were apnea-hypopnea index and odds ratio product during nonrapid eye movement sleep; the additional contribution of nocturnal hypoxemia to this correlation was confined to those with chronic hypoventilation treated with bilevel PAP. The Adherence Index derived from these measures, during both diagnostic PSG and PAP titration, was strongly correlated with PAP adherence 12 months later.

Conclusions: Long-term adherence with PAP therapy can be predicted from diagnostic PSG in patients with severe obstructive sleep apnea, which may facilitate a precision-based approach to PAP management.

Keywords: obstructive sleep apnea, polysomnography, odds ratio product, CPAP, BPAP adherence

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BRIEF SUMMARY

Current Knowledge/Study Rationale: The efficacy of positive airway pressure (PAP) therapy for obstructive sleep apnea is limited by poor long-term adherence. Early prediction of long-term adherence with PAP therapy would enable health care providers to identify patients with obstructive sleep apnea who require more support in their management.

Study Impact: Long-term PAP adherence can be predicted from the "Adherence Index," based upon analysis of conventional sleep measures and the odds ratio product in the diagnostic polysomnogram. The availability of this information, before PAP therapy is started, can facilitate a personalized approach to PAP management.

INTRODUCTION

Obstructive sleep apnea (OSA) is common and is estimated to occur in 38% of the world's population.[1] Untreated OSA is associated with immediate and long-term complications, including unrefreshing sleep and excessive daytime sleepiness,[2] road traffic accidents,[3] cognitive impairment,[4] reduced work productivity,[5] and increased health care costs.[6] In addition, OSA is a risk factor for cardiovascular disease,[7] metabolic syndrome,[8] chronic kidney disease,[9] and dementia.[10] Both OSA and associated symptoms can be treated effectively with continuous positive airway pressure (CPAP), which can also reduce the risk of long-term complications.[11] The limitation of CPAP therapy is that a significant proportion of patients are unable to use it effectively; long-term adherence with CPAP therapy is estimated to be 25%–60% depending on the population assessed and the time over which adherence is measured.[11–13]

Multiple factors have been proposed to influence CPAP adherence, including patient demographics, severity of OSA and associated symptoms, medical comorbidities, psychological factors, financial status, social support, and specific issues related to claustrophobia, upper airway symptoms, and issues with the interface.[14–17] However, 2 potential determinants of long-term adherence have received relatively little attention: the

improvement in sleep depth and the relief of sleep hypoventilation and/or hypoxemia associated with positive airway pressure (PAP) therapy. Complaints of nonrestorative sleep are a common and troubling symptom of severe OSA. Although the primary objective of PAP therapy is to relieve upper airway obstruction, it is the downstream effect on sleep depth that is most likely to improve symptoms and determine long-term adherence with this treatment. Furthermore, given the negative impact of hypercapnia on cognitive function,[18,19] it may be expected that patients with OSA-related hypoventilation would sustain additional symptomatic benefit from PAP therapy.

Some previous studies have correlated polysomnography (PSG) changes during both diagnostic PSG and CPAP titration with subsequent adherence.[20–23] However, these studies have been limited by small sample size[22] and short-term follow-up.[20–23] Further, the PSG index that was correlated with good CPAP adherence has differed between studies and has included a decrease in oxygen desaturation index and increased deep sleep,[20] increased sleep efficiency,[23] and decreased stage 2 non-rapid eye movement (NREM) sleep and increased rapid eye movement (REM) sleep.[22] The challenge of using conventional, manually scored indices of sleep quality is that they are subject to scorer bias[24–26] and reflect different, specific features of sleep that may not change harmoniously.[27] Under such conditions, it is difficult to determine whether sleep improved or not, and consequently the change in conventional PSG indices of sleep quality during CPAP titration is not used in clinical practice to predict long-term adherence.

The odds ratio product (ORP) is a validated[28–32] continuous index of sleep depth with a range from 0 (very deep sleep) to 2.5 (full wakefulness). This index provides a more detailed and specific assessment of sleep depth than conventional PSG scoring, and both the depth of sleep and the change with CPAP can be expressed numerically on a continuous scale. Furthermore, in contrast to conventional PSG indices of sleep quality, ORP is a single metric that is objectively obtained by automated analysis.

We hypothesized that patients with OSA who have improvement of sleep depth (reflected by a decrease in sleep ORP) and/or relief of OSA-related hypoventilation with PAP therapy will have better long-term PAP adherence than those in whom sleep depth and/or sleep hypoventilation does not improve during PAP titration. In our sleep center, patients who show severe OSA during the diagnostic PSG are routinely titrated on PAP (CPAP and/or bilevel positive airway pressure [BPAP]) as discussed in the latter part of the study. The current data were obtained from these single split-night PSGs.

METHODS

This study included a subset of patients (n = 236) enrolled in the multicenter Canadian Sleep and Circadian Network OSA observational cohort study of adults referred to participating academic sleep centers for suspected OSA.[4] Patients from a single center (Sleep Centre, Foothills Medical Centre, Calgary, Alberta, Canada) who underwent split-night PSG for assessment of OSA and PAP therapy and in whom we had long-term objective PAP adherence data were included in the study. Participants also completed a sleep questionnaire before their PSG. This study was performed according to the Declaration of Helsinki and was approved by the Conjoint Health Research Ethics Board of the University of Calgary (REB16-0211).

Sleep questionnaire

The sleep questionnaire included patient demographics, medical history, comorbidities, medications, sleep schedule, symptoms of restless legs syndrome, and insomnia, reflected by the Insomnia Severity Index.[33] The Epworth Sleepiness Scale[34] and the Pittsburgh Sleep Quality Index[35] were used to assess daytime sleepiness and sleep quality. Additional details, including the criteria for diagnosis and severity of restless legs syndrome, are provided in the supplemental material and a recent publication.[4]

PSG and arterial blood gases

All patients underwent split-night PSG that included electroencephalogram (C3, C4, M1, M2, O1, O2), left and right electrooculograms, submental electromyograms, airflow using nasal pressure (Braebon; Ottawa, ON, Canada) and oral thermistor (Protech; Philips Respironics, Murraysville, PA), thoracic and abdomen respiratory excursions (Respitrace; Ambulatory Monitoring, Ardsley, NY), finger pulse oximetry (NATUS Embla Systems; Tonawanda, NY), and continuous measurement of the transcutaneous partial pressure of CO_2 (TCM4; Radiometer Medical, Copenhagen, Denmark; details in supplemental material). All data were continuously recorded and stored electronically (Sandman; Tyco Healthcare, Kanata, ON) for subsequent scoring. Awake arterial blood gas tensions were measured in 204 patients immediately before the PSG (details in supplemental material).

Once the diagnosis of OSA was established on the diagnostic portion of the PSG, a standardized protocol for PAP titration was followed as previously described.[36] This protocol required CPAP titration to a maximum of 18 cm H_2O, with conversion to BPAP for persistent hypoxemia (oxygen saturation [SpO_2] < 85% for 5 consecutive minutes), uncontrolled OSA in the absence of mask leak, or an increase in the transcutaneous partial pressure of CO_2 by 10 mm Hg from the baseline awake value. Once BPAP was initiated, expiratory PAP was titrated to control OSA and inspiratory PAP was titrated to achieve tidal volumes of 6–8 mL/kg of ideal body weight. If tidal volume was sufficient and hypoxemia persisted, then supplemental O_2 was added to maintain an $SpO_2 > 85\%$.

PAP therapy and adherence

All patients who were prescribed CPAP or BPAP after the interpretation of their PSG by a sleep physician were referred to a respiratory home care provider in the community for a trial of therapy. The PAP settings were left to the discretion of the prescribing sleep physician who interpreted the sleep study. The interface was determined by a respiratory therapist at the home care provider company who continued to see the patient for ongoing support and management of any technical issues with

PAP therapy. Patients who received treatment with BPAP were followed up both by the home care provider in the community and at the Foothills Medical Centre Sleep Centre. Adherence with PAP therapy was obtained 1, 3, 6, and 12 months after the PAP trial started and included the following indices of PAP use: number of days PAP was used, number of hours PAP was used per day, number of days that PAP was used for > 4 hours/day expressed as the percentage of days PAP was monitored, and estimated apnea-hypopnea index (AHI) events/h.

Data analysis

Sleep duration was quantified from the Pittsburgh Sleep Quality Index question 4 ("How many hours of actual sleep do you get at night?"). Patients were categorized as having short sleep duration if they reported < 6 hours of sleep per night.[37]

Self-reported medications were categorized according to their drug classification.[38] For clinical relevance, we have reported only medications known to impact sleep[39] (antidepressants, atypical antipsychotics, benzodiazepines, cannabinoids, dopaminergics, gabapentinoids, nonbenzodiazepines, and opioids).

Automated digital scoring of the PSG (Michele Sleep Scoring, Winnipeg, Canada) provided conventional indices of OSA and sleep architecture according to the American Academy of Sleep Medicine criteria.[40] An obstructive apnea was defined as a decrease in respiratory airflow amplitude by ≥ 90% for at least 10 seconds with continued respiratory efforts. An obstructive hypopnea was defined as a decrease in respiratory airflow amplitude of ≥ 30% lasting for at least 10 seconds followed by a decrease in SpO_2 of ≥ 3% or an arousal from sleep. The Michele Sleep Scoring system also provided measurements of ORP, as previously described.[28] Average ORP was calculated for wake time (ORP_W), NREM sleep (ORP_{NREM}), and total recording time (ORP_{TRT}). Differences in ORP_W reflected differences in fractions of wake epochs with full wakefulness and wake epochs with sleep features (eg, some theta activity, microsleep periods). The ORP in the 3 stages (W, NREM, and TRT) was calculated separately for the diagnostic and PAP sections of the PSG and differences between the 2 sections were used to determine associations between change in sleep quality with PAP and adherence data.

Statistical analysis

The primary outcome was adherence with PAP therapy 12 months after it was started, calculated over the last 6 months of follow-up. Accordingly, we classified each patient into 1 of the following 4 groups: (1) never used PAP therapy despite the fact that it was prescribed ("never"), (2) quit using PAP therapy within 12 months despite the fact that a PAP trial was performed ("quit"), (3) using PAP therapy at 12 months with poor adherence (defined as an average of < 4 hours per night for 70% of nights over the previous 6 months; "poor adherence"), and (4) using PAP therapy at 12 months with good adherence (defined as an average of > 4 hours per night for 70% of nights over the previous 6 months; "good adherence").

Demographic data, Epworth Sleepiness Scale score, comorbidities, medications, smoking history, self-reported sleep complaints, and OSA severity, along with conventional indices of sleep architecture and ORP-based indices in the diagnostic and PAP titration parts of the PSG and the difference in these variables between the 2 parts of the study, were tabulated for the 4 adherence groups and compared using 1-way analysis of variance.

Pearson regression coefficients were used to evaluate (1) the relationship between changes in different conventional variables (change in sleep efficiency, change in AHI, change in stage 1 NREM sleep, change in stage 3 NREM sleep, change in REM sleep) on PAP, (2) the relationship between OSA severity (AHI) in the diagnostic study and the various ORP measures, and (3) the relationship between selected variables in the diagnostic part of the PSG and their change on PAP therapy.

Associations between changes in conventional PSG indices and ORP metrics with PAP adherence were determined by multiple regression analyses with backward elimination. Elimination continued until *P* values for all remaining variables were < .10. The dependent variable was PAP adherence (1 = never, 2 = quit, 3 = poor adherence, and 4 = good adherence). Independent variables included 3 ORP indices (ORP_W, ORP_{NREM}, and ORP_{TRT}) and 8 conventional indices (sleep efficiency [SE], stage 1 NREM sleep [%TRT], stage 3 NREM sleep [%TRT], REM sleep [%TRT], AHI, arousal/awakening index, periodic limb movement index, and mean SpO_2 during sleep) measured in the diagnostic portion of the PSG. A second multiple regression analysis was done using the changes in these 11 variables on PAP as independent variables. A third multiple regression analysis was done using the significant variables identified in the first 2 multiple regression analyses to determine whether prediction models are improved by combining variables from the diagnostic and PAP titration portions of the PSG.

Next, the coefficients of the significant PSG variables in the first analysis were used to calculate prediction values for PAP adherence (Adherence Index) in each patient. In addition, logistic regression (XLSTAT, Kovach Computing Services, Anglesey, Wales, UK) was used to determine the probability of different categories of PAP adherence (1–4, as described in the paragraph above) in each patient using the significant variables in the third analysis (n = 236).

RESULTS

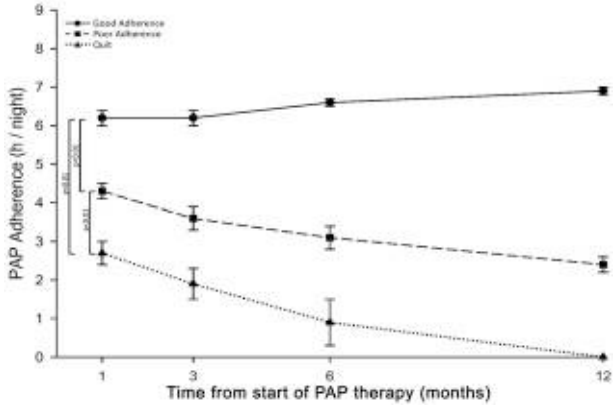
Two hundred thirty-six patients were recruited, of whom 121 (51%) had good PAP adherence 12 months after starting therapy (**Table S1** in the supplemental material). Participants were predominantly White, obese, with a median age of 55 yrs and interquartile range of 44-64 yrs. Sleep symptoms were common, reflected by a high prevalence of poor sleep quality, short sleep duration, insomnia, and daytime sleepiness. Patients with good adherence tended to be younger, more obese, and with higher Insomnia Severity Index and Epworth Sleepiness Scale scores, but the differences between groups were not significant. Although the prevalence of restless legs syndrome was lower in those with good adherence, the difference was only marginally significant (*P* = .04) and the severity of restless legs syndrome was not different (**Table S1**). Relatively few participants were active smokers, and there was no difference in smoking history

or pulmonary function tests between the groups (**Table S2** in the supplemental material). The prevalence of comorbidities was high and similar between the groups, and medication use was not different (**Table S2**). Overall, these data reflect a sleep clinic population with severe, symptomatic OSA and a high prevalence of medical comorbidities.

By study design, adherence with PAP therapy differed significantly between the 3 groups for whom it was prescribed (**Table S3** in the supplemental material). The majority of patients who were started on PAP received treatment with fixed or auto-CPAP (n = 178, 82%; **Table S3**). Of these, 33 (19%) quit, 57 (32%) had poor adherence, and 88 (49%) had good adherence (**Table S3**). Of 38 BPAP users, only 1 patient quit and 33 (87%) had good adherence (**Table S3**). Adherence was significantly higher in the BPAP group (χ^2 test, $P = .0002$). The level of CPAP was slightly higher in the good-adherence group. Although the estimated AHI was normalized by PAP therapy in all patients, there was a marked difference in how much it was used between those with good and poor adherence (**Table S3**). Finally, 10 patients received supplemental O2 at the start of their PAP therapy, but only 3 continued to require it 12 months later, all of whom were in the good-adherence group. The hours of PAP use per night over 12 months in the 3 groups showed an early decline in PAP use that continued in those who quit and those who had poor adherence, in contrast to those with good adherence, in whom it continued to improve (**Figure 1**). The exclusion of patients who received BPAP did not alter the PAP adherence results.

Most patients who were prescribed PAP therapy had severe OSA, although AHI was higher and SpO_2 was lower in those with good adherence (**Table 1**). Conventional scoring of the diagnostic PSG showed a higher frequency of arousals and awakenings in the patients with good adherence but no other differences between groups (**Table 1**). Digital scoring showed that ORP_{NREM} was higher in those with good adherence. Arterial blood gas analysis preceding the PSG showed a significantly higher bicarbonate level in the good-adherence group (**Table 1**). Conventional scoring of the PAP titration part of the split-night PSG showed that SpO_2 was lower and the proportion of REM sleep was slightly higher in those with good adherence but showed no other differences in sleep architecture between the groups (**Table S4** in the supplemental material). Digital scoring showed no differences in ORP values between the 4 adherence groups (**Table S4**).

Figure 1—Adherence with PAP therapy over 12 months in patients categorized into PAP adherence groups.



PAP = positive airway pressure.

Table 2 shows the changes in conventional and ORP indices of sleep between the diagnostic and PAP titration parts of the PSG. AHI and the arousal/awakening index decreased substantially more ($P = 7.E-05$ and 3.E-04, respectively) and SE increased more ($P = 4.E-03$) on PAP in the good-adherence group than in the other groups. The increase in stage 3 NREM sleep in the good-adherence group was marginally significant, and there were no significant intergroup differences in stage 1 and 2 NREM sleep. As expected, AHI decreased in almost all patients (94%). There were no significant intergroup differences in ORP_W. However, ORP_{NREM} and ORP_{TRT} improved significantly more in the good-adherence group (3.E-05, and 3.E-04, respectively).

Figure 2 illustrates the difficulty of using conventional sleep architecture indices to evaluate the improvement of sleep on PAP therapy. In many patients a conventional index improved while another worsened, and the number of patients in whom all conventional PSG metrics improved was only 58 (24.6%). Furthermore, while correlations between changes in the different indices were mostly significant, they were quite weak with r^2 being < 0.25 except for the relationship between the change in arousal index and the change in stage 1 NREM sleep percentage, where it was 0.44 (**Figure 2**, panel F). The strength of this correlation was partly because of the conventional scoring criteria, which require a change to stage 1 NREM sleep whenever an arousal occurs until the reappearance of a spindle or a K complex[40]; consequently, a reduction in arousals will reduce the number of epochs scored as stage 1 NREM sleep.

Figure 3, top, shows the relationship between OSA severity (AHI) and ORP indices during diagnostic PSG. As reported previously,[32] increasing OSA severity was associated with lower ORP_W (because of more microsleep features in epochs scored awake), higher ORP_{NREM} (lighter sleep), and higher ORP_{TRT}. However, at any given AHI, ORP metrics were highly variable. For example, at an AHI of 60 events/h, ORP_{NREM} ranged from ≈0.8, which indicates stable sleep,[32] to ≈1.4, which is a transitional state with a mix of wake and sleep features.[32] A similarly wide range was seen for ORP_W and ORP_{TRT}. **Figure 3**, bottom, shows that these abnormalities tended to reverse during PAP titration, but the changes were also highly variable among individuals, with the change being undesirable in many (points below zero in ORP_W and above zero in ORP_{NREM} and ORP_{TRT}).

Figure 4 shows scatter plots of the relationship between selected variables. There were highly significant correlations between diagnostic PSG values of ORP_{NREM}, AHI, and mean SpO_2 and the changes in these variables during PAP titration (**Figure 4**, panels A–C) but the correlation was considerably weaker for SE, where the changes on PAP were bidirectional across the entire range of SE (**Figure 4**, panel D).

PSG variables associated with PAP adherence

Multiple regression analysis between PAP adherence (categories 1–4) and all 11 conventional and ORP indices during

Table 1—Respiratory measures, arterial blood gases, conventional indices of sleep architecture, and ORP during diagnostic PSG.

	Never	Quit	Poor Adherence	Good Adherence	*P*
n	20	34	61	121	
OSA severity					
AHI (events/h)	45.6 ± 29.2	65.6 ± 32.3	68.5 ± 33.8*	80.3 ± 32.8*	< .01
Mean SpO_2 (%)	89.2 ± 2.6	86.9 ± 4.4	88.2 ± 3.5	85.8 ± 4.7*	< .01
Arterial blood gases					
PaO_2 (mm Hg)	65.6 ± 8.3	63.4 ± 11.5	65.2 ± 9.8	64.4 ± 10.3	.85
$PaCO_2$ (mm Hg)	40.7 ± 4.8	40.6 ± 3.7	40.7 ± 4.5	41.9 ± 4.6	.52
pH_a	7.43 ± 0.03	7.42 ± 0.03	7.43 ± 0.03	7.43 ± 0.03	.24
Bicarbonate (mEq/L)	26.4 ± 2.3	26.3 ± 2.1	26.8 ± 2.4	27.8 ± 2.8†	.01
Sleep architecture					
N1 (% TRT)	18.7 ± 13.2	16.0 ± 15.1	15.6 ± 13.2	19.7 ± 13.6	.22
N2 (% TRT)	37.0 ± 12.0	38.6 ± 15.2	39.9 ± 15.8	35.7 ± 15.0	.34
N3 (% TRT)	11.9 ± 15.5	9.0 ± 10.3	10.0 ± 12.8	8.3 ± 12.5	.62
REM sleep (% TRT)	5.2 ± 5.3	5.7 ± 7.2	3.1 ± 5.0	3.3 ± 6.0	.09
Sleep efficiency (%)	73.2 ± 11.3	69.9 ± 17.1	69.5 ± 18.6	67.5 ± 18.7	.55
Arousal/awakening index (/h)	45.7 ± 25.9	42.1 ± 23.0	44.7 ± 24.8	56.5 ± 28.3†¶	< .01
ORP measures					
ORP_W	2.17 ± 0.10	2.10 ± 0.18	2.14 ± 0.15	2.11 ± 0.18	.29
ORP_{NREM}	0.97 ± 0.26	0.98 ± 0.28	1.07 ± 0.29	1.17 ± 0.31*†	< .01
ORP_{TRT}	1.32 ± 0.22	1.34 ± 0.32	1.40 ± 0.34	1.48 ± 0.34	.06

Mean ± SD; *P* value = ANOVA. *$P \leq .05$ vs never; †$P \leq .05$ vs quit; ¶$P \leq .05$ vs poor adherence. AHI = apnea-hypopnea index, ANOVA = analysis of variance, mean SpO_2 = mean arterial oxyhemoglobin saturation during sleep, N1 = stage 1 NREM sleep, N2 = stage 2 NREM sleep, N3 = stage 3 NREM sleep, NREM = nonrapid eye movement, ORP = odds ratio product, ORP_{NREM} = ORP during NREM sleep, ORP_{TRT} = ORP total recording time, ORP_w = ORP at wake stage, OSA = obstructive sleep apnea, $PaCO_2$ = partial pressure of arterial carbon dioxide, PaO_2 = partial pressure of arterial oxygen, pHa = arterial pH, PSG = polysomnography, REM = rapid eye movement, SD = standard deviation, TRT, total recording time.

diagnostic PSG identified 3 significant variables with the following equation (n = 236; $r^2 = 0.12$, F ratio = 10.8, $P = 1E\text{-}06$):

$$\text{Adherence Index} = 5.51 + 0.51\ ORP_{NREM} + 0.005\ AHI - 0.037\ \text{mean}\ SpO_2 \quad \text{Eq. 1}$$

Multiple regression between PAP adherence (categories 1–4) and the changes in 11 conventional and ORP indices on PAP yielded the following equation (n = 236; $r^2 = 0.13$, F ratio = 11.4, $P = 1E\text{-}06$):

$$\text{Adherence Index} = 3.02 - 0.68DORP_{NREM} + 0.009DSE + 1.46DORP_W \quad \text{Eq. 2}$$

Finally, multiple regression between PAP adherence (categories 1–4) and the 6 significant variables in **Equation 1** and **Equation 2** yielded the following equation (n = 236; $r^2 = 0.16$, F ratio = 10.9, $P = 1E\text{-}07$):

$$\text{Adherence Index} = 5.82 + 0.56\ ORP_{NREM} - 0.038\ \text{mean}\ SpO_2 + 0.011DSE + 1.30DORP_W \quad \text{Eq. 3}$$

Figure 5 shows the relationship between the Adherence Index calculated for each patient according to **Equation 1** and the probability for each of the 4 adherence categories to occur in the same patient, as calculated by logistic regression. Because the Adherence Index increased, the probability of good adherence (category 4) increased monotonically ($r^2 = 0.98$) whereas the probabilities of the other 3 adherence outcomes (categories 1–3) decreased monotonically ($r^2 = 0.81$, 0.95, and 0.84, respectively). At an Adherence Index of 4.0, the probability of good adherence was approximately 90%.

Comparison of BPAP and CPAP users

As indicated above, BPAP users had significantly better adherence. BPAP users had significantly lower mean SpO_2 during diagnostic PSG than CPAP users (82.7 ± 4.3 vs 87.7 ± 3.9%; $P = 1E\text{-}11$) and, as a result, a higher Adherence Index (3.37 ± 0.37 vs 3.22 ± 0.34; $P = .02$), predicting better adherence. However, the proportion of BPAP users with good adherence was above the predicted value for an Adherence Index of 3.37 (87% [from **Table S3**] vs 60% from Figure 5).

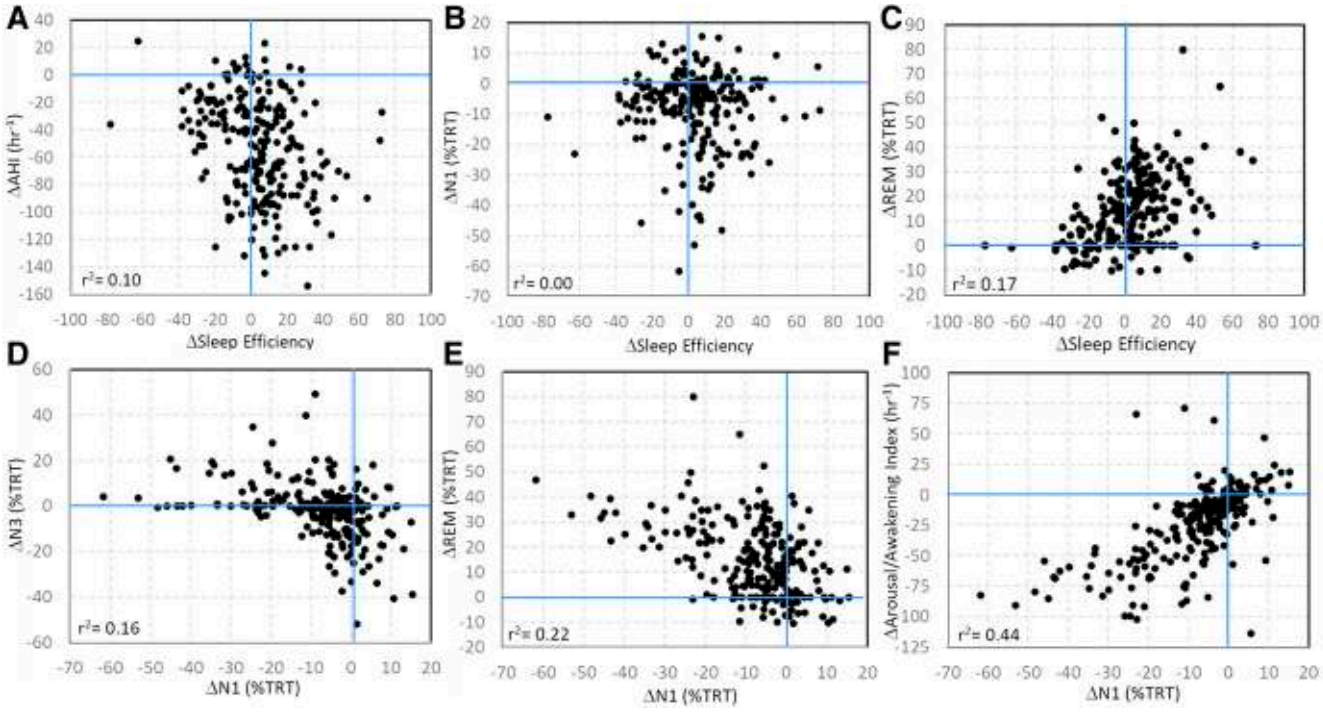
To determine whether the superior PAP adherence resulted from the use of BPAP per se or to other differences that might encourage greater adherence, and which lead to BPAP selection in the first place, we matched every BPAP user with a CPAP user who had a similar or the nearest available mean SpO_2 during the diagnostic PSG and compared several variables that were not included in the multiple linear regression analysis. Thirty-seven of 38 BPAP users and 35 of the 38 matched CPAP users had awake arterial blood gas data, and these were included in the

Table 2—Change in respiratory measures, conventional indices of sleep architecture, and ORP between diagnostic and treatment PSG.

	Never	Quit	Poor Adherence	Good Adherence	*P*
n	20	34	61	121	
OSA severity					
AHI (events/h)	–25.9 ± 31.9	–51.0 ± 34.4	–44.6 ± 39.2	–61.7 ± 33.4*¶	< .01
Mean SpO_2 (%)	1.5 ± 2.2	3.7 ± 4.2	2.9 ± 2.7	3.9 ± 3.3*	< .01
Sleep architecture					
N1 (% TRT)	–8.1 ± 12.6	–7.0 ± 14.5	–4.7 ± 11.8	–10.0 ± 12.1	.06
N2 (% TRT)	–5.8 ± 18.6	–0.2 ± 14.5	–0.5 ± 18.3	0.3 ± 17.1	.54
N3 (% TRT)	–4.1 ± 12.1	–4.6 ± 7.9	–4.4 ± 11.9	0.5 ± 13.2¶	.02
REM sleep (% TRT)	11.0 ± 17.7	14.3 ± 14.6	11.6 ± 14.3	17.4 ± 14.2	.05
Sleep efficiency (%)	–7.4 ± 20.4	1.9 ± 17.7	0.4 ± 17.7	8.3 ± 22.2*	< .01
Arousal/awakening index (/h)	–12.2 ± 31.3	–18.9 ± 26.0	–13.9 ± 24.9	–31.7 ± 31.8*¶	< .01
ORP measures					
ORP_W	–0.06 ± 0.18	–0.02 ± 0.16	–0.01 ± 0.12	0.02 ± 0.15	.16
ORP_{NREM}	–0.05 ± 0.28	–0.16 ± 0.28	–0.14 ± 0.26	–0.30 ± 0.28*†¶	< .01
ORP_{TRT}	0.06 ± 0.36	–0.09 ± 0.34	–0.08 ± 0.32	–0.24 ± 0.34*¶	< .01

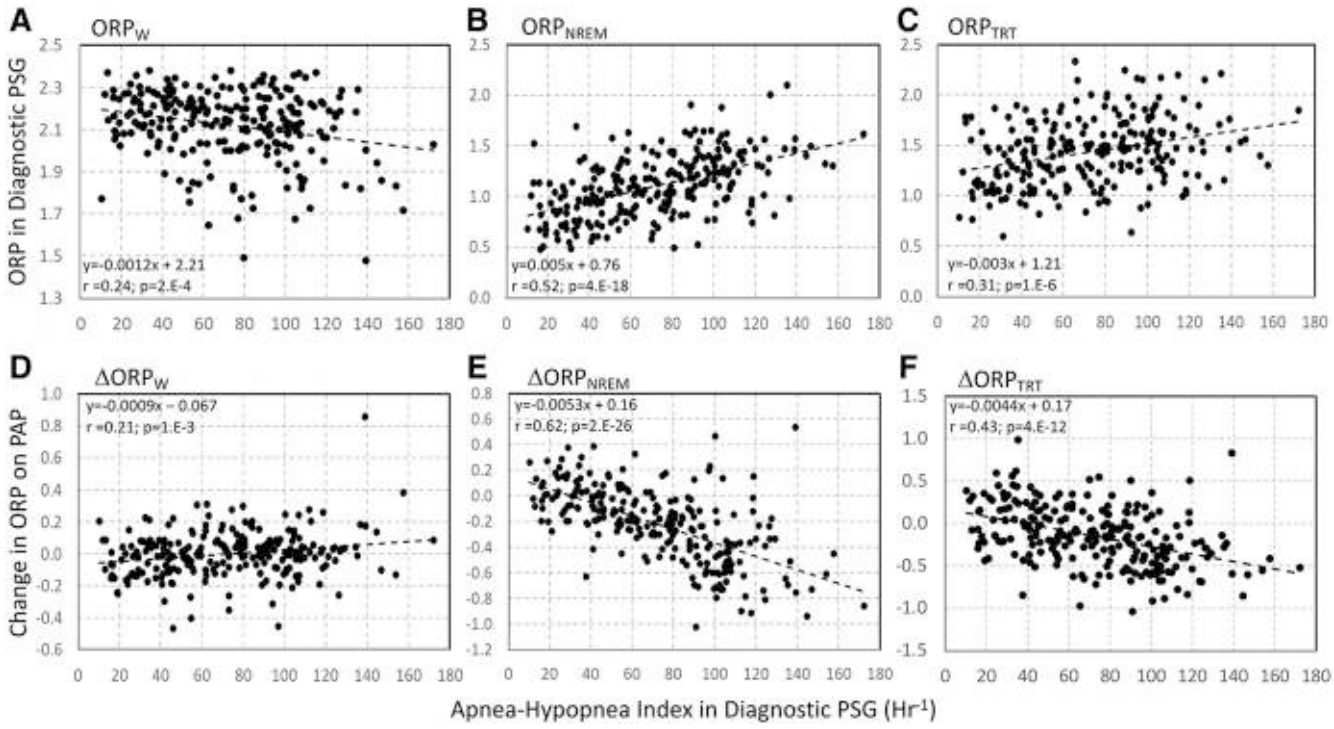
Mean ± SD; *P* value = ANOVA. *$P \leq .05$ vs never; †$P \leq .05$ vs quit; ¶$P \leq .05$ vs poor adherence. AHI = apnea-hypopnea index, ANOVA = analysis of variance, mean SpO_2 = mean arterial oxyhemoglobin saturation during sleep, N1 = stage 1 NREM sleep, N2 = stage 2 NREM sleep, N3 = stage 3 NREM sleep, NREM = nonrapid eye movement, ORP = odds ratio product, ORP_{NREM} = ORP during NREM sleep, ORP_{TRT} = ORP total recording time, ORP_w = ORP at wake stage, OSA = obstructive sleep apnea, PSG = polysomnography, REM = rapid eye movement, SD = standard deviation, TRT, total recording time.

Figure 2—Relationship between the changes in conventional PSG indices during PAP titration compared to their diagnostic values.



AHI = apnea-hypopnea index, N1 = stage 1 NREM sleep, N3 = stage 3 NREM sleep, PAP = positive airway pressure, PSG = polysomnography, REM = rapid eye movement (expressed as percentage of TRT), TRT = total recording time.

Figure 3—AHI and ORP in the diagnostic PSG.



Top: Relationship between AHI and ORP in the diagnostic PSG. **Bottom:** Relationship between AHI in the diagnostic PSG and change in ORP on PAP therapy. ORP during wake stage (ORP_W), NREM sleep stage (ORP_{NREM}), and total recording time (ORP_{TRT}). Note that at AHI < 40 events/h, the changes in all ORP metrics with PAP (**Bottom**) are bidirectional and predominantly undesirable (negative for ORP_W and positive for ORP_{NREM} and ORP_{TRT}). AHI = apnea-hypopnea index, NREM = nonrapid eye movement, ORP = odds ratio product, PAP = positive airway pressure, PSG = polysomnography.

comparison (Table 3). At a similar mean SpO_2, BPAP users continued to represent a significantly higher proportion of patients with good adherence ($P < .01$; Table 3) despite no difference in the Adherence Index, in variables included in the Adherence Index, or in other variables included in **Equation 1** (ORP_{WAKE}, ORP_{TRT}, arousal/awakening index, periodic leg movement index). However, BPAP users had significantly higher awake partial pressure of arterial carbon dioxide and serum bicarbonate (HCO_3) HCO_3^-, consistent with compensated respiratory acidosis. Interestingly, when the multiple regression analysis using the 11 variables derived from diagnostic study was repeated after excluding BPAP users (n = 197), there was no longer an association between mean SpO_2 and the adherence category (1–4). ORP_{NREM} and AHI remained the only variables to show significant associations with adherence with similar predictive power before excluding BPAP data ($P = 2E\text{-}07$):

$$\text{Adherence Index} = 1.78 + 0.83 * ORP_{NREM} + 0.005 * AHI \quad \text{Eq. 4}$$

In the entire group of CPAP users, awake blood gas analysis showed a normal acid balance (partial pressure of arterial CO_2 = 40.2 ± 4.0 mm Hg, pH = 7.40 ± 0.03, HCO_3^- =26.5 ± 2.4 mmol/L). These results suggest that the association between mean SpO_2 and adherence is limited to patients who met our PSG criteria for BPAP use and who showed evidence of chronic hypoventilation (Table 3).

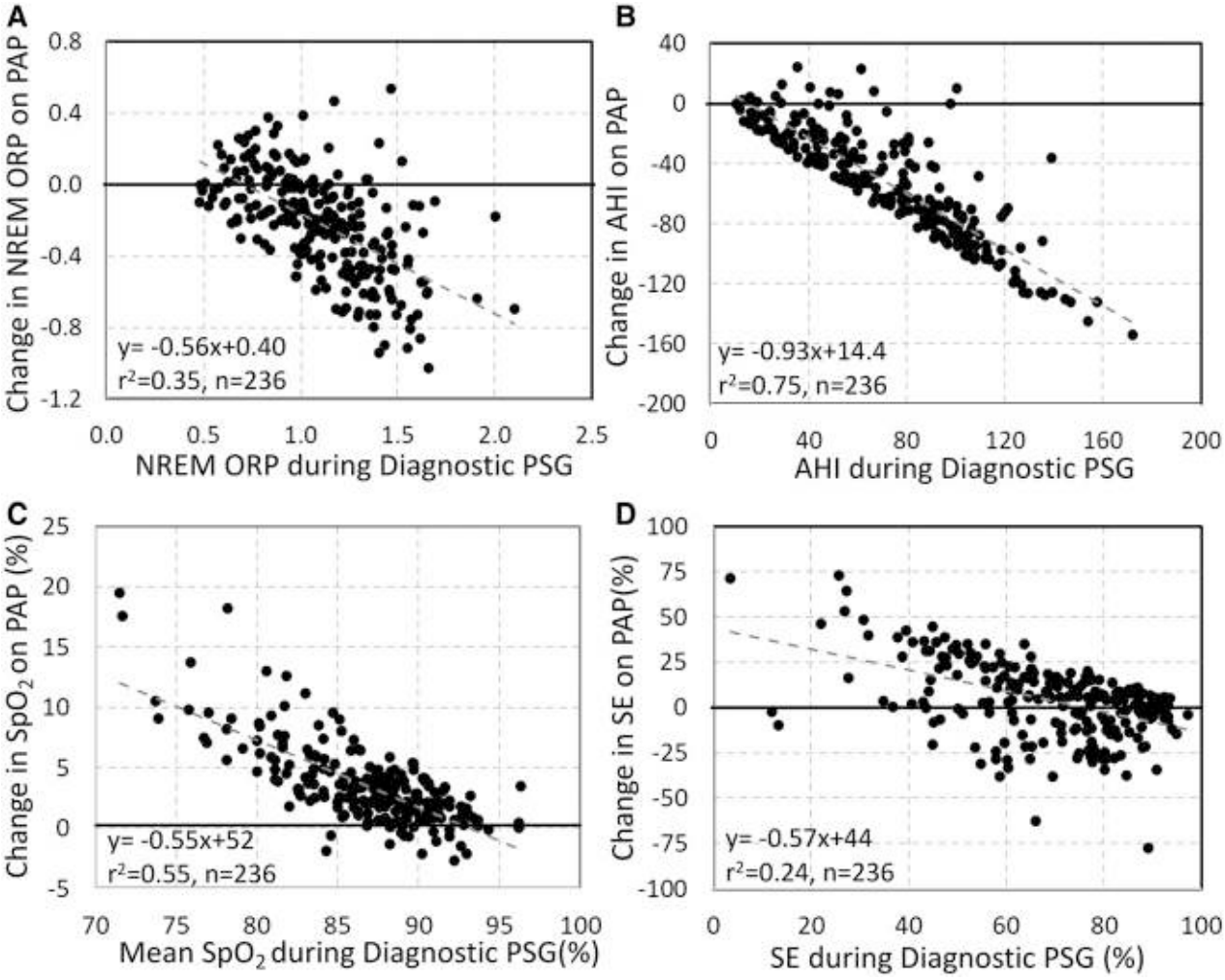
DISCUSSION

We investigated whether a validated index of sleep depth (ORP) and a surrogate index of sleep hypoventilation (mean nocturnal SpO_2) and their change with PAP therapy predicted long-term adherence with this treatment. We found that the combination of these 2 objective metrics with conventional measures of sleep quality provided a composite index (the Adherence Index) that was robustly associated with the probability of good long-term adherence to PAP therapy. Furthermore, Adherence Indices determined from diagnostic PSG alone (**Equation 1**) were only marginally inferior to those obtained during PAP titration (**Equation 2** and **Equation 3**), indicating that PAP adherence can be predicted from diagnostic PSG data before the initiation of PAP therapy in most patients. However, adherence was clearly superior to what was predicted from the first analysis (diagnostic PSG variables) in a subgroup of patients with hypoxemia associated with chronic hypoventilation, who were identified during PAP titration and were treated with BPAP.

Variables used to predict PAP adherence

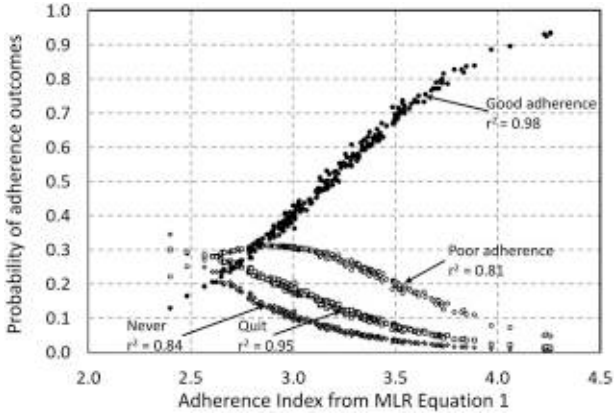
In this study, we investigated 2 PSG variables not previously explored in studies of PAP adherence—ORP and mean nocturnal SpO_2—based on our hypothesis that a collapsible upper

Figure 4—Relationship between selected variables in the diagnostic PSG and their change during PAP titration.



AHI = apnea-hypopnea index, NREM = nonrapid eye movement, ORP = odds ratio product, PAP = positive airway pressure, PSG = polysomnography, SE = sleep efficiency, SpO2 = oxy-hemoglobin saturation.

Figure 5—Probability of each adherence outcome based on the Adherence Index.



MLR = multiple linear regression.

airway may impair sleep quality by disrupting sleep and/or by resulting in hypoventilation, depending on the arousal threshold and the ventilatory response to asphyxia.[41] Because both high sleep ORP (light sleep) and hypercapnia can result from causes other than upper airway collapse, the other condition we imposed was that these abnormalities should be reversed by PAP titration. We reasoned that if these conditions are met, then sleep quality should improve on PAP to the point where the clinical benefits outweigh the challenges of using this therapy, resulting in good long-term adherence.

In developing the prediction model, we included all variables, conventional and ORP-related, that are readily available during routine diagnostic and PAP titration PSG and potentially contribute to nocturnal and daytime symptoms such that their improvement on PAP may facilitate PAP acceptance. Of the 1 such variables available in the diagnostic PSG studies, the 3 that were most strongly associated with PAP adherence were ORP_{NREM}, AHI, and mean nocturnal SpO_2 (from the first analysis).

It is plausible that improvement in objective measures of sleep depth (reflected by a decrease in ORP_{NREM}) would be accompanied by improvement in perceived sleep quality and thereby promote PAP adherence. The continued association of AHI with PAP adherence after controlling for changes in sleep depth indicates that the frequency of obstructive events is important whether sleep is light or deep. In the case of light sleep and, given that light sleep is not restricted to OSA, a high AHI increases the likelihood of the light sleep being OSA-related and hence likely to improve on PAP. On the other hand, when OSA occurs during deep sleep, ORP often increases at the end of the respiratory event, and this increase may or not be sufficient to be scored as a conventional arousal (**Figure S1** in the supplemental material, panel A). Regardless, such brief decreases in sleep depth represent transient interruptions of deep sleep, and this would be eliminated with the relief of obstructive respiratory events.

The negative association between mean nocturnal SpO_2 and PAP adherence was only evident when BPAP users, who had evidence of chronic hypoventilation (**Table 3**), were included in the regression analysis. This finding is in keeping with previous reports that chronic hypercapnia in the setting of OSA is an important determinant of impaired cognitive function and excessive sleepiness.[18,19] The coexistence of hypoventilation in the BPAP group would be expected to result in greater symptomatic relief and, by extension, better adherence following the relief of OSA. Whether the use of BPAP per se accounted for better adherence, eg, because it is better tolerated or is more effective in managing hypoventilation, cannot be determined in this study.

Analysis of the association between the change in PSG variables during PAP titration and PAP adherence showed that the change in both SE and ORP_{WAKE} (**Equation 2** and **Equation 3**) were associated with better adherence. It is not surprising that an improvement in SE would improve cognitive function and thereby promote PAP adherence.[37,42,43] What was unexpected was the improvement in SE with PAP in most patients with low SE in the diagnostic study (**Figure 4**, panel D) because a recent study found that excessive wake time in patients with OSA is not the result of OSA.[30] However, OSA in the latter study was only mild/moderate (AHI [mean, 5–95 percentile] 21 events/h; 3–75), whereas it was very severe in the current study (AHI 73 events/h; 19–127). This finding implies that excessive wake time may be directly related to OSA when OSA is severe.

We reported previously that ORP_{WAKE} decreases as a function of OSA severity,[32] and this was confirmed in the current study ($r^2 = 0.059$, $P < .0002$; **Figure 3**, panel A). Low ORP during the wake stage indicates the presence of sleep features within epochs scored as awake by conventional criteria.[32] One such sleep feature is the presence of microsleep episodes (sleep intrusions) during which ORP is below the usual wake range (> 1.75; **Figure S1,** panel B).[32] Although frequent microsleep periods are nonspecific, they are commonly seen in patients with very severe OSA where obstructive events occur as the

Table 3—Adherence and other variables in BPAP and CPAP users matched for nocturnal hypoxemia.

	BPAP	CPAP	*P*
n	38	38	
Adherence category			
Good adherence, n (%)	33 (86.9)	20 (52.6)	< .01
Poor adherence, n (%)	4 (10.5)	6 (15.8)	
Quit, n (%)	1 (2.6)	12 (31.6)	
Adherence Index			
Adherence Index (model 1)	3.37 ± 0.37	3.44 ± 0.36	.38
ORP_{NREM}	1.06 ± 0.36	1.18 ± 0.30	.14
AHI (events/h)	74.7 ± 35.3	83.9 ± 34.7	.26
Mean SpO_2 (%)	82.6 ± 4.3	82.7 ± 4.1	.93
Other variables			
ORP_W	2.12 ± 0.16	2.08 ± 0.20	.35
ORP_{TRT}	1.36 ± 0.42	1.40 ± 0.34	.67
Arousal/awakening index (/h)	50.1 ± 29.3	51.5 ± 26.6	.83
PLM index (/h)	13.1 ± 27.4	9.0 ± 10.9	.40
PaO_2 (mm Hg)	58.2 ± 11.3	63.8 ± 11.4	.04
$PaCO_2$ (mm Hg)	45.1 ± 4.1	40.9 ± 3.8	< .01
pH_a	7.42 ± 0.03	7.43 ± 0.03	.80
Bicarbonate (mEq/L)	29.3 ± 2.5	26.8 ± 2.2	< .01

Number (%), (*P* value = χ^2); mean ± SD (*P* value = *t* test). AHI = apnea-hypopnea index, BPAP = bilevel positive airway pressure, CPAP = continuous positive airway pressure, ORP = odds ratio product, ORP_{NREM} = ORP during NREM sleep, ORP_{TRT} = ORP total recording time, ORP_w = ORP at wake stage, $PaCO_2$ = partial pressure of arterial carbon dioxide, PaO_2 = partial pressure of arterial oxygen, pHa = arterial pH, PLM = periodic limb movements, SD = standard deviation, SpO_2 = oxyhemoglobin saturation, TRT = total recording time.

patient drifts toward sleep but progression to sleep is aborted by the obstructive event (**Figure S1,** panel B). ORP_{WAKE} in the diagnostic PSG was not associated with better PAP adherence (**Equation 1**), which likely reflected the nonspecific nature of low ORP_{WAKE}. However, an increase in ORP_{WAKE} on PAP suggested that sleep intrusions during wake epochs are in part related to OSA. The fact that reversal of these intrusions, as indicated by a higher ORP_{WAKE} on PAP, was associated with improved PAP adherence to CPAP (**Equation 2** and **Equation 3**) suggests that sleep intrusions during the wake stage adversely impact sleep quality.

Predictions based on diagnostic PSG variables vs changes in PSG variables on PAP

We had expected that the changes in PSG variables associated with PAP titration would be more predictive than diagnostic PSG measures of sleep. However, predictions based on diagnostic PSG measures were almost as strong as those based on PAP-induced changes (**Equation 1** vs **Equation 2**). The reason for this welcome finding is that changes in the relevant PSG variables on PAP were directly correlated with the diagnostic PSG measures (**Figure 4**, panels A–D). Thus, ORP_{NREM} or AHI cannot decrease much if they are already low at baseline, and SpO_2 and SE cannot increase much if they are already high. It is also possible that split-night PSG studies, representing the first and brief exposure to PAP, do not indicate the full benefit of PAP when the patient has not been acclimated to it. Notwithstanding this limitation, it appears that predictions of PAP adherence based on diagnostic PSG measures may be adequate in most patients. This may be useful in patients who are treated with auto-CPAP without a PAP titration PSG. It would also be of interest to determine whether patients with OSA and chronic hypoventilation do as well on CPAP as on BPAP given more time on CPAP to allow for the slower adjustment of the acid-base balance in the presence of chronic respiratory acidosis.

The Adherence Index and its clinical implications

The Adherence Index provides an indication of the likelihood that a patient diagnosed with OSA will be adherent with PAP therapy. The exact probabilities were derived using logistic regression and are shown in **Figure 5**. The likelihood of good adherence increases progressively as the index increases from 2.5 (16% probability) to 4.2 (> 90% probability). At the same time, the index gives quantitative information about how disruptive OSA is to the patient's sleep quality. Thus, an index of 2.5 using **Equation 1** means that sleep is quite deep (low ORP_{NREM}) and that there is no significant sleep hypoventilation despite OSA, whereas a value of 4 indicates serious disturbance in both variables. This information can add to a precision medicine–based approach in the management of an individual patient's sleep-disordered breathing. For example, a high Adherence Index increases the likelihood that PAP therapy will improve sleep quality, whereas a low Adherence Index makes a good response to PAP less likely and should prompt re-evaluation of the relevance of OSA to the patient's sleep symptoms. On the other hand, a patient who has difficulty using PAP despite a high Adherence Index may require evaluation of new medical or environmental factors that may be responsible. The use of a low Adherence Index obtained from a diagnostic PSG may be valuable both in patients with mild to moderate OSA, for whom alternative therapies to PAP may be considered, and in patients with severe OSA, for whom additional support may be required to improve their ability to use PAP therapy.

Limitations

The study has a number of limitations. First, this was a retrospective analysis of PSGs from a single center. Although this was a sleep clinic population referred for investigation of OSA, the proportion of female patients in each of our 4 PAP adherence groups was 40% or higher (**Table S1**). The predominance of White patients reflects the demographics of the community we serve. Although the sample size was relatively small (n = 236), it compares favorably to previous publications that have addressed this topic.[15,16,20–23] Furthermore, a strength of our cohort is the detailed clinical and PSG data in addition to arterial blood gas analysis and nocturnal transcutaneous PCO_2 monitoring, which were not included in previous publications. Second, the Adherence Indices were derived from only a few hours of PSG recordings in split-night studies. Although split-night PSG studies have their limitations, they provided the opportunity to compare the strength of the Adherence Index on and off PAP therapy in a single night without the potential for confounding variables that may arise between 2 separate nights to influence our results. Third, most patients had severe OSA, which limits the generalizability of our findings to all patients with OSA. However, poor PAP adherence was not limited to those with mild and moderate OSA, reflected by the fact that the AHI was not significantly different between the 4 PAP adherence groups (**Table S4**); consequently, patients with different OSA severity who had poor PAP adherence were included in our analysis. Fourth, we did not measure all of the multiple additional factors that can influence PAP adherence, including potential differences in how patients were followed up once they were started on PAP therapy. Consequently, these results need to be validated in prospective studies utilizing full-night PSG with and without PAP titration and including patients with a broader spectrum of OSA severity. However, this limitation should not detract from the main findings of the current study, which highlights the importance of improved sleep quality and the correction of nocturnal hypoxemia as significant determinants of long-term adherence with PAP therapy. Furthermore, the study provides a general template for obtaining the probability of good PAP adherence that can be implemented in future studies.

CONCLUSIONS

In summary, we have shown that combining conventional sleep measures and an index of sleep depth, based on the ORP, in the diagnostic PSG provides an Adherence Index that predicts long-term adherence with PAP therapy. This added value of the diagnostic PSG is available before PAP therapy is started and can provide an early indication of whether individual patients require additional resources in their management. Future

prospective studies are required to determine whether the use of this index will improve long-term adherence with PAP therapy and its impact on clinical outcomes.

ABBREVIATIONS

AHI, apnea-hypopnea index
BPAP, bilevel PAP
CPAP, continuous PAP
NREM, nonrapid eye movement
ORP, odds ratio product
ORP_{NREM}, ORP during NREM sleep
ORP_{TRT}, ORP total recording time
ORP_{W}, ORP during wake stage
OSA, obstructive sleep apnea
PAP, positive airway pressure
PSG, polysomnography
REM, rapid eye movement
SE, sleep efficiency
SpO_2, arterial oxyhemoglobin saturation measured by pulse oximetry

REFERENCES

1. Benjafield AV, Ayas NT, Eastwood PR, et al. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. *Lancet Respir Med.* 2019;7(8):687–698.
2. Moyer CA, Sonnad SS, Garetz SL, Helman JI, Chervin RD. Quality of life in obstructive sleep apnea: a systematic review of the literature. *Sleep Med.* 2001; 2(6):477–491.
3. Tregear S, Reston J, Schoelles K, Phillips B. Obstructive sleep apnea and risk of motor vehicle crash: systematic review and meta-analysis. *J Clin Sleep Med.* 2009;5(6):573–581.
4. Beaudin AE, Raneri JK, Ayas NT, et al. Cognitive function in a sleep clinic cohort of patients with obstructive sleep apnea. *Ann Am Thorac Soc.* 2021;18(5):865–875.
5. Hillman DR, Murphy AS, Pezzullo L. The economic cost of sleep disorders. *Sleep.* 2006;29(3):299–305.
6. Albarrak M, Banno K, Sabbagh AA, et al. Utilization of healthcare resources in obstructive sleep apnea syndrome: a 5-year follow-up study in men using CPAP. *Sleep.* 2005;28(10):1306–1311.
7. Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet* 2005; 365(9464):1046–1053.
8. Almendros I, Basoglu ÖK, Conde SV, Liguori C, Saaresranta T. Metabolic dysfunction in OSA: is there something new under the sun? *J Sleep Res.* 2021;31(1):e13418.
9. Beaudin AE, Raneri JK, Ahmed SB, et al. Risk of chronic kidney disease in patients with obstructive sleep apnea. *Sleep.* 2021;45(2):zsab267.
10. Bubu OM, Pirraglia E, Andrade AG, et al.; Alzheimer's Disease Neuroimaging Initiative. Obstructive sleep apnea and longitudinal Alzheimer's disease biomarker changes. *Sleep*. 2019;42(6):zsz048.
11. Jordan AS, McSharry DG, Malhotra A. Adult obstructive sleep apnoea. *Lancet* 2014;383(9918):736–747.
12. Wolkove N, Baltzan M, Kamel H, Dabrusin R, Palayew M. Long-term compliance with continuous positive airway pressure in patients with obstructive sleep apnea. *Can Respir J.* 2008;15(7):365–369.
13. Rosen CL, Auckley D, Benca R, et al. A multisite randomized trial of portable sleep studies and positive airway pressure autotitration versus laboratory-based polysomnography for the diagnosis and treatment of obstructive sleep apnea: the HomePAP study. *Sleep.* 2012;35(6):757–767.
14. Mehrtash M, Bakker JP, Ayas N. Predictors of continuous positive airway pressure adherence in patients with obstructive sleep apnea. *Lung.* 2019;197(2):115–121.
15. Jacobsen AR, Eriksen F, Hansen RW, et al. Determinants for adherence to continuous positive airway pressure therapy in obstructive sleep apnea. *PLoS One.* 2017;12(12):e0189614.
16. May AM, Gharibeh T, Wang L, et al. CPAP adherence predictors in a randomized trial of moderate-to-severe OSA enriched with women and minorities. *Chest.* 2018; 154(3):567–578.
17. Crawford MR, Espie CA, Bartlett DJ, Grunstein RR. Integrating psychology and medicine in CPAP adherence—new concepts? *Sleep Med Rev.* 2014;18(2):123–139.
18. Wang D, Piper AJ, Yee BJ, et al. Hypercapnia is a key correlate of EEG activation and daytime sleepiness in hypercapnic sleep disordered breathing patients. *J Clin Sleep Med.* 2014;10(5):517–522.
19. Beaudin AE, Raneri JK, Ayas NT, Skomro RP, Smith EE, Hanly PJ. Contribution of hypercapnia to cognitive impairment in severe sleep-disordered breathing. *J Clin Sleep Med.* 2022;18(1):245–254.
20. Chen YF, Hang LW, Huang CS, Liang SJ, Chung WS. Polysomnographic predictors of persistent continuous positive airway pressure adherence in patients with moderate and severe obstructive sleep apnea. *Kaohsiung J Med Sci.* 2015; 31(2):83–89.
21. Hoshino T, Sasanabe R, Murotani K, et al. Polysomnographic parameters during non-rapid eye movement sleep predict continuous positive airway pressure adherence. *Nagoya J Med Sci.* 2016;78(2):195–203.
22. Somiah M, Taxin Z, Keating J, et al. Sleep quality, short-term and long-term CPAP adherence. *J Clin Sleep Med.* 2012;8(5):489–500.
23. Drake CL, Day R, Hudgel D, et al. Sleep during titration predicts continuous positive airway pressure compliance. *Sleep.* 2003;26(3):308–311.
24. Norman RG, Pal I, Stewart C, Walsleben JA, Rapoport DM. Interobserver agreement among sleep scorers from different centers in a large dataset. *Sleep.* 2000;23(7):901–908.
25. Collop NA. Scoring variability between polysomnography technologists in different sleep laboratories. *Sleep Med.* 2002;3(1):43–47.
26. Younes M, Kuna ST, Pack AI, et al. Reliability of the American Academy of Sleep Medicine Rules for Assessing Sleep Depth in Clinical Practice. *J Clin Sleep Med.* 2018;14(2):205–213.
27. Qanash S, Giannouli E, Younes M. Assessment of intervention-related changes in non-rapid-eye-movement sleep depth: importance of sleep depth changes within stage 2. *Sleep Med.* 2017;40:84–93.
28. Younes M, Ostrowski M, Soiferman M, et al. Odds ratio product of sleep EEG as a continuous measure of sleep state. *Sleep*. 2015;38(4):641–654.
29. Penner CG, Gerardy B, Ryan R, Williams M. The odds ratio product (an objective sleep depth measure): normal values, repeatability, and change with CPAP in patients with OSA. *J Clin Sleep Med.* 2019;15(8):1155–1163.
30. Younes M, Giannouli E. Mechanism of excessive wake time when associated with obstructive sleep apnea or periodic limb movements. *J Clin Sleep Med.* 2020;16(3):389–399.
31. Younes M, Schweitzer PK, Griffin KS, Balshaw R, Walsh JK. Comparing two measures of sleep depth/intensity. *Sleep.* 2020;43(12):zsaa127.
32. Younes M, Azarbarzin A, Reid M, Mazzotti DR, Redline S. Characteristics and reproducibility of novel sleep EEG biomarkers and their variation with sleep apnea and insomnia in a large community-based cohort. *Sleep.* 2021;44(10):zsab145.
33. Bastien CH, Vallières A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Med.* 2001;2(4):297–307.
34. Johns MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. *Sleep.* 1991;14(6):540–545.
35. Buysse DJ, Reynolds CF III, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res.* 1989;28(2):193–213.
36. Braganza MV, Hanly PJ, Fraser KL, Tsai WH, Pendharkar SR. Predicting CPAP failure in patients with suspected sleep hypoventilation identified on ambulatory testing. *J Clin Sleep Med.* 2020;16(9):1555–1565.
37. Grandner MA, Patel NP, Gehrman PR, Perlis ML, Pack AI. Problems associated with short sleep: bridging the gap between laboratory and epidemiological studies. *Sleep Med Rev.* 2010;14(4):239–247.

38. Kane SP. Drug List by Therapeutic Category. https://clincalc.com/Downloads/Top250Drugs-DrugList.pdf. Accessed May 17, 2022.
39. Lusic Kalcina L, Pavlinac Dodig I, Pecotic R, Valic M, Dogas Z. Psychomotor performance in patients with obstructive sleep apnea syndrome. *Nat Sci Sleep.* 2020;12:183–195.
40. Berry RB, Brooks R, Gamaldo CE, et al; for the American Academy of Sleep Medicine. *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications.* Version 2.2. Darien, IL: American Academy of Sleep Medicine; 2015.
41. Younes M. Role of respiratory control mechanisms in the pathogenesis of obstructive sleep disorders. *J Applied Physiol.* 2008;105(5):1389–1405.
42. Lim J, Dinges DF. A meta-analysis of the impact of short-term sleep deprivation on cognitive variables. *Psychol Bull.* 2010;136(3):375–389.
43. Williamson AM, Feyer AM. Moderate sleep deprivation produces impairments in cognitive and motor performance equivalent to legally prescribed levels of alcohol intoxication. *Occup Environ Med.* 2000;57(10):649–655.

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