The Correlation Between Patient-Reported Outcome Measures and

Mean Nightly Apnea Hypopnea Index

After Six Months of Continuous Positive Airway Pressure Treatment

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Abstract

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Objectives: The changes in patient-reported measures of obstructive sleep apnea (OSA) burden are largely discordant with the change in apnea hypopnea index (AHI) before and after treatment. For patients treated with continuous positive airway pressure (CPAP), some investigators have theorized that this discordance is due in part to the variability in CPAP use. We aim to test the hypothesis that patient-reported outcomes of CPAP treatment have stronger correlations with AHI when it is corrected for mean nightly CPAP use.

Methods: This was a cross sectional study of 459 adults treated with CPAP for OSA. Five patient-reported measures of OSA burden were collected at baseline

and after six months of CPAP therapy. The correlations between the change in each patient-reported measure and the change in AHI as well as mean nightly AHI (corrected for CPAP use with a weighted average formula) were measured.

Results: The change in AHI was weakly but significantly correlated with change in two of the five clinical measures. The change in mean nightly AHI demonstrated statistically significant correlations with four out of five clinical measures, though each with coefficients less than 0.3.

Conclusions: Correction for CPAP use yielded overall small but significant improvements in the correlations between patient-reported measures of sleep apnea burden and AHI after six months of treatment.

INTRODUCTION

The changes in patient-reported measures of the clinical burden of obstructive sleep apnea (OSA) before and after treatment are largely discordant with apnea hypopnea index (AHI) before and after treatment (1-3). For patients treated with continuous positive airway pressure (CPAP), some investigators have theorized that this discordance is due in part to the variability in CPAP use. They have suggested formulas for calculating a mean nightly AHI weighted by the proportion of sleep time that the CPAP is used (4, 5). For example, if a patient who sleeps 8 hours per night has an improvement in AHI from 25/h to 5/h on CPAP and uses CPAP 4 hours per night on 5 nights per week (and none on 2 nights per week), then after applying the weighted average formula, the mean nightly AHI would be 18/h.

This study aimed to test whether the changes in five patient-reported outcome measures after 6 months of CPAP treatment correlated better with the improvement in AHI on CPAP when it was corrected for the amount of time the CPAP was used. We hypothesized that there would be a weak correlation (< 0.3) between the change in each of the patient-reported outcome measures and the change in AHI on CPAP treatment. We hypothesized that the change in each of the patient-reported outcome measures would have a significantly stronger correlation with the change in mean nightly AHI on CPAP treatment.

METHODS

Study Design

This was a cross-sectional study of adult participants recruited between July 2004 and October 2008 to the Seattle Sleep Cohort at the University of Washington Sleep Disorders Center at Harborview Medical Center, Seattle, Washington.

Subjects

Subjects included all patients aged 18 years or older who presented to the sleep laboratory for overnight polysomnography for suspected obstructive sleep apnea, had the linguistic and cognitive ability to answer questionnaires and give informed consent, consented to participate in the study, completed both baseline and titration polysomnography, were prescribed CPAP and followed up after 6 months of CPAP treatment. Subjects were excluded for prior diagnosis of sleep apnea, other upper airway obstructive disease, or neurologic, neuromuscular, or pulmonary disease. Patients with either full-night or split-night polysomnography were included in the study. The University of Washington institutional review board approved this study.

Data collection

Data were collected on the night of the first diagnostic polysomnography and at 6 months by mail or in person in the Sleep Disorders Clinic. Consenting

participants were administered the Epworth Sleepiness Scale, Sleep Apnea

Quality of Life Index, Pittsburgh Sleep Quality Index, and the Short Form–36 (SF-

36) by trained research assistants in a standardized fashion. The Epworth

Sleepiness Scale is an 8-question measure of daytime sleep propensity widely

used in the clinical setting (6). It is scored from 0 – 24 with a higher score

indicating worse daytime sleep propensity.   The Sleep Apnea Quality of Life

Index is an OSA-specific quality of life index with a total score from 1 (poor

quality of life) to 7 (excellent quality of life) (7), while the Pittsburgh Sleep Quality

Index is a sleep-specific quality of life index scored on 0 – 21 scale, with a score

of 5 or greater indicating a "poor" sleeper (8). The SF-36 is a generic health

status instrument with two mutually exclusive component summary scores,

Physical Health and Mental Health. Each component score is calculated from

normalized aggregate scores, where 50 ± 10 represents the normalized score

and standard deviation of the general US 1998 population norms (9-11); a lower

score indicates worse health status than the 1998 norms. Patients also

completed a demographic questionnaire at baseline and body mass index (BMI)

was calculated from height and weight measurements made on the night of the

diagnostic polysomnography.

　　　　All patients underwent overnight, monitored, in-laboratory

polysomnography, from which AHI, apnea index, oxyhemoglobin desaturation

index, arousal index, and the lowest oxyhemoglobin saturation were extracted.

All polysomnography tests included recordings of sleep state parameters (4-lead

electroencephalogram, bilateral electro-oculogram, and submental and bilateral

leg electromyogram), breathing (nasal pressure transducer and oronasal thermistor, as well as thoracic and abdominal excursion by strain gauge), pulse oximetry, electrocardiogram, and infrared video. All studies were manually scored in standard fashion by trained technicians and confirmed by board-certified sleep physicians. Apnea was defined as an 80% to 100% reduction in airflow lasting ≥10 seconds. Hypopnea was defined as a 30% to 80% reduction in airflow lasting ≥10 seconds. The definition of a hypopnea changed following the publication of the 2007 American Academy of Sleep Medicine (AASM) guidelines. The alternative definition of hypopnea (30% to 90% reduction in airflow lasting ≥10 seconds, associated with an arterial desaturation ≥3% from baseline or a cortical arousal) was implemented at the University of Washington sleep lab in October of 2007. Since this change occurred near the end of data collection for this study, we included those who had polysomnography prior to October 2007 in the primary analysis, and conducted a separate analysis in the group of subjects who were recruited after October 2007. AHI was defined as the number of apnea and hypopneas per hour of sleep. Apnea index was defined as the number of apnea per hour of sleep. Oxyhemoglobin desaturation index was defined as the number of desaturations ≥3% from baseline per hour of sleep. Arousal index was the number of cortical arousals per hour of sleep.

All subjects included in this study were prescribed CPAP machines containing data cards that collected nightly data on the amount of time the CPAP was used. At the 6-month follow, data from the preceding four weeks of

treatment was downloaded and averaged to obtain the number of nights per week and number of hours per night that the CPAP was used.

Analysis

The use-corrected mean nightly AHI (AHI_{mean}) was calculated using the following equation proposed by Ravesloot & de Vries (5):

$$AHI_{mean} = \frac{nights_{ON}}{7} \times \left[\frac{(sleep\ hours_{ON} \times AHI_{ON}) + (sleep\ hours_{OFF} \times AHI_{OFF})}{sleep\ hours_{TOTAL}} \right] + \left[\frac{nights_{OFF}}{7} \times AHI_{OFF} \right]$$

where $nights_{ON}$ and $nights_{OFF}$ are the number of nights in a week the CPAP is used and not used, respectively; $sleep\ hours_{ON}$ and $sleep\ hours_{OFF}$ are the number of sleep hours per night the CPAP is used and not used, respectively; $sleep\ hours_{TOTAL}$ is the self-reported number of hours slept in a typical night; AHI_{ON} is the AHI measured on titration polysomnography at the prescribed CPAP pressure; and AHI_{OFF} is the baseline AHI measured on the diagnostic polysomnography. The uncorrected change in AHI was calculated by subtracting AHI_{ON} from AHI_{OFF}. The change in mean nightly AHI was calculated by subtracting AHI_{mean} from AHI_{OFF}.

Statistical analysis was conducted with Stata/SE 12 software (StataCorp LP, College Station, Texas). The descriptive summaries for continuous variables are reported as range and mean ± standard deviation, whereas frequencies are reported for categorical variables. Associations between baseline patient-reported instrument scores (Epworth Sleepiness Scale, Sleep Apnea Quality of

Life Index, Pittsburgh Sleep Quality Index, SF-36 Mental Health Component, and SF-36 Physical Health Component) and the AHI at baseline (AHI_{OFF}) were tested using Spearman correlation coefficients. Spearman correlation was also used to test the association between the change in each of the patient-reported instrument scores and both change in AHI and change in mean nightly AHI. The sample size provides >80% power to detect a correlation of 0.15 or greater. Steiger's Z-test was used to test for statistically significant differences between the correlation coefficients found between each of the five patient-reported outcome measures and change in AHI versus change in mean nightly AHI(12).

Multivariable linear regression using robust standard errors to account for non-normality of data was used to examine the association between the change in each of the five patient-reported instrument scores and change in AHI as well as change in mean nightly AHI while adjusting for age, sex, and BMI. The resulting β coefficient is the improvement in instrument score associated with a one-unit improvement in AHI among those of the same age, sex and BMI. A *P* value < 0.05 was considered statistically significant for all statistical tests.

This analysis was repeated for the sample recruited after the change in AASM guidelines implemented in October 2007. In addition, as an exploratory analysis, each test above was repeated for the four additional polysomnography measures, including apnea index, oxyhemoglobin desaturation index, arousal index, and lowest oxyhemoglobin saturation, where mean nightly scores were calculated as for mean nightly AHI above.

RESULTS

Of the 1452 subjects who consented to participate, 558 had complete data available for analysis (Figure 1). Eighty-three subjects had a paradoxical worsening of their AHI on CPAP (e.g., induced central apneas) and were excluded from the analysis. Of the 558 with complete data, 459 underwent polysomnography with the pre-2007 AASM guidelines and comprised the sample used for the primary analysis. The study sample was middle-aged, obese, and predominantly male and white (Table 1). The sample had a wide range of CPAP use and amount of self-reported nightly sleep (Table 1).

On average, the sample had severe baseline OSA, which improved to mild-moderate OSA while on prescribed CPAP. The improvement in AHI while using prescribed CPAP was approximately twice the improvement in mean nightly AHI (Table 2). The sample had borderline excessive sleep propensity, moderate OSA-specific quality of life, poor sleep quality, and deficits in health status as measured on the patient-reported instruments. On average, the sample experienced modest improvements in all instrument scores after CPAP treatment, aside from the SAQLI, for which there was no change from baseline (Table 3). The final sample was not significantly different from those excluded with regard to age, sex, race, or any of the baseline patient-reported instrument scores. However, the study sample had a higher BMI (35 ± 9 vs. 33 ± 9, $p<0.001$) and baseline AHI (64 ± 33 vs. 50 ± 32, $p<0.001$) than those who were excluded.

The correlations between baseline patient-reported questionnaire scores

and baseline AHI ranged from 0.05 to 0.17 and three of the five were statistically significantly different from zero (Table 4). When the correlations between the change in patient-reported outcome scores and the improvement in AHI on CPAP were measured without correcting for CPAP use, all correlation coefficients were weak (<0.3), though most were statistically significantly different from zero (Table 5). When the improvement in AHI on CPAP was corrected for CPAP use, the correlations between the change in patient-reported outcome scores and the improvement in mean nightly AHI increased and the *P* values decreased for all of the patient-reported measures except for the SF-36 Physical Component score, which was no longer significant (Table 5). Steiger's Z test demonstrated that the improvements in correlation after adjustment for CPAP use were statistically significant for three of the five patient-centered measures (Table 5). Similar associations were found with multiple linear regression adjusting for age, sex and BMI (Table 6).

The analysis was repeated for the 99 subjects who were recruited after the initiation of the updated AASM guidelines in October 2007. Though the magnitude of the correlations differed, the overall trend was the same, with the change in patient-reported outcome measures demonstrating consistently stronger correlations with the change in mean nightly AHI (i.e., corrected for CPAP use) than with the change in AHI (results not shown). A similar pattern of results was found in the exploratory analysis conducted for the four additional polysomnography measures (results not shown).

DISCUSSION

       Our results demonstrate that correlations between changes in patient-reported outcome measures and AHI after treatment improve when the change in AHI is corrected for CPAP use, suggesting that the discordance seen in previous studies may be due at least in part to individual CPAP adherence.

       A similar lack of correlation between patient-reported measures and change in AHI is seen after OSA surgery, which does not depend on patient adherence (13). If the correlations are poor in patients who have undergone a treatment that does not rely on adherence, one might wonder why we would expect adherence to impact the correlations. We believe the answer lies in one inherent difference between CPAP and surgery: CPAP is titrated to reduce the AHI while surgery is targeted to reduce anatomic obstruction, not to reduce the AHI specifically. Therefore, we would expect that the amount of time the CPAP is used would more directly impact the correlations between AHI and patient-reported measures after CPAP treatment.

       It is important to note that, while the use-corrected correlations were stronger than the uncorrected correlations between polysomnography parameters and patient-reported measures, they were still weak across all patient-reported measures. Our results suggest that at best 6% of the variance in the change in the five patient-reported measure scores could be explained by the variance in the change in AHI alone (i.e., highest coefficient of determination, r^2, was 0.06 for the Epworth Sleepiness Scale). This finding suggests that, even when the AHI is corrected for CPAP use, it is not a comprehensive measure of

OSA burden. This is not a new finding(1), but deserves emphasis as patients

seek treatment for improvement in symptoms and other clinical outcomes, yet

clinical standards have evolved to focus more on surrogate physiologic outcomes

like AHI (14). AHI is an important surrogate measure of future cardiovascular

disease and death(15-18); however, it is critically important to consider both

short-term patient-centered outcomes and long-term health consequences when

evaluating treatments for OSA. The former are best measured directly while the

latter are more practically measured by surrogates such as AHI or

oxyhemoglobin desaturation index.

This study has several limitations. The weighted average method of

correcting for CPAP adherence assumes a linear relationship between the

amount of time CPAP is used and the benefit received. This linear relationship

has not been established definitively but is suggested as a reasonable

approximation for both short-term clinical outcomes and long-term health

consequences (19-21). In addition, the corrected AHI calculation relies on self-

report of total sleep time, which may be prone to inaccuracy.   However, it is

unlikely that the accuracy of self-reported total sleep time would vary by quality-

of-life index, and therefore it would be unlikely to bias the associations tested.

Complete data were not available for all subjects, leaving results subject to

potential selection bias. The analyzed sample had higher BMI and more severe

sleep apnea than the unanalyzed sample, although both samples were obese

and had severe OSA. On the other hand, the analyzed sample appeared similar

to those not analyzed with respect to age, gender, race, and baseline patient-

reported outcome scores. It is unclear how an individual's baseline AHI would impact the correlation between the improvement in AHI on CPAP and change in outcome measures, so the potential selection bias is unclear. Our study sample was similar to the general United States sleep apnea population with regard to age, gender, and BMI (22). However the 82% white sample in this study may limit the generalizability of these results to other racial groups.

Despite these limitations, our findings have implications for studies of the effectiveness of CPAP therapy utilizing AHI as an outcome measure. The corrected AHI will be particularly useful when comparing AHI outcomes of CPAP to other treatments that have a different adherence profile (e.g., oral appliances) or that do not depend on adherence (e.g., surgery). Moreover, the short-term patient-centered outcomes should be measured directly and not be inferred from AHI or other polysomnography parameters. Future work may include examining the impact of this correction on the relationship between AHI and long-term health consequences of OSA.

In conclusion, although the AHI has value for diagnosing and monitoring OSA, it does not capture the full complexity of OSA disease burden or outcome. AHI correlates poorly with patient-reported measures of OSA burden and outcome. While the correlations between AHI and patient-reported outcomes improve after correcting AHI for CPAP use, the correlations remain weak. The use of weighted average formulas strengthen AHI as a surrogate measure and should be used whenever measuring AHI outcomes with CPAP, but patient-centered outcomes like symptoms and quality of life should be measured directly.

Figure 1 - Description of Cohort

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│hypopnea  │ │hypopnea  │
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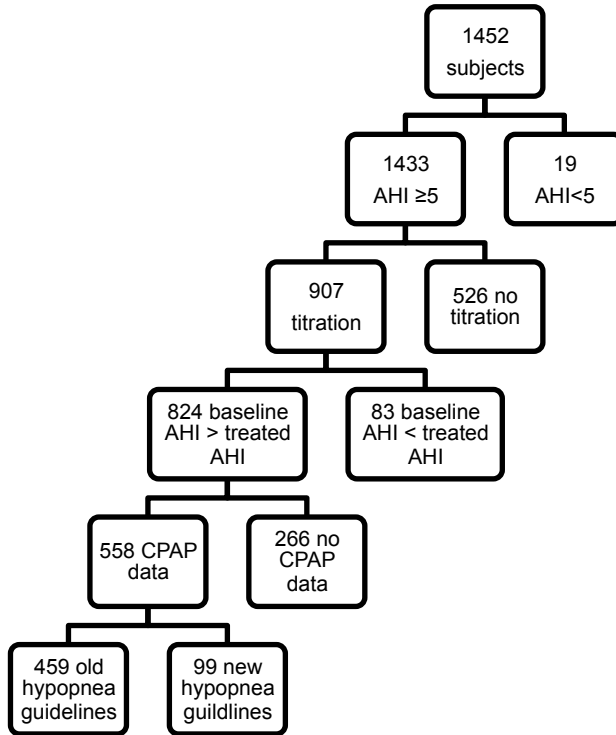
Table 1 - Sample Characteristics (N=459)

Variable	Missing(%)	Frequency (%)	Mean ± SD	Range
Age (years)	2 (<1)	-	48 ± 12	19 - 88
Body Mass Index (kg/m^2)	0	-	35 ± 9	16 - 76
Total sleep hours	0	-	6.8 ± 1.6	1.4 - 14.0
CPAP use (hours/night)	0	-	3.2 ± 2.9	0.0 - 10.9
Sex (male)	2 (<1)	263 (58)	-	-
Race (white)	7 (1)	370 (82)	-	-

Table 2 - Summary of Polysomnography Measures

Variable	N	Mean ± SD	Range
Baseline			
Apnea Hypopnea Index (events/hr)	459	64 ± 33	8 - 185
Desaturation Index (events/hr)	420	30 ± 31	0 - 156
Apnea Index (events/hr)	430	33 ± 35	0 - 178
Arousal Index (events/hr)	404	56 ± 31	7 - 178
Lowest oxyhemoglobin saturation (%)	441	83 ± 10	49 - 96
Change in score*			
Δ Apnea Hypopnea Index (events/hr)	459	47 ± 33	1 - 172
Δ Desaturation Index (events/hr)	420	27 ± 29	0 - 154
Δ Apnea Index (events/hr)	430	30 ± 33	0 - 172
Δ Arousal Index (events/hr)	404	37 ± 31	0 - 174
Δ Lowest oxyhemoglobin saturation (%)	441	10 ± 9	0 - 50
Change in mean nightly score*			
Δ Apnea Hypopnea Index (events/hr)	459	23 ± 30	0 - 167
Δ Desaturation Index (events/hr)	420	13 ± 21	0 - 132
Δ Apnea Index (events/hr)	430	15 ± 26	0 - 167
Δ Arousal Index (events/hr)	404	17 ± 25	0 - 171
Δ Lowest oxyhemoglobin saturation (%)	441	5 ± 7	0 - 32

Table 3 - Summary of Clinical Outcome Measures (N=459)

Variable	Missing (%)	Mean ± SD	Range
Baseline			
Epworth Sleepiness Scale	2 (<1)	10 ± 5	0 - 24
Sleep Apnea Quality of Life Index	1 (<1)	4.2 ± 1.1	1.3 - 6.7
Pittsburgh Sleep Quality Index	2 (<1)	10 ± 4	0 - 21
SF-36 Mental Health Component	10 (2)	43 ± 13	1 - 65
SF-36 Physical Health Component	10 (2)	43 ± 12	10 - 66
Change in score			
Δ Epworth Sleepiness Scale*	23 (5)	-2 ± 5	-20 - 17
Δ Sleep Apnea Quality of Life Index**	20 (4)	0.0 ± 1.0	-3.2 - 2.9
Δ Pittsburgh Sleep Quality Index*	22 (5)	-2 ± 4	-15 - 12
Δ SF-36 Mental Health Component**	33 (7)	1 ± 10	-34 - 30
Δ SF-36 Physical Health Component**	33 (7)	1 ± 6	-20 - 31

*Decrease in score denotes improvement
**Increase in score denotes improvement

Table 4 - Correlation between baseline patient reported-outcome measures and baseline apnea hypopnea index

	n	ρ	p
Epworth Sleepiness Scale	457	0.16	0.001
Sleep Apnea Quality of Life Index	458	0.11	0.02
Pittsburgh Sleep Quality Index	457	0.05	0.33
SF-36 Mental Health Component	449	0.05	0.28
SF-36 Physical Health Component	449	0.17	<0.001

Positive coefficient indicates a correlation in the expected direction

Table 5 - Correlation between change in patient-reported outcome measures and both change in apnea hypopnea index and change in mean nightly apnea hypopnea index after six months of continuous positive airway pressure treatment

	Δ Apnea Hypopnea Index			Δ Mean Nightly Apnea Hypopnea Index			Steiger's Z test	
	ρ	p-value	n	ρ	p-value	n	Z	p-value
Δ Epworth Sleepiness Scale	0.11	0.03	436	0.24	<0.001	436	-2.91	0.004
Δ Sleep Apnea Quality of Life Index	0.14	0.004	439	0.18	<0.001	439	0.89	0.37
Δ Pittsburgh Sleep Quality Index	0.11	0.02	437	0.20	<0.001	437	-2.01	0.04
Δ SF-36 Mental Health Component	0.02	0.63	426	0.13	0.007	426	2.42	0.02
Δ SF-36 Physical Health Component	0.12	0.01	426	0.08	0.09	426	-0.88	0.38

Positive coefficient indicates a correlation in the expected direction

Table 6 - Linear regression analysis of the association between change in patient-reported outcome measures and both change in apnea hypopnea index and change in mean nightly apnea hypopnea index after six months of continuous positive airway pressure treatment, adjusted for age, sex and body mass index

	Δ Apnea Hypopnea Index			Δ Mean Nightly Apnea Hypopnea Index		
	β	95% CI	p	β	95% CI	p
Δ Epworth Sleepiness Scale	0.022	0.006, 0.038	0.007	0.046	0.029, 0.062	<0.001
Δ Sleep Apnea Quality of Life Index	0.004	0.001, 0.007	0.009	0.007	0.003, 0.014	<0.001
Δ Pittsburgh Sleep Quality Index	0.006	-0.007, 0.019	0.350	0.028	0.015, 0.040	<0.001
Δ SF-36 Mental Health Component	0.027	-0.006, 0.060	0.112	0.064	0.034, 0.093	<0.001
Δ SF-36 Physical Health Component	0.028	0.007, 0.074	0.008	0.014	-0.006, 0.033	0.171

Positive coefficient indicates a linear association in the expected direction

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