

# Effective Apnea-Hypopnea Index (“Effective AHI”): A New Measure of Effectiveness for Positive Airway Pressure Therapy

Scott B. Boyd, DDS, PhD<sup>1,2</sup>; Raghu Upender, MD<sup>1</sup>; Arthur S. Walters, MD<sup>1</sup>; R. Lucas Goodpaster, BA<sup>1</sup>; Jeffrey J. Stanley, MD<sup>3</sup>; Li Wang, MS<sup>4</sup>; Rameela Chandrasekhar, PhD<sup>4</sup>

<sup>1</sup>Department of Neurology, Sleep Disorders Division, Vanderbilt University School of Medicine, Nashville, TN; <sup>2</sup>Department of Oral and Maxillofacial Surgery, Vanderbilt University School of Medicine, Nashville, TN; <sup>3</sup>Departments of Neurology and Otolaryngology, University of Michigan, Ann Arbor, MI; <sup>4</sup>Department of Biostatistics, Vanderbilt University School of Medicine, Nashville, TN

**Study Objectives:** To assess a new measure of positive airway pressure (PAP) effectiveness, the *Effective AHI*, which accounts for sleep disordered breathing events during the time PAP is (PAP On) and is not (PAP Off) being used. A secondary aim was to test the accuracy of the Watch-PAT 200 (WP) portable monitor for measurement of the Effective AHI.

**Methods:** A prospective two-center cohort study design was used to evaluate patients who had been prescribed PAP therapy for  $\geq 2$  months. The primary outcome measure was the Effective AHI as determined by an in-laboratory polysomnogram (PSG) where patients used their PAP machine as they did at home, and concomitantly wore the WP. The Effective AHI equals the sum of apneas and hypopneas with PAP On and PAP Off divided by hours of total sleep time.

**Results:** Twenty-eight adult patients (75% men, age  $51.4 \pm 10.8$  years [mean  $\pm$  SD]) comprised the study sample. The mean Effective AHI of 18.3, was significantly lower than the mean Diagnostic AHI of 67.9 ( $P < 0.0001$ ). All patients using PAP  $\geq 6$  h had an Effective AHI  $< 5$ . For patients using PAP  $< 6$  h, Effective AHI scores  $< 5$  only occurred in patients who slept in a non-supine position during PAP Off time; leaving 63.6% of patients with residual moderate-to-severe OSA. There was a high correlation between the PSG and WP for the Effective AHI ( $r = 0.871$ ).

**Conclusions:** Significant disease burden, as objectively measured by the Effective AHI, may still exist in many patients with severe OSA in whom PAP therapy is not utilized for the entire sleep period. The WP is a reasonably accurate device to measure the Effective AHI.

**Keywords:** obstructive sleep apnea, sleep disordered breathing, apnea hypopnea index, CPAP, continuous positive airway pressure, Effective AHI, treatment effectiveness, peripheral arterial tonometry, ambulatory monitoring

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## Significance

The accepted metric to define the effectiveness of positive airway pressure (PAP), for the treatment of obstructive sleep apnea (OSA), is hours of home use. However, it is a surrogate measure, as it does not directly assess the apnea hypopnea index (AHI). We developed the *Effective AHI*, which accounts for sleep disordered breathing events during the time PAP is and is not being used, to quantify residual disease burden. The Effective AHI could also be used to assess the effectiveness of any OSA treatment, thereby facilitating selection of the most effective therapy for a patient. Further studies are needed to determine how well the Effective AHI predicts important health outcomes such as sleepiness, quality of life, and incidence of cardiovascular events.

## INTRODUCTION

Positive airway pressure (PAP) is the accepted first-line therapy for patients with obstructive sleep apnea (OSA), and is highly efficacious, virtually eliminating OSA.<sup>1</sup> PAP is compliance-based therapy and the effectiveness of managing sleep disordered breathing (SDB) is dependent on adequate use of the device in the home setting on a nightly basis. It is important to distinguish between treatment *efficacy* and treatment *effectiveness*, as the effectiveness of treatment in the real-world setting is a better measure of residual disease burden. When adequate PAP adherence is defined as greater than four hours of nightly use, 46% to 83% of patients with OSA have been reported to be non-adherent to treatment.<sup>2</sup> The observed low partial adherence rates may leave patients exposed to high apnea/hypopnea burden with attendant chronic intermittent hypoxia and sleep fragmentation when therapy is not being used. This is of particular concern in patients with severe OSA who are at increased risk for fatal and non-fatal cardiovascular events.<sup>3,4</sup>

Although hours of use in the home setting is the accepted clinical metric to assess the adequacy of adherence to PAP, it is a surrogate measure as it does not directly quantify the AHI over the total sleep period—which is likely the more important

outcome measure from a pathophysiologic perspective. We developed the *Effective AHI* to more accurately quantify the residual disease burden, as measured by the AHI. The Effective AHI equals the sum of apneas and hypopneas during the time the patient is using PAP (PAP On) and is not using PAP (PAP Off) divided by hours of total sleep time. To the best of the authors' knowledge, no one has examined the Effective AHI during the total sleep period for patients with severe OSA. Furthermore, it is not known if four hours or more of nightly PAP use provides adequate control of severe OSA, as measured by the Effective AHI.

One of the major challenges in assessing the comparative effectiveness of PAP therapy and non-PAP therapy, such as surgical treatment of OSA, comes from the complexity of comparing a treatment that requires compliance for clinical effectiveness to one that does not. As a result, there is no universally agreed-upon outcome metric for SDB to assess the comparative effectiveness of different OSA treatments. The Effective AHI has the potential to overcome this comparative effectiveness problem as it measures the AHI during both the time therapy is and is not being used. Knowledge of the true Effective AHI could provide the treating clinician with a very

**Table 1**—Definition of terms.

Term	Definition
"Effective AHI"	The AHI value measured over the entire sleep period including both the time therapy is and is not being used.
Diagnostic AHI	The AHI value measured during the pretreatment Diagnostic PSG (either full night or split night).
PAP Titration AHI	The AHI value measured at the optimal PAP setting during the pretreatment PAP Titration PSG (either full night or split night).
PAP On AHI	The AHI value measured during the time PAP is being used during the PAP Research PSG.
PAP Off AHI	The AHI value measured during the time PAP is not being used during the PAP Research PSG.
PAP Machine AHI	The AHI value reported by the PAP machine during the time PAP is being used during the PAP Research PSG.
"Effective AHI"-WP	The AHI value reported by the WatchPAT 200 ambulatory sleep monitor over the entire sleep period including both the time therapy is and is not being used.
"Effective AHI"-PSG	The AHI value over the entire sleep period including both the time therapy is and is not being used, as measured from the polysomnogram.
Diagnostic PSG	The pretreatment polysomnogram performed during routine clinical care to determine the presence and severity of OSA (either full night or split night)
PAP Titration PSG	The pretreatment polysomnogram performed during routine clinical care to determine the optimal PAP setting to control OSA (either full night or split night)
PAP Research PSG	The research polysomnogram performed during the routine use of PAP therapy including both the time PAP is and is not being used.

valuable tool to assess which specific therapy may provide the highest level of control of SDB, as measured by treatment-related changes in the AHI.

Polysomnography is the gold standard for the determination of the presence, severity, and therapeutic control of OSA. However, it is expensive and there may be problems with accessibility and timeliness in performing the study. Additionally, in-laboratory testing may not accurately capture the sleep patterns a patient experiences in the natural home setting. Portable monitoring (PM) devices, despite their known limitations, have been developed to perform home sleep testing to efficiently diagnose OSA.<sup>5</sup>

Most PM devices use flow-based technology to compute the AHI, which represents a significant obstacle in determining the Effective AHI for an entire night. This is particularly problematic for those patients who use PAP for only a portion of the sleep period because it would be necessary to place a nasal cannula when a patient removes the PAP mask to continue to measure the AHI when PAP is not being used. There is a PM device that employs peripheral arterial tonometry (PAT) to calculate the AHI, in contrast to flow-based technology, that can measure the AHI both during the time PAP is and is not being used. Several studies have demonstrated a relatively high correlation between the AHI determined by PSG and PAT devices for the diagnosis of OSA.<sup>6,7</sup> However, to the best of our knowledge, no studies have been conducted to assess the correlation between PSG and a PAT device to measure the Effective AHI. This is important because the ability to measure the Effective AHI in the home setting could provide a very meaningful clinical outcome metric to assess the effectiveness of PAP therapy as used at home vs. an attended in-laboratory PSG.

The specific aims of this pilot study were to: (1) measure the Effective AHI in patients with severe OSA who varied widely in adherence to PAP therapy, (2) determine the optimal

level of PAP use necessary to normalize Effective AHI values (AHI < 5), (3) test the agreement between the Diagnostic AHI obtained during the Diagnostic PSG and the AHI obtained during the time PAP is not being used (PAP Off AHI) during a research polysomnogram (PAP Research PSG), (4) test the agreement between the PAP Titration AHI obtained at the optimal PAP setting during the PAP Titration PSG, and the AHI obtained during the time PAP is being used (PAP On AHI) during the PAP Research PSG, and (5) test the agreement between the WP derived Effective AHI values (Effective AHI-WP) and the PSG derived Effective AHI values (Effective AHI-PSG), measured during the same PAP Research PSG.

All the terms used in the study, as well as their definitions, can be found in Table 1.

## METHODS

### Study Design and Patient Recruitment

This is a prospective two-center observational cohort study. The study cohort was composed of patients who were currently undergoing PAP treatment for severe OSA at Vanderbilt University Medical Center (VUMC) and at the University of Michigan (UM). Patients were recruited to undergo an in-laboratory research PSG (PAP Research PSG) where they used PAP for the portion of the night that they normally would do at home. Patients concomitantly wore the WP device during the PAP Research PSG. A flow chart of the study design is depicted in Figure 1. This research protocol was approved by the Vanderbilt University IRB (Human Research Protection Program) and the IRB at the University of Michigan and ethical standards were used to conduct the study.

Screening inclusion criteria included: (1) adult 18 years or older, (2) diagnosis of severe OSA (AHI > 30 events/h) as determined by a standard multichannel overnight in-laboratory

attended Diagnostic PSG (full night or split night), (3) availability of sleep reports for the Diagnostic and PAP Titration PSGs, and (4) completion of greater than one month of PAP therapy with concomitant remote monitoring of treatment adherence. Exclusion criteria included: (1) complicated or uncontrolled cardiovascular disease, pulmonary disease, diabetes, or psychiatric disease, (2) finger deformity precluding the use of the WP portable monitor finger probe, (3) history of peripheral vascular disease or autonomic nervous system disorder, (4) use of  $\alpha$ -adrenergic receptor-blocking agents, (5) unavailability of the Diagnostic PSG and PAP Titration PSG results, and (6) inability or unwillingness to give written informed consent.

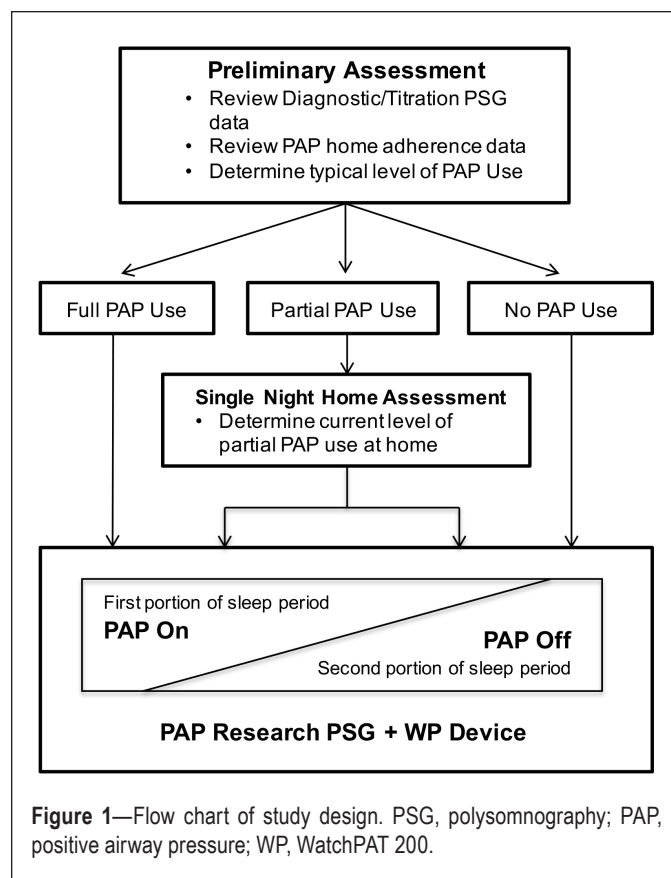
A focused medical record query was conducted for current OSA patients at VUMC and UM who met the inclusion criteria to identify potential study participants. Qualifying patients were contacted, with the goal of recruiting a relatively even distribution of subjects across the spectrum of adherence ranging from 0 to  $\geq 8$  h nightly PAP use. Investigators met with eligible patients, obtained informed consent, and reviewed the adherence data downloaded from their PAP device.

After reviewing the PAP home adherence data download reports (mean length of report,  $2.7 \pm 1.8$  months) for each consented patient, a determination was made for how many hours the patient would use PAP during the PAP Research PSG. Patients who routinely used PAP for the entire sleep period were designated to wear PAP for the complete sleep period during the PAP Research PSG. In contrast, patients who normally did not use PAP during any portion of the sleep period were designated not to use PAP during the PAP Research PSG. Patients who routinely used PAP for only a portion of the sleep period underwent a preliminary single-night home assessment where they were instructed to use PAP as they typically do, to capture a current measurement of their home PAP use. After reviewing the data download obtained from the patient's PAP machine, the patient was assigned to wear PAP during the PAP Research PSG for the same number of hours as the preliminary single night home assessment.

On a subsequent night, within 30 days, all consented study participants underwent a multichannel overnight in-laboratory attended PSG (PAP Research PSG) while wearing their PAP machine for the designated period of time (entire sleep period, none of the sleep period, or a portion of the sleep period), to facilitate determination of the Effective AHI during normal PAP usage. Each subject concomitantly wore the WP device during the PAP Research PSG.

## Outcomes

The primary outcome measure was the Effective AHI as measured during the in-laboratory PAP Research PSG. The Effective AHI equals the sum of apneas and hypopneas with PAP On and PAP Off divided by hours of total sleep time. Individual PAP On and PAP Off AHI values were also computed, and were then compared to the PAP Titration AHI and Diagnostic AHI values respectively, to determine if significant differences existed between the values. The Diagnostic AHI and PAP Titration AHI values were derived from the Diagnostic PSG and PAP Titration PSG that were obtained during routine clinical care. The Effective AHI was concomitantly measured



by the WP device to assess the validity of using the WP device to measure the Effective AHI.

Demographic characteristics and other secondary outcomes measures included age (years), gender, body mass index (BMI,  $\text{kg}/\text{m}^2$ ), average hours of nightly home PAP use, hours of PAP use during the preliminary single night home assessment, hours of PAP use during the PAP Research PSG, % REM sleep, % sleep in the supine position, and presence of positional OSA (supine AHI  $\geq 2$  times non-supine AHI)<sup>8,9</sup> during Diagnostic PSG. Comparisons were conducted for selected outcome measures between the Diagnostic PSG and PAP Research PSG.

## PAP Research PSG Recording

The PAP Research PSG was performed for each consented subject at the Vanderbilt Sleep Research Core or the University of Michigan Sleep Disorders Center. For each study participant, the same methods were used to conduct and score the PAP Research PSG, as were used to perform the Diagnostic and PAP Titration PSGs. Comprehensive video-polysomnography was conducted using digital video to monitor sleep, movements, and behaviors. Signals recorded during the PSG included: frontal, central and occipital electroencephalogram (EEG), two channels of electrooculogram (EOG), submental electromyogram (EMG), anterior tibialis EMG, respiratory effort (including chest and abdominal channels), airflow (including oral thermistor and nasal pressure channels), oxygen saturation by pulse oximetry, and electrocardiogram (ECG). Respiratory effort was measured using inductance plethysmography belts over the thorax and abdomen. Airflow was measured indirectly

using a piezoelectric thermistor placed over the philtrum, and an oro-nasal cannula connected to a piezoelectric pressure transducer during the time PAP was off (PAP Off), and airflow was recorded directly from the PAP machine during the time PAP was on (PAP On). Each participant initiated use of their prescribed PAP machine (Philips Respironics), with their normal settings, without any intervention from the attendant sleep technician during use of the PAP machine. For patients with partial PAP use, once the patient had achieved the time of PAP use that coincided with the time of PAP use in the preliminary single-night home assessment, a licensed sleep technician assisted the patient in removal of the PAP mask and then placed a nasal pressure transducer and oral thermistor to measure airflow.

All PSGs were scored using the 2007 guidelines from the American Academy of Sleep Medicine (AASM).<sup>10</sup> Scoring of the PAP Research PSG was performed by an experienced polysomnographic technologist and then reviewed and interpreted by a board-certified sleep medicine specialist, both of whom were blinded to the clinical status and previous PSG results of the patient. To facilitate accurate comparison to the Diagnostic and PAP Titration PSGs, each PAP Research PSG was scored using the same scoring rules that were used to score the Diagnostic and PAP Titration PSGs. The alternative hypopnea scoring rules were used for most patients (85.7%, 24/28), while the recommended hypopnea scoring rules were used for the remaining patients (14.3%, 4/28). Sleep stages were scored as a percentage of total sleep time, using the AASM scoring rules.<sup>10</sup>

### WatchPAT 200 (WP) Recording

The Watch-PAT 200 ([WP] Itamar Medical, Caesarea, Israel) was used for portable sleep monitoring in this study. The device is self-contained, battery-powered, lightweight, and is worn around the wrist. It has two finger probes that extend from the main body of the device. The WP is easy to apply and is unobtrusive, thereby minimizing any disruption of the patient's normal sleep patterns. This device has been previously described in detail.<sup>6,7</sup> In summary, the 4-channel device measures peripheral arterial tone (PAT), heart rate, oxygen saturation, and actigraphy for automatic analysis of the apnea-hypopnea index (AHI), oxygen desaturation index (ODI), and sleep-wake state. The PAT signal measures arterial pulsatile volume changes regulated by  $\alpha$ -adrenergic innervation of the smooth muscle vasculature of the finger, and thus reflects sympathetic nervous system activity. Because discrete obstructive airway events (e.g., apneas, hypopneas) cause arousal from sleep, sympathetic activation, and peripheral vasoconstriction, these events are associated with attenuation of the PAT signal.<sup>11,12</sup> The Effective AHI values for the WP were derived from the automated computerized algorithm of the device. An experienced polysomnographic technologist, blinded to the clinical status and previous PSG results of the subject, reviewed each WP report to confirm there were no technical problems with the recording.

### Data Collection and Statistical Analysis

Data were directly entered into a customized clinical research database (REDCap)<sup>13</sup> that was designed to store all

demographic, polysomnographic and clinical data collected. Data were analyzed using the R (The R Foundation, Vienna, Austria) statistical software. Descriptive statistics were obtained for all demographic and outcome variables. Data are reported as mean  $\pm$  standard deviation, median and interquartile range (IQR) for continuous variables and frequency and percent for categorical variables. Ninety-five percent confidence intervals (CI) were calculated for the mean differences in AHI scores. The Wilcoxon signed rank test was used to compare differences between: (1) Diagnostic AHI and the Effective AHI during the PAP Research PSG, (2) Diagnostic AHI and PAP Off AHI during the PAP Research PSG, and (3) the PAP Titration AHI and the PAP On AHI during the PAP Research PSG. Pearson correlation coefficients were calculated to assess: (1) the correlation between the Effective AHI derived from the PAP Research PSG and the Effective AHI derived from the WP device and (2) the correlation between the magnitude of the Diagnostic AHI from the Diagnostic PSG and the magnitude of reduction in AHI when PAP was not being used (PAP Off) during the PAP Research PSG. Linear regression analysis was performed and Bland-Altman plots were constructed to show the agreement between the PSG derived Effective AHI (Effective AHI-PSG) and the WP derived Effective AHI (Effective AHI-WP). The Kruskal-Wallis test was used for subgroup analysis to test for differences in the Effective AHI between those patients who used PAP: 0–2 h, 2–4 h, 4–6 h, and  $\geq 6$  h; as well as the proportion of patients reaching specific levels of treatment effectiveness. Patients were classified for severity of OSA as: normal (AHI < 5 events/h), mild (AHI 5–15 events/h), moderate (AHI > 15–30 events/h), or severe (AHI > 30 events/h). For all analyses, a P value of < 0.05 was considered statistically significant.

## RESULTS

### Patient Characteristics

Thirty-one patients were consented to participate in the study and underwent the PAP Research PSG. Three patients had insufficient sleep, defined as less than 1 hour, and were excluded from the study. The remainder of patients slept an average of  $5.3 \pm 1.0$  h with a range from 3.8 to 6.8 hours. The average hours of time in bed (total recording time) during the PAP Research PSG was  $7.1 \pm 0.6$ . The final study cohort included 28 patients composed primarily of middle age (mean age,  $51.4 \pm 10.8$  years), obese (mean body mass index,  $36.1 \pm 7.0$  kg/m<sup>2</sup>), white (81.5%) men (75%) with severe OSA (mean Diagnostic AHI,  $67.9 \pm 29.0$ ) and significant oxyhemoglobin desaturations (mean diagnostic minimum SpO<sub>2</sub>%,  $80.2 \pm 7.3$ ), where PAP was found to be highly efficacious (mean PAP titration AHI,  $3.7 \pm 3.3$ ). The vast majority of patients (71.4%, 20/28) used CPAP (Philips Respironics-REMstar Auto, C-Flex), while some patients used AutoPAP (Philips Respironics-REMstar, A-Flex; 21.4%, 6/28) or bilevel PAP (Philips Respironics-BiPAP Auto Bi-Flex; 7.1%, 2/28). The average time between the Diagnostic PSG and PAP Research PSG was  $8.3 \pm 3.9$  months. On average, the study patients had used PAP for  $7.5 \pm 3.4$  months with a range from 2.6 to 17 months. The PAP home adherence download data showed the study group had used PAP at home an average of  $4.1 \pm 2.4$  h,

**Table 2**—Comparison of AHI scores for different levels of PAP use.

PAP Use Group	PAP Use (hours) <sup>a</sup>	Diagnostic AHI <sup>b</sup>	"Effective AHI" <sup>c</sup>	Change	P value
Cohort (n = 28)	4.0 ± 2.8	67.9 ± 29	18.3 ± 16.1	-49.7 ± 30.4	< 0.0001
0–2 hours (n = 6)	0.3 ± 0.8	53 ± 25	33.9 ± 17.2	-18.7 ± 16.6	0.094
2–4 hours (n = 9)	3.1 ± 0.5	67 ± 30	16.9 ± 12.8	-50.1 ± 24.7	0.004
4–6 hours (n = 7)	4.7 ± 0.6	80 ± 33	21.3 ± 12.2	-58.8 ± 34.9	0.016
≥ 6 hours (n = 6)	7.9 ± 0.8	71 ± 25	1.2 ± 1.1	-69.4 ± 23.7	0.031

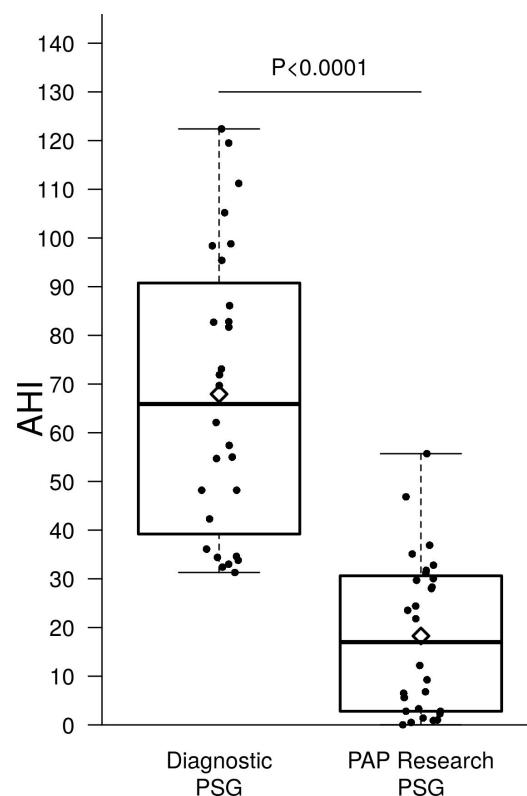
P values are based on Wilcoxon signed rank test for differences between the Diagnostic AHI and the Effective AHI for each group. P values for intergroup comparisons based on Kruskal-Wallis test. <sup>a</sup> Mean ± SD hours of PAP Use. <sup>b</sup> No significant difference ( $P > 0.05$ ) between subgroups for Diagnostic AHI. <sup>c</sup> Effective AHI for ≥ 6 hours PAP use group was significantly lower ( $P < 0.05$ ) than the Effective AHI for the 0–2 h, 2–4 h, and 4–6 h subgroups. Effective AHI for 2–4 h PAP use group was significantly lower ( $P < 0.05$ ) than the Effective AHI for the 0–2 h subgroup. AHI, apnea-hypopnea index; PAP, positive airway pressure; Effective AHI, the AHI value measured over the entire sleep period including both the time PAP is and is not being used. Diagnostic AHI, the AHI value measured during the pretreatment Diagnostic PSG.

with a range from 0 to 8.5 hours. In comparison, the average hours of PAP use during the PAP Research PSG was  $4.0 \pm 2.8$  with a range from 0 to 8.7 h, with a relatively even distribution of participants across the range of hours of use (Table 2). There was no significant difference between the hours of PAP use during the PAP Research PSG and the average hours of PAP use at home as documented by PAP home adherence download data ( $P = 0.626$ ). Six patients used PAP for the entire sleep period during the PAP Research PSG, while 5 patients did not use PAP during the PAP Research PSG. Seventeen patients used PAP for a portion of the sleep period during the PAP Research PSG. All partial use patients used PAP for the first portion of the night. For patients who used PAP for only a portion of the night, there was no significant difference between the average hours of PAP use during the PAP Research PSG (mean,  $3.7 \pm 1.0$  h) and the average hours of PAP use at home as documented by the preliminary single night home assessment adherence report (mean,  $3.8 \pm 1.3$  h;  $P = 0.678$ ).

### Effective AHI

PAP therapy resulted in a significant reduction in the AHI for the study cohort ( $n = 28$ ). The mean AHI decreased 73% from a mean Diagnostic AHI of 67.9 events/h (median, 65.9; IQR, 40.8 to 88.4) to a mean Effective AHI of 18.3 events/h (median, 17.0; IQR, 2.8 to 30.3;  $P < 0.0001$ ), with a mean change in AHI scores of  $-49.7 \pm 30.4$  (95%CI, -61.5 to -37.9) (Figure 2, Table 2). Following PAP therapy, 32.1% of patients reached an Effective AHI of  $< 5$  events/h, while 50% of patients continued to have moderate (AHI  $> 15$ –30 events/h) to severe (AHI  $> 30$  events/h) OSA, as measured by the Effective AHI (Table 3).

After subgrouping patients by hours of PAP use, all subgroups showed a reduction in mean AHI scores (Table 2). The changes in AHI scores were statistically significant for all groups, except for those patients who only used PAP for 0–2 hours. There were no significant differences in the Diagnostic AHI scores between any of the subgroups, although there was a tendency for patients who used PAP more, to have higher Diagnostic AHI values (Table 2). The Effective AHI scores for patients using PAP  $\geq 6$  h (mean Effective AHI,  $1.2 \pm 1.1$ ; median, 1.0; IQR, 0.6 to 1.3) were significantly lower than patients using PAP 0–2 h (mean Effective AHI,  $33.9 \pm 17.2$ ; median, 33.4; IQR, 29.2 to 43.9;  $P = 0.002$ ), 2–4 h (mean Effective AHI,



**Figure 2**—Comparison of changes in AHI scores following treatment by positive airway pressure (PAP). The bottom and top of the box represent the 25<sup>th</sup> percentile (lower quartile) and 75<sup>th</sup> percentile (upper quartile), which is bisected by the median value; diamond represents the mean value; whiskers are used to represent the upper and lower values. A significant reduction (73%) in AHI scores was observed when comparing the AHI from the Diagnostic PSG to the Effective AHI measured during the PAP Research PSG, with a mean change in AHI scores of -49.7. AHI, apnea-hypopnea index; PSG, polysomnography; PAP, positive airway pressure.

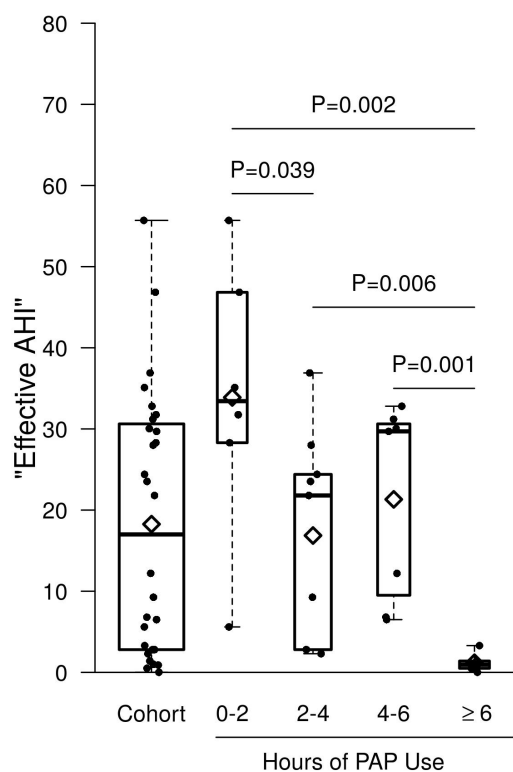
$16.9 \pm 12.8$ ; median, 21.8; IQR, 2.8 to 24.4,  $P = 0.006$ ), or 4–6 h (mean Effective AHI,  $21.3 \pm 12.2$ ; median, 29.7; IQR, 9.5 to 30.6,  $P = 0.001$ ) (Figure 3).

There was a large and statistically significant difference in the Effective AHI scores between those patients who used

**Table 3**—Comparison of “Effective AHI” severity at different levels of PAP use.

AHI Severity	Diagnostic AHI		“Effective AHI”			
	Cohort (n = 28)	Cohort (n = 28)	0–2 hours PAP (n = 6)	2–4 hours PAP (n = 9)	4–6 hours PAP (n = 7)	≥ 6 hours PAP (n = 6)
< 5	0 (0)	32.1 (9)	0 (0)	33.3 (3)	0 (0)	100 (6)
5–15	0 (0)	17.9 (5)	16.7 (1)	11.1 (1)	42.9 (3)	0 (0)
> 15–30	0 (0)	25.0 (7)	16.7 (1)	44.4 (4)	28.6 (2)	0 (0)
> 30	100 (28)	25.0 (7)	66.7 (4)	11.1 (1)	28.6 (2)	0 (0)

Shown are total percentage of study patients (total number of patients) at designated AHI severity levels for the Diagnostic AHI and Effective AHI scores for the study cohort and hours of use subgroups (0–2, 2–4, 4–6, and ≥ 6 hours of PAP use). AHI, apnea-hypopnea index; PAP, positive airway pressure; Effective AHI, the AHI value measured over the entire sleep period including both the time PAP is and is not being used.



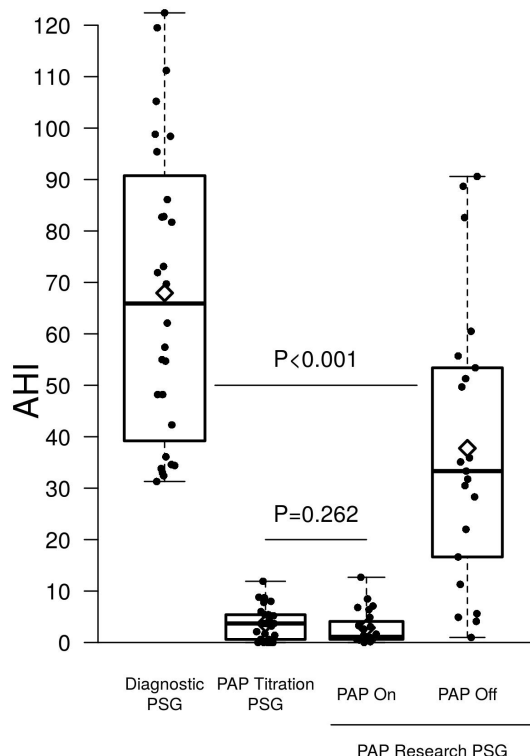
**Figure 3**—Relationship between hours of PAP use and the Effective AHI. The bottom and top of the box represent the 25<sup>th</sup> percentile (lower quartile) and 75<sup>th</sup> percentile (upper quartile), which is bisected by the median value; diamond represents the mean value; whiskers are used to represent the upper and lower values. After subgrouping the study cohort by hours of PAP use, the Effective AHI scores for patients using PAP 6 hours or more were significantly better than those patients using PAP 0–2 h, 2–4 h, or 4–6 h. AHI, apnea-hypopnea index; PAP, positive airway pressure.

PAP ≥ 6 h and those who used PAP < 6 h (PAP ≥ 6 h, mean Effective AHI,  $1.2 \pm 1.1$  vs. PAP < 6 h mean Effective AHI,  $22.9 \pm 15.0$ ,  $P < 0.0001$ ), with a mean difference in Effective AHI scores of  $21.7 \pm 6.2$ . Furthermore, 100% of patients using PAP ≥ 6 h achieved Effective AHI scores of < 5 events/h, with a mean Effective AHI of 1.2 events/h (Tables 2 and 3). In comparison, for those patients using PAP < 6 h, an Effective AHI of < 5 was reached in a minority of patients (13.6%, 3/22);

leaving most patients with residual moderate-to-severe OSA (63.6%, 14/22) (Table 3). Additionally, there was a relatively large difference in the Effective AHI for patients using PAP < 4 h ( $n = 15$ ) compared to those patients using PAP ≥ 4 h ( $n = 13$ ), although this difference did not reach the level of statistical significance (PAP < 4 h, mean Effective AHI,  $23.7 \pm 16.6$  vs. PAP ≥ 4 h, mean Effective AHI,  $12.0 \pm 13.6$ ,  $P = 0.065$ ), with much of the difference in Effective AHI scores being attributable to normalization of the Effective AHI scores in patients who used PAP ≥ 6 hours.

A significant reduction in the AHI scores was observed when comparing the AHI from the Diagnostic PSG to the AHI measured during the time PAP was off (PAP Off AHI) during the PAP Research PSG (Diagnostic AHI, mean ± standard deviation,  $67.9 \pm 29.0$ ; median, 65.9; IQR, 40.8 to 88.4; range, 31.3 to 122.4 vs PAP Off AHI, mean ± standard deviation,  $37.8 \pm 27.4$ ; median, 33.3; IQR, 16.6 to 53.4; range, 1.0 to 90.6,  $P < 0.001$ ), with a mean difference in AHI scores of  $-30.4 \pm 31.5$  (median, -29; IQR, -17.8 to -42, 95% CI = -44.7 to -16.0) (Figure 4). The mean percent reduction in the AHI was  $38.3\% \pm 46.2\%$  (median, 41.0; IQR, 25.0 to 62.0; 95% CI, 17.3 to 59.4) (Figure 5). Greater than 90% (19/21) of patients had a reduction in the AHI, although there was considerable variation in the magnitude of the reduction (range, -110.0 to 97.0%).

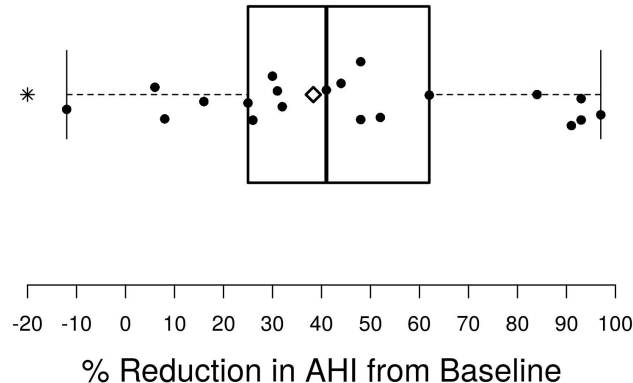
The magnitude of reduction in AHI scores during the PAP Off time was found to be important for patients using PAP < 6 h, as only those patients with a > 90% reduction in the AHI scores achieved an Effective AHI of < 5 (mean reduction, 94.3%,  $n = 3$ ). A common finding in each of these patients was that no sleep time was spent in the supine position, during the PAP Research PSG. In contrast, the remainder of the study cohort spent a considerable amount of time in the supine position during PAP Off sleep time, (mean % supine position,  $60.9 \pm 29.7$ ; range, 6.7 to 100). For the entire study cohort, a moderate negative correlation was found between the percent reduction in the AHI and the percent time in the supine position during PAP Off time ( $r = -0.572$ ; 95% CI = -0.82 to -0.16). Additionally, 37% of study participants were found to have positional OSA (supine AHI ≥ 2 times non-supine AHI), as measured from the Diagnostic PSG. The patients with positional OSA had lower, but not significantly different, Effective AHI scores compared to participants with non-positional OSA (Positional OSA mean Effective AHI,  $12.6 \pm 13.6$  vs. Non-Positional OSA mean Effective AHI,  $21.3 \pm 17.4$ ,  $P = 0.2587$ ),



**Figure 4**—Comparisons of differences in AHI scores between the Diagnostic PSG, PAP Titration PSG and the PAP Research PSG. The bottom and top of the box represent the 25<sup>th</sup> percentile (lower quartile) and 75<sup>th</sup> percentile (upper quartile), which is bisected by the median value; diamond represents the mean value; whiskers are used to represent the upper and lower values. A significant reduction in the AHI scores was observed when comparing the AHI from the Diagnostic PSG to the AHI measured during the time PAP was off (PAP Off AHI) during the PAP Research PSG, with a mean difference in scores of  $-30.4 \pm 31.5$  events/h. There was no significant difference in AHI scores when comparing the pretreatment AHI values, obtained during the PAP Titration PSG, and the AHI achieved during the time PAP was on (PAP On AHI) during the PAP Research PSG, with a mean difference in AHI scores of  $0.9 \pm 3.9$  events per hour. AHI, apnea-hypopnea index; PSG, polysomnography; PAP, positive airway pressure.

with a mean difference in Effective AHI scores of  $8.6 \pm 6.4$ . Furthermore, there was no significant difference between the positional OSA and non-positional OSA patients for the percentage of time spent in the supine position during PAP Off sleep time (Positional OSA mean % supine  $49.4 \pm 35.6$  vs. Non-Positional OSA mean % supine  $45.5 \pm 36.1$ ,  $P = 0.5341$ ).

Beyond the amount of time in supine position, no additional factors were found to explain the magnitude of reduction in AHI scores when comparing the Diagnostic AHI and PAP Off AHI. A weak correlation was found between the magnitude of the Diagnostic AHI and the magnitude of reduction in the PAP Off AHI ( $r = 0.139$ ). Furthermore, a very weak negative correlation was found between the average hours of nightly PAP use and the magnitude of reduction in the AHI ( $r = -0.031$ ). There was a significant increase in BMI observed between the time of the Diagnostic PSG and the PAP Research PSG (Diagnostic PSG BMI, mean  $\pm$  standard deviation,  $35.6 \pm 6.6$  kg/m<sup>2</sup> vs. PAP



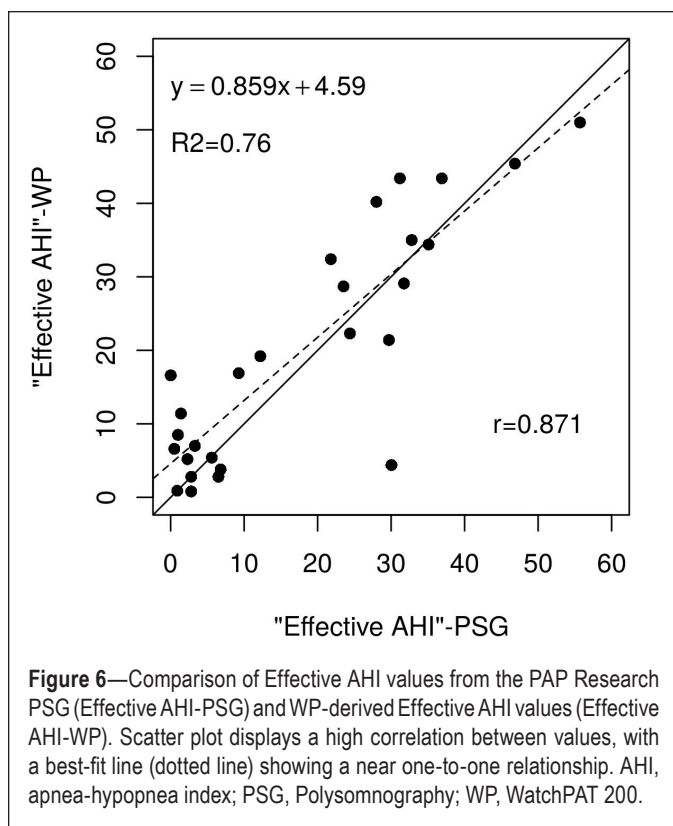
**Figure 5**—Percentage reduction in AHI scores when comparing the Diagnostic PSG AHI and the AHI achieved when PAP was not being used (PAP Off) during the PAP Research PSG. The bottom and top of the box represent the 25<sup>th</sup> percentile (lower quartile) and 75<sup>th</sup> percentile (upper quartile), which is bisected by the median value; diamond represents the mean value; whiskers are used to represent the upper and lower values; asterisk denotes one outlier value of  $-110\%$  that was not plotted. The results show a substantial mean percent reduction in the AHI scores (38%). Greater than 90% (19/21) of patients had a reduction in the AHI, although there was considerable variation in the magnitude of the reduction. AHI, apnea-hypopnea index.

Research PSG BMI,  $36.1 \pm 7.0$  kg/m<sup>2</sup>,  $P = 0.008$ ). A significant increase in % REM sleep was observed when comparing the Diagnostic PSG to the PAP Off portion of the PAP Research PSG (Diagnostic PSG %REM sleep,  $14.0 \pm 9.7$  vs PAP Off %REM sleep,  $20.6 \pm 15.6$ ,  $P = 0.037$ ). This increase in % REM sleep was expected due to the design of the study, where the PAP OFF sleep time, for patients using PAP for only a portion of the night, was usually at the last half of the night when there is typically more REM sleep.

There was no significant difference in AHI scores when comparing the pretreatment AHI values, obtained during the PAP Titration PSG, and the AHI achieved during the time PAP was on (PAP On AHI) during the PAP Research PSG (PAP Titration AHI, mean  $\pm$  standard deviation,  $3.7 \pm 3.3$ ; median, 3.7; IQR, 0.6 to 5.4 vs PAP On AHI, mean  $\pm$  standard deviation,  $2.9 \pm 3.3$ ; median, 1.1; IQR, 0.6 to 4.1,  $P = 0.262$ ) (Figure 4). The mean difference in AHI scores between PAP Titration and PAP On values was  $0.9 \pm 3.9$  events per hour (median, 0.8; IQR,  $-1.0$  to 4.3; 95% CI =  $-0.6$  to 2.4). There was a small yet statistically significant difference between the PAP On AHI and the PAP Machine AHI, recorded during the PAP Research PSG (PAP Machine AHI, mean  $\pm$  standard deviation,  $4.3 \pm 4.6$ ,  $P = 0.003$ ). PAP Machine AHI values were typically higher with a mean difference in AHI scores of  $1.6 \pm 2.3$  events/h.

#### WatchPAT 200 (WP)

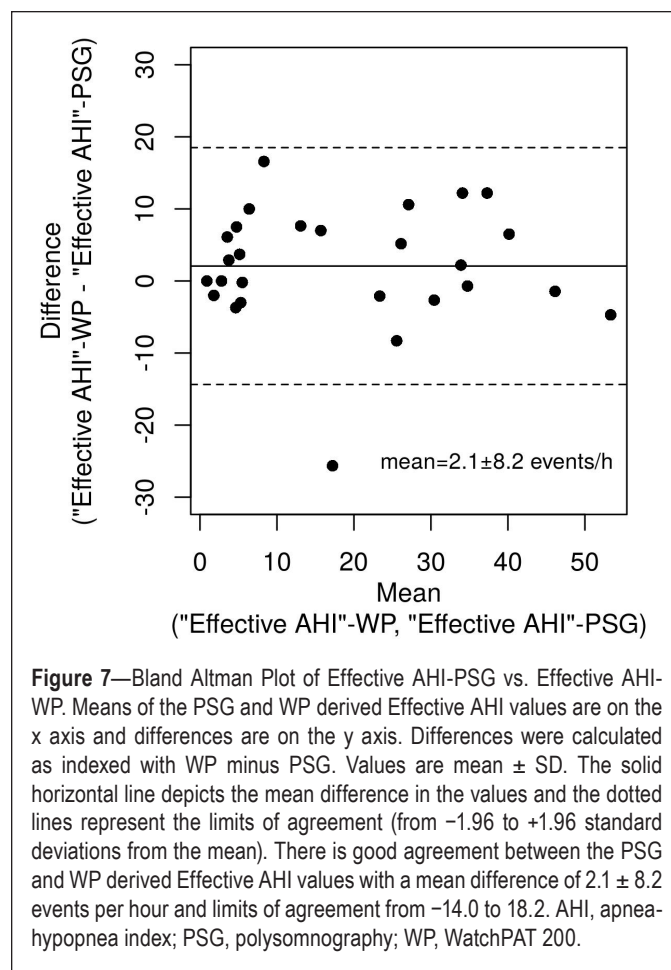
A high correlation ( $r = 0.871$ ; 95% CI = 0.73 to 0.94) was found between the Effective AHI derived from the PAP Research PSG (Effective AHI-PSG) and the Effective AHI computed from the WP device (Effective AHI-WP) (Figure 6). There was a nearly one-to-one correlation between the values with a best-fit line of  $y = 0.859x + 4.59$ . Good agreement was



found between the Effective AHI values (Effective AHI-PSG, mean  $\pm$  standard deviation,  $18.3 \pm 16.1$  events/h vs Effective AHI-WP, mean  $\pm$  standard deviation,  $20.0 \pm 16.1$  events/h), with Effective AHI-WP values on average being slightly higher than Effective AHI-PSG values (mean difference of  $2.1 \pm 8.2$  events per hour; median, 2.2; IQR,  $-2$  to 7.2) (Figure 7). The limits of agreement (from  $-1.96$  to  $+1.96$  standard deviations from the mean) were from  $-14.0$  to  $18.2$ .

## DISCUSSION

This pilot study was performed to determine the Effective AHI for PAP therapy in patients with severe OSA. We developed the Effective AHI to more accurately quantify the residual disease burden, as measured by the AHI. The Effective AHI equals the sum of apneas and hypopneas with PAP On and PAP Off divided by hours of total sleep time. To the best of the authors' knowledge, no one has examined the Effective AHI for PAP therapy during the total sleep period for patients with severe OSA. Furthermore, we sought to determine what level of PAP usage would consistently normalize Effective AHI values ( $\text{AHI} < 5$ ). A secondary aim was to test the validity of using the WP portable sleep monitoring device to measure the Effective AHI. We found, as expected, that PAP therapy resulted in a significant reduction in the AHI (mean reduction 73%), and that sleep-disordered breathing is essentially eliminated during the time PAP is being used (mean PAP On AHI,  $2.9 \pm 3.3$ ). However, it was not until patients used  $\text{PAP} \geq 6$  hours that the Effective AHI values were consistently normalized (100% of patients with an  $\text{AHI} < 5$ ). For patients using PAP less than 6 hours, Effective AHI scores were normalized only in those patients who slept exclusively in a non-supine position when



PAP was not being used. Overall, 63.6% of patients using PAP less than 6 hours still had moderate to severe OSA (Effective AHI  $> 15$ ). We observed a significant reduction in AHI scores (mean reduction 38%) when comparing the Diagnostic AHI to the AHI observed during the time PAP was not being used, during the PAP Research PSG. Finally, we established the validity of the WP portable monitor as a reasonably accurate device to measure the Effective AHI.

The finding of needing 6 hours or more of nightly PAP use to normalize the Effective AHI values is analogous to the findings of a number of studies that suggest 6 hours or more of PAP use is needed to improve a variety of important outcome measures to near normal levels. Weaver et al. reported that the greatest gains in the number of patients reaching normal values for subjective sleepiness (Epworth Sleepiness Scale), objectively measured sleepiness (Multiple Sleep Latency Test) and disease specific quality of life (Functional Outcomes of Sleepiness Questionnaire) required 4, 6, and 7.5 hours of nightly CPAP use, respectively.<sup>14</sup> Others have reported that  $> 6$  hours of PAP use optimizes normalization of memory performance<sup>15</sup> and provides the greatest mortality risk reduction<sup>16</sup>; while Barbe et al. found improvements in blood pressure only evident in OSA patients who used CPAP more than 5.6 hours per night.<sup>17</sup> In summary, the evidence indicates that the cut point for defining optimal adherence to PAP therapy for patients with severe OSA should be 6 or more hours of nightly

PAP use, essentially the entire sleep period, as this is the level of use where the largest number of patients will likely reach near normal levels of several important outcome measures.

One of the most interesting findings of this study was exposure to PAP resulted in a significant reduction in the AHI (mean reduction 38%), when comparing the Diagnostic AHI to the AHI measured when PAP was not being used during the PAP Research PSG. The finding of a reduction in the AHI scores is similar to the findings of others who have reported changes in AHI scores following withdrawal of CPAP therapy. Several studies have shown a decrease in the mean AHI scores following CPAP withdrawal, in comparison to pretreatment AHI scores, ranging from 18% to 47%.<sup>18–25</sup> Interestingly, Collop et al. and Young et al. found a decrease in AHI scores only for patients with severe OSA,<sup>25,26</sup> which are analogous to our study cohort that consisted only of patients with severe OSA. Because the reduction in AHI scores after CPAP withdrawal is perceived as temporary, it has been termed the “washout period”—the time before the AHI may return to near the pretreatment level. The design of this study was fundamentally different from previous CPAP withdrawal studies because there was no specified withdrawal of PAP therapy, as the patients used PAP as they routinely did at home. Therefore, the reduction in the AHI, during the time PAP is off, is likely representative of what is occurring on an ongoing basis, providing the patient’s pattern of PAP use does not change significantly.

The mechanism by which a prolonged reduction in the AHI may occur, during the portion of the sleep period when PAP is not being used is unclear, but several potential contributing factors exist that may explain the suppression of respiratory events. It is important to elucidate these factors, because the residual AHI disease burden observed in this study was almost exclusively defined by the number of respiratory events occurring during the time PAP was not being used. Some of the contributing factors may include changes in the BMI,<sup>27,28</sup> %REM sleep,<sup>29</sup> or % supine position,<sup>30</sup> as these measures are associated with the severity of OSA.

The time spent in supine position, when PAP is not being used during the sleep period, may be a very important factor in defining the magnitude of reduction in the AHI for patients using PAP less than six hours a night. In this study, patients who slept in a non-supine position, during the time they were not using PAP, had a > 90% reduction in AHI values, which translated to normalization of Effective AHI scores for each of these patients. In contrast, the majority of patients who used PAP less than 6 hours and slept the majority of time in the supine position (mean % supine position,  $60.9 \pm 29.7$ ), had residual moderate-to-severe OSA. A contributing factor to the high residual OSA may be the finding that 37% of the study cohort were found to have positional OSA (supine AHI > 2 times non-supine AHI) during the Diagnostic PSG. The results of this study suggest that patients with positional OSA may benefit from combination therapy where positional therapy is used to minimize sleeping in the supine position during the time PAP is not being used. Further studies are needed to determine if positional therapy could play a role in decreasing the Effective AHI in patients who use PAP for only a portion of the sleep period.

Interestingly, changes in BMI and % REM sleep appeared to have little impact on changes in AHI scores as significant increases in mean BMI (35.6 to 36.1) and mean % REM sleep (14.0% to 20.6%) were observed; both of which would be expected to increase the AHI scores. Furthermore, neither the average hours of nightly PAP use ( $r = -0.031$ ) nor the magnitude of the Diagnostic AHI values ( $r = 0.139$ ) were correlated with the magnitude of reduction in the AHI.

There are other anatomic and non-anatomic factors that could potentially modulate SDB events leading to a change in the AHI during the time PAP is not being used. Ryan et al. reported an increase in pharyngeal volume following CPAP therapy, which may have occurred through resolution of upper airway edema.<sup>31</sup> In contrast, Collop et al. did not find any increase in pharyngeal volume after use of CPAP.<sup>26</sup> Interestingly, investigators have shown that fluid redistribution from the lower extremities to the soft tissue tissues of the upper airway, which may occur during bedtime, leads to a decrease in the cross-sectional area of the upper airway.<sup>32,33</sup> A decrease in pharyngeal volume would likely result in a worsening of the AHI throughout the night, in contrast to the decrease in the AHI that was observed in this study. Non-anatomic mechanisms that could contribute to the control of respiratory events include variations in upper airway dilator muscle responsiveness during sleep, respiratory arousal threshold, and changes in ventilatory control.<sup>30,34</sup> Clearly, further research is needed to confirm the results of this pilot study and to elucidate the mechanisms that lead to a reduction in the AHI during the time PAP is not being used, as this information could have significant ramifications for patient care.

The results of this study demonstrate that the PAP Titration AHI provides a very good estimate of the AHI achieved during the time patients use PAP as they do at home. No significant difference was found between the mean PAP Titration AHI ( $3.7 \pm 3.3$ ) and the mean PAP On AHI ( $2.9 \pm 3.3$ ) measured during the PAP Research PSG (mean difference  $0.9 \pm 3.9$ ; 95% CI:  $-0.6$  to  $2.4$ ). The mean PAP Machine AHI scores ( $4.3 \pm 4.6$ ) were similar but slightly higher than the mean PAP On AHI scores during the PAP Research PSG (mean difference,  $1.6 \pm 2.3$ ). In summary, OSA is essentially eliminated (AHI values are normalized) during the time PAP is used by the patient, and both the PAP Titration AHI and the PAP Machine AHI provide reasonably accurate approximations of the AHI during the time PAP is being used. These results were expected and are similar to those reported by others that AHI values are normalized during the time PAP is being used.<sup>1,19,20,22,24,25,35,36</sup>

In addition to measuring the Effective AHI for PAP therapy using the gold standard in-laboratory PSG, we have validated the use of the WP ambulatory device to facilitate measurement of the Effective AHI in the home setting. Our results indicate that the WP provides a reasonably accurate measure of the Effective AHI as the WP Effective AHI values correlated closely with the Effective AHI values computed from the laboratory-based PAP Research PSG ( $r = 0.871$ ), with a mean difference in Effective AHI values of  $2.1 \pm 8.2$  events/h. To the best of our knowledge, no studies have examined the use of the WP device to assess the Effective AHI over the entire sleep period,

including instances when PAP is used for only a portion of the sleep period. However, our results are similar to the findings of a recent systematic review and meta-analysis that examined the use of PAT devices for the diagnosis of OSA, where a high correlation was found between the AHI values from the PAT device and the laboratory-based PSG ( $r = 0.899$  [95%CI: 0.862 to 0.927]).<sup>37</sup> Additionally, our results are similar to those of Pittman et al.<sup>38</sup> who found a high correlation ( $r = 0.79$ ) between the AHI values from a PAT device and laboratory-based PSG, while patients used CPAP during the entire sleep period.

There are several important potential benefits to using the Effective AHI for the clinical management of OSA patients. First, the Effective AHI assesses the true effectiveness of OSA therapy, as it directly measures treatment-related changes in the AHI. Secondly, the Effective AHI could be applied more broadly for assessment of any OSA therapeutic intervention, including both compliance-based (e.g., PAP and oral appliances), and non-compliance based therapy (e.g., surgery); thereby facilitating determination of the comparative effectiveness of different therapies, with the goal of selecting the most effective therapy for an individual patient. Thirdly, it is important to have the ability to measure the Effective AHI in the real-world home setting, and we have validated the accuracy of a portable monitor (WP) which can be used to measure the Effective AHI for any OSA therapy in the home setting on single or multiple nights without significantly disrupting sleep. The ability to measure multiple sleep periods is important as nightly AHI values may vary due to: (1) night-to-night fluctuations in OSA or (2) variations in patterns of device use for compliance-based therapy. Further research will be required to determine how well the Effective AHI predicts important health outcomes such as sleepiness, health-related quality of life, and the incidence of cardiovascular events.

There are several potential limitations to this study. This is a pilot study that examined a group of patients with severe OSA who varied widely in their adherence to PAP therapy, and consequently the study group may not be representative of the population of patients with severe OSA who are treated with PAP therapy. However, the study cohort did use PAP therapy for an average of 4 hours per night with 54% of patients using PAP < 4 hours per night, which is similar to the report of Weaver and Grunstein, who found 46% to 83% of patients with OSA to use PAP four hours or less per night.<sup>2</sup> Furthermore, a systematic review of CPAP adherence suggested that the average use of CPAP in adults in the U.S. and U.K. was about 4.7 hours per night,<sup>39</sup> which is slightly more use than was observed in this study. This investigation was conducted in the laboratory setting, which may not accurately represent what occurs in the home setting. However, the study was designed to recreate the typical conditions from the home setting (patterns and hours of PAP use) and therefore we have every reason to believe that the observed results are indicative of what happens in the home setting. This study was a single-night study performed in the laboratory to examine the Effective AHI and to validate the WP device. However, it is known that patterns of sleep disordered breathing may vary from night to night and a remaining question is how many nights of assessment are necessary to obtain a representative sampling of the Effective

AHI. Furthermore, since the study group was composed only of patients with severe OSA, the results of the study cannot be applied to patients with milder levels of disease, where the hours of use necessary to normalize the Effective AHI may be considerably less. Additionally, significant reduction in the AHI while PAP is off during the sleep period has not been shown to occur in patients with mild-to-moderate OSA. Although the Effective AHI may provide a very important measure of disease burden it is recognized that the AHI is not the sole outcome measure to define successful treatment. It is understood that other important outcomes, such as improvement in functional outcomes and comorbidities, should also be considered and in the future a composite of several important outcomes may be the best approach to comprehensively delineate the overall effectiveness of any OSA therapy.

## CONCLUSIONS

To the best of our knowledge, this is the first time the Effective AHI for PAP therapy has been reported for patients with severe obstructive sleep apnea; where the Effective AHI is defined as the sum of apneas and hypopneas when PAP is and is not being used divided by hours of total sleep time. Since the AHI is currently the primary metric used to define the presence and severity of OSA, as well as the efficacy of treatment, measuring the Effective AHI may for the first time provide the treating clinician with the ability to directly measure residual disease burden. The residual disease burden for patients with severe OSA in this study was almost exclusively defined by the number of respiratory events occurring during the time PAP was not being used, which underscores the clinical value of measuring the Effective AHI. We observed that Effective AHI values could be normalized (Effective AHI < 5) in one of two ways. First, using PAP the entire sleep period ( $\geq 6$  h) normalized the Effective AHI in all patients. Secondly, for patients using PAP less than 6 hours, Effective AHI scores were normalized only in those patients who slept in a non-supine body position when they were not using PAP. We have validated the use of a portable monitoring device (WatchPAT 200) for measurement of the Effective AHI, to facilitate measurement of the Effective AHI in a home setting. This methodology could be used to assess the Effective AHI for any therapeutic intervention—both compliance-based therapy and surgery—which would give the clinician a potentially important tool to aid in the development of a care pathway to facilitate selection of the most effective therapy for an individual patient, thereby providing personalized medical care.

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Address correspondence to: Scott B. Boyd, DDS, PhD; Research Professor, Vanderbilt University School of Medicine, CCC 3322 MCN 2103, 1161 21st Ave. S., Nashville, TN 37232-2103; Tel: (615) 343-6832; Cell: (615) 604-3593; Fax: (615) 322-2793; Email: [scott.boyd@vanderbilt.edu](mailto:scott.boyd@vanderbilt.edu)

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