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SCIENTIFIC INVESTIGATIONS

The Association Between Adherence to Positive Airway Pressure Therapy and Long-Term Outcomes in Patients With Obesity Hypoventilation Syndrome: A Prospective Observational Study

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Study Objectives: To assess the role of different levels of adherence and long-term effects of positive airway pressure (PAP) therapy on gas exchange, sleepiness, quality of life, depressive symptoms, and all-cause mortality in patients with obesity hypoventilation syndrome (OHS).
Methods: A total of 252 patients with newly diagnosed OHS were followed up for a minimum of 2 years after PAP initiation. PAP adherence (h/night) was monitored. Arterial blood gas samples were taken with patients being alert for more than 4 hours after morning awakening. Subjective daytime sleepiness (Epworth Sleepiness Scale [ESS]), quality of life (Short Form 36 [SF-36]) and patient's depressive symptoms (Beck Depression Inventory [BDI]) were assessed before and at the end of the follow-up period, along with all-cause mortality.
Results: At the end of the follow-up period (median duration [25th–75th percentile], 30 [24–52] months), PaO_2 increased from baseline (72.7 ± 10.3 versus 63.2 ± 10.6, $P < .001$) and both $PaCO_2$ and HCO_3^- decreased (43.0 [39.2–45.0] versus 50.0 [46.7–55.4] and 27.5 ± 3.2 versus 31.4 ± 4.2, respectively, $P < .001$). In addition, PAP therapy significantly improved ESS (7 [4–9] versus 14 [11–16], $P < .001$), BDI (8.8 ± 4.9 versus 15.5 ± 7.3, $P < .001$) and SF-36 (82 [78–87] versus 74 [67–79], $P < .001$) scores. Over the follow-up period 11 patients died. Patients who used PAP for > 6 h/night had significant improvements ($P < .05$) in blood gases and SF-36 scores than less adherent patients.
Conclusions: Increased hours of use and long-term therapy with PAP are effective in the treatment of patients with OHS. Clinicians should encourage adherence to PAP therapy in order to provide a significant improvement in clinical status and gas exchange in these patients.
Commentary: A commentary on this article appears in this issue on page 1455.
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BRIEF SUMMARY
Current Knowledge/Study Rationale: There are limited data concerning the effect of long-term effects of positive airway pressure (PAP) therapy on survival and functional status in individuals with obesity hypoventilation syndrome (OHS). This study aimed to assess the role of different levels of adherence and long-term effects of PAP therapy on gas exchange, sleepiness, quality of life, depressive symptoms, and all-cause mortality in patients with OHS after 2 years of PAP therapy.
Study Impact: Our results show that PAP therapy for ≥ 6 h/night, at least for a 2-year period in patients with OHS, resulted in significant improvements of arterial blood gases, quality of life, cardiovascular morbidity, and mortality. Clinicians should encourage PAP adherence to provide a significant improvement in clinical status and gas exchange of these patients.

INTRODUCTION

Obesity is the main risk factor for obstructive sleep apnea (OSA)[1] and a determining factor for obesity hypoventilation syndrome (OHS).[2] As the prevalence of obesity is increasing rapidly, chronic alveolar hypoventilation resulting in chronic hypercapnic respiratory failure develops in a considerable percentage of severely obese patients.[3] Although the prevalence of OHS is currently unknown, 0.3% to 0.48% in the general population are estimated to be affected, whereas in obese patients referred to sleep clinics the prevalence of OHS ranges from 8% to 20%.[4,5]

Patients with OHS have decreased quality of life, tend to have more comorbidities and increased health care expenses, and are at higher risk of the development of serious cardiovascular disease leading to early mortality, compared to normocapnic morbidly obese patients and normocapnic patients with OSA.[6] Despite these worse outcomes, the diagnosis of OHS is typically established late, in the fifth or sixth decade of life; therefore, clinicians need to maintain a high index of

suspicion, particularly given that early diagnosis and therapy are considered important to avoid the adverse effects of OHS and reduce the high burden of morbidity and mortality associated with this syndrome.[7]

Treatment of OHS is based on the underlying pathophysiology of the condition. The upper airway obstruction is an important factor in the pathogenesis of OHS, with 90% of patients exhibiting coexistent OSA. There is evidence that strategies for reversing upper airway obstruction, such as positive airway pressure (PAP), are effective in most patients with stable OHS, particularly in the subgroup with severe OSA. PAP therapy improves blood gases, morning headaches, excessive daytime sleepiness and vigilance, dyspnea, pulmonary hypertension, and secondary erythrocytosis.[8–11] Improvements in symptoms and blood gases are directly related to adherence to therapy and maximal improvement in blood gases can be achieved as early as 2 to 4 weeks after initiation of PAP therapy.[12]

Various forms of PAP therapy are effective in providing short- and long-term benefits in these patients with or without OSA. However, there are limited data concerning the long-term effects of PAP therapy on survival and functional status in individuals with OHS and OSA. Therefore, we aimed to assess the role of different levels of adherence and long-term effects of PAP therapy on gas exchange, sleepiness, quality of life, depressive symptoms, and all-cause mortality in patients with OHS.

METHODS

We conducted a single-center, prospective, long-term follow-up study of patients with a new diagnosis and who fulfilled OHS diagnostic criteria. Between June 2009 and June 2012, consecutive patients aged between 18 and 80 years, who were admitted to the Sleep Disorders Center, Department of Thoracic Medicine, University of Crete Medical School, for evaluation of suspected sleep-disordered breathing, were considered as potential recruits for this study. OHS was determined by an arterial blood gas with partial pressure of carbon dioxide in the arterial blood ($PaCO_2$) at rest > 45 mmHg and a body mass index (BMI) > 30 kg/m^2 in the absence of other causes of hypoventilation, such as neuromuscular, chest wall disorders, and chronic obstructive pulmonary disease. To be included in the study, patients had to be clinically stable for at least 4 weeks prior to enrollment. In addition, all included patients had to have achieved higher than elementary-school education. The exclusion criteria were: refusal to participate, refusal of PAP therapy, central sleep apnea syndromes, chronic obstructive pulmonary disease or asthma, restrictive ventilation syndromes, severe congestive heart failure, a history of life-threatening arrhythmias, severe cardiomyopathy, significant chronic kidney disease, untreated hypothyroidism, family or personal history of mental illness, drug or alcohol abuse, sedative use, severe cognitive impairment, concurrent oncological diseases, and history of narcolepsy or restless legs syndrome.

All subjects provided written informed consent and ethical approval was provided by the University Hospital Ethics Committee.

Initial Visit/Evaluation Data Collection

All patients underwent a detailed evaluation that included age, measurement of BMI, medical history focused on sleep-related symptoms, associated conditions and comorbidities, menopausal status, smoking history, and alcohol intake. In addition, we performed spirometry and overnight attended polysomnography (PSG) and collected arterial blood gas (ABG) samples. Furthermore, patients were classified into three groups according to $PaCO_2$ values: (1) mild ($PaCO_2$ 46–50 mmHg), moderate ($PaCO_2$ 51–55 mmHg), severe ($PaCO_2 \geq 56$ mmHg), based on the suggestions of Damiani et al.[13] Subjective daytime sleepiness was assessed by the Epworth Sleepiness Scale (ESS),[14] quality of life by Short Form 36 Health Survey (SF-36), and patient's depressive symptoms by the Beck Depression Inventory (BDI) at baseline and at 2 years after initiation of PAP therapy.

Short Form 36 Health Survey

The SF-36 is a reliable and validated 36-item questionnaire for the assessment of general (physical and mental) health and quality of life, each of which is scored separately from 0 (worst) to 100 (best).[15–17]

Beck Depression Inventory

The BDI is a 21-item questionnaire that is a widely used and well-validated self-reported inventory of depressive symptoms.[18–20] Total scores range from 0 to 63 and represent the sum of the highest levels endorsed on each item. Scores lower than 10 are considered normal.

Spirometry

Spirometry was performed with the patient in the seated position, according to approved standards.[21]

ABG Samples

ABG samples were taken with patients being alert for more than 4 hours after morning awakening, seated and breathing room air, and having remained at rest for 10 minutes. In patients on long-term oxygen therapy, supplemental oxygen was removed 30 minutes before the measurement of blood gases.

Sleep Study and PAP Treatment

Polysomnography

In-laboratory PSG was performed in clinically stable patients at a median (25th–75th percentile) 58.9 (28.2–47.3) days after the diagnosis. All patients underwent a single-night full diagnostic PSG study (Alice 5, Diagnostics System, Respironics, Murrysville, Pennsylvania, United States) according to standard techniques, with monitoring of the electroencephalogram, electro-oculogram, electromyogram, flow (by oronasal thermistor and nasal air pressure transducer), thoracic and abdominal respiratory effort (by respiratory inductance plethysmography), pulse oximetry (SpO_2), and body position. Snoring was recorded by a microphone placed on the anterior neck. In addition, we performed sleep capnography, (CO2SMO, Respironics Novametrix, Wallingford, Connecticut, United States) with transcutaneous carbon dioxide ($PtcCO_2$) monitoring, in order to identify sleep hypoventilation and to guide

the titration of PAP therapy, ensuring that ventilation is adequately maintained.[22] We identified the average $PtcCO_2$ values by downloading the overnight records. We excluded unreliable records (n = 18) (inexplicable, abrupt, and excessive increases in $PtcCO_2$). PSG recordings were manually interpreted over 30-second periods by experienced staff in accordance with the 2007 American Academy of Sleep Medicine (AASM) guidelines.[23] The scorer was blinded to the origin of the data. The definition of apnea and hypopnea followed the AASM standard criteria.[23] The apnea-hypopnea index (AHI), calculated as the number of apnea and hypopnea events per hour of sleep, was used to diagnose OSA and assess its severity. OSA was categorized as mild (AHI 5 to < 15 events/h), moderate (AHI 15 to < 30 events/h), and severe (AHI ≥ 30 events/h).

PAP Titration

During in-laboratory PAP titration with full PSG, performed 11.8 ± 8.9 days after the diagnostic PSG, the appropriate PAP settings were established. Continuous positive airway pressure (CPAP) was initially tested in all patients, and manually titrated in order to abolish all nocturnal respiratory events. If oxygen desaturation persisted after obstructive apneas and hypopneas had been eliminated with CPAP, we changed to bilevel PAP ventilation in spontaneous mode (ie, no backup respiratory rate). The level of CPAP that eliminated obstructive apneas and hypopneas was used as the expiratory positive pressure and positive inspiratory pressure was gradually increased until oxygen saturation was steadily over 90% or high inspiratory pressures (equal or above 20 cmH_2O) were reached. Oxygen was added when significant oxygen desaturation persisted ($SpO_2 \leq 88\%$ for ≥ 5 minutes in the absence of obstructive respiratory events) despite the use of these high inspiratory pressures. In addition, oxygen therapy was added if, prior to the PAP titration, the patient's awake supine SpO_2 while breathing room air was ≤ 88%.[24] All patients received education prior to the PAP titration night and completed a questionnaire at the end of the first night, reporting their quality of sleep under PAP titration and any side effects.

Follow-Up

All study groups received individual counseling during scheduled clinic appointments, at their initial sleep clinic consultation, and after the completion of overnight in-laboratory polysomnography. After PAP therapy was started, patients were followed up in the outpatient sleep clinic at 1 month, then at 3-month intervals during the first year, and every 6 months thereafter. Patients were advised to bring their PAP device and interface to every sleep clinic visit. The importance of good adherence to PAP therapy was emphasized, encouraging the patients to use PAP therapy throughout the entire sleep period every day. This format adhered to a standardized approach according to our PAP clinic procedures.[25] In the first month, separate from treatment adherence encouragement, an ABG analysis was performed, and changes to oxygen therapy or PAP settings were made if necessary. At each visit a clinical nurse, under the supervision of a sleep physician, re-evaluated the exclusion criteria and recorded anthropometric variables, weight, PAP adherence, medications, alcohol and tobacco consumption, and other clinically relevant events. Furthermore, in patients requiring supplemental oxygen, oxygen was withdrawn based on awake ABG levels, effective PAP therapy (PAP adherence), and nocturnal oximetry results.

The study was designed to follow patients for at least 2 years. However, in some patients, follow-up stopped when the patient withdrew informed consent or was unable to complete follow-up.

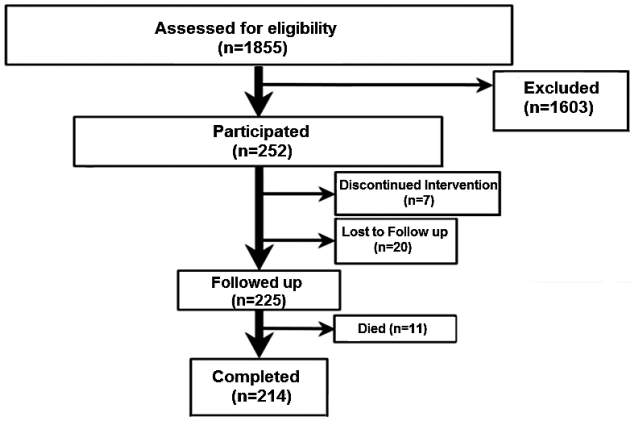
PAP Adherence

PAP usage data included mask type (nasal or full face), number of nights on PAP, average use (h/night), air leakage, and air pressure delivered. Regular PAP adherence was defined as using PAP therapy for an average of 4 h/night for and at least 70% of the nights.[26] However, we used the cutoff point of 6 h/night of PAP use for subgroup analysis, as studies in patients with eucapnic OSA indicate that with use more than 6 h/night a greater percentage of patients will achieve normal levels of objectively measured and self-reported daytime sleepiness, as well as significantly improved memory, daily functioning, and improved survival rates.[25,27]

Statistical Analysis

All continuous variables were tested for normality using several methods (skewness and kurtosis, the proximity of the mean to the median, visual inspection of their histograms, Q-Q plots, and box plots). Results are presented as mean ± standard deviation (SD) for continuous variables if normally distributed and as median (25th–75th percentile) if not. Qualitative variables are presented as absolute number (percentage). Variables that were normally distributed were compared among the three groups (mild, moderate and severe OHS) using analysis of variance. If analysis of variance was significant, we used Tukey-Kramer *post hoc* test to compare each pair (moderate versus mild, severe versus mild, and moderate versus mild OHS groups). For variables that are not normally distributed, we used the Kruskal-Wallis test to compare the three groups. If Kruskal-Wallis test results were significant, we used the Mann-Whitney *U* test to compare each pair. For categorical variables, we used the chi-square test to compare the three groups. To compare changes from baseline to follow-up, the paired samples *t* test (for normally distributed data) and the Wilcoxon signed-rank test (for non-normally distributed data) were used. Changes of continuous variables from baseline to follow-up were defined as follow-up minus baseline values. Correlation coefficients were calculated using the Pearson or Spearman (for non-normally distributed data) correlation test for all the independent predictors of mean change of PaO_2, $PaCO_2$, HCO_3^-, and questionnaire scores. As independent variables we included clinically relevant variables such as age, sex, BMI, ESS, smoking history, comorbidities, AHI, oxygen desaturation index, mean SpO_2 and minimum SpO_2 during sleep, awake and asleep transcutaneous CO_2 ($PtcCO_2$), sleep time with $SpO_2 < 90\%$, ABG, spirometric measurements, h/night of PAP use, percentage of nights PAP was used, type of PAP (bilevel PAP or fixed CPAP and auto-PAP) mode. Only the variables that were found to be significant were further

Figure 1—Study flow diagram illustrating how the final group of patients were obtained.



analyzed. Multivariate linear regression analysis was used to examine any association of PAP treatment with changes in PaO_2, $PaCO_2$, HCO_3^-, and questionnaires scores at follow-up, after controlling for the potential confounders that were found to be significant. Furthermore, we applied a binary logistic regression analysis model to assess the ability of the previous variables to predict the prescription of O_2 supplementation to PAP therapy and mortality. As a large proportion of patients were smokers and obesity can falsely increase the forced expiratory volume in one second/forced vital capacity ratio leading to probable false-negative results for the presence of obstructive airways disease, we performed our analysis separately in patients who never smoked. A value of $P < .05$ was considered statistically significant. Data were analyzed using PAWP 17.0 software (SPSS Inc, Chicago, Illinois, United States).

RESULTS

Baseline Characteristics

During the study period, 1,855 patients were referred to the sleep disorders clinic for clinical suspicion of OSA. Most were obese (BMI > 30 kg/m^2) and had an AHI ≥ 5 events/h (1,623, 87.5%). Among the 1,855 patients, 241 received a diagnosis of OHS and OSA, 11 OHS without OSA (ie, AHI < 5 events/h), 1,227 OSA without hypercapnia, 211 OSA with hypercapnia (mainly due to COPD diagnosis), and 165 no OSA. The overall prevalence of OHS among the 1,855 patients referred was 13.6% and among obese patients with OSA it was 15.5%. All 252 patients with OHS participated, of whom 7 patients abandoned PAP therapy before the 24-month period and 20 did not show up for the final assessment (**Figure 1**). Thus, the final study sample comprised 225 patients, 108 men (48%) and 117 women (52%). These patients did not differ from those who did not complete the study regarding age, sex, BMI, comorbidities, AHI, mean nighttime SpO_2, baseline $PaCO_2$ and PaO_2 and type of PAP therapy prescribed (data not shown).

Demographics, spirometric measurements, and ABG analysis of the final sample at baseline are shown in **Table 1**. PSG data and questionnaires scores are shown in **Table 2**. Time that $PtcCO_2$ was above 50 mmHg was 72.3 ± 30.1 minutes. None of the patients included in the study had a significant number of central apneas during sleep. Based on OHS grading according to $PaCO_2$ level, 123 patients (55%) were categorized as mild, 46 (20%) as moderate, and 56 (25%) as severe. No difference was found among groups in terms of BMI, current smoking, spirometry results, BDI, and ESS scores (**Table 1** and **Table 2**).

At baseline, 100 patients (45%) required daytime and/or nocturnal supplemental oxygen (flow 1–3 L/min) therapy (**Table S1** in the supplemental material). These patients were older and mostly female, had more comorbidities, higher baseline $PaCO_2$, and lower AHI. In logistic regression models, the prescription of O_2 supplementation with PAP therapy was associated with the moderate to severe OHS group (14.1; 95% CI 4.4, 45.4, $P < .001$) after controlling for the potential confounders.

Adherence With PAP Therapy

Of 225 patients with OHS, 84 (37.3%) used PAP (either fixed CPAP [17.8%] or auto-PAP [82.2%] with the mean CPAP pressure of 10.5 ± 2.5 cmH_2O) and 141 (62.6%) used bilevel PAP (mean IPAP of 13.9 ± 2.7 cmH_2O and mean EPAP of 9.2 ± 2.1 cmH_2O). In the mild OHS group, 55% of subjects used bilevel PAP; the percentage was 75% in the moderate OHS group and 76% in the severe OHS group, which was slightly but not significantly increased compared to moderate OHS, but was significantly increased compared to mild OHS.

The mean daily use of PAP therapy at the most recent visit was 6.0 ± 1.7 h/night. Most patients (95.9%) had objective usage of ≥ 4 h/night and 56.9% had objective usage of ≥ 6 h/night. Patients who used bilevel PAP therapy also had greater PAP usage (6.3 ± 1.7 h/night versus 5.6 ± 1.6 h/night, $P = .027$). PAP usage was also significantly different among OHS severity groups (mild: 5.8 ± 1.4 h/night; moderate: 6.9 ± 1.9 h/night; severe: 5.9 ± 2.0 h/night; $P = .03$). The moderate group had higher usage compared to the mild group ($P = .025$).

No significant weight loss or improvement in spirometry tests were observed at the end of the follow-up period (data not shown). Two patients (1 mild, 1 severe) underwent weight reduction surgery, and both lost a significant amount of weight and no longer required PAP therapy. Although initially 45% of the patients required daytime and/or nocturnal supplemental oxygen, oxygen was discontinued in a significant proportion of patients (based on awake ABG levels, effective PAP therapy and nocturnal oximetry results) and only 8.9% were still on oxygen therapy at the end of the follow-up period.

Arterial Blood Gases

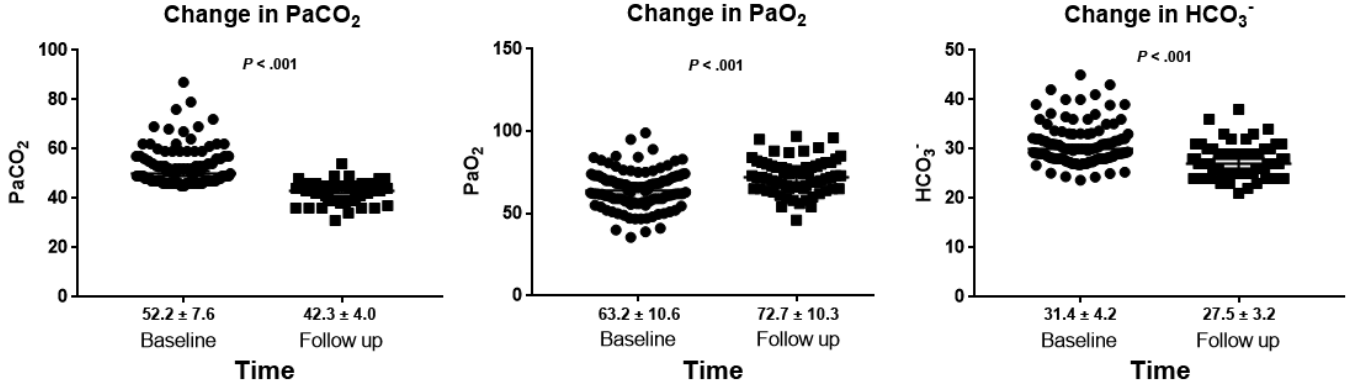
Table 3 describes the observed $PaCO_2$, HCO_3^-, and PaO_2 values as well as the ESS, BDI, and SF-36 scores at baseline, after the end of the follow-up period, and the mean change from baseline. At the end of the follow-up period, PaO_2 had increased from baseline ($P < .001$) and both $PaCO_2$ and HCO_3^- had decreased ($P < .001$) (**Figure 2**). Similar results were found in the subgroup of patients who never smoked (**Table S2** in the supplemental material). In all three OHS groups separately, the comparison of pretreatment with the last posttreatment

Table 1—Baseline demographics, spirometric measurements, and ABG analysis results of the study population.

Characteristics	All Patients (n = 225)	Mild OHS (n = 123)	Moderate OHS (n = 46)	Severe OHS (n = 55)	*P* Across All
Age (years)	63 (48–69)	59 (45–65)	67 (57–73) *	67 (63–76) †	< .001
Sex (male), n (%)	108 (48%)	73 (59%)	13 (29%) *	21 (38%)	.019
BMI (kg/m^2)	43.3 (39–50)	45 (40–51)	41 (39–47)	41 (36–48)	.1
Neck circumference (cm)	45.2 ± 4.1	45.6 ± 4.3	45.1 ± 3.8	44.7 ± 4.5	.64
Waist circumference (cm)	133 (123–144)	136 (123–146)	131 (124–142)	128 (124–137)	.34
Hip circumference (cm)	134 (123–145)	134 (122–146)	132 (124–145)	128 (119–144)	.78
Smoking status, n (%)					
Current smokers	37 (16)	17 (14)	8 (17)	9 (17)	.39
Ex-smokers	46 (20)	34 (28)	8 (17)	6 (10)	
Comorbidities					
Diabetes mellitus	75 (33)	41 (33)	13 (29)	21 (38)	.79
Hypertension	137 (61)	70 (57)	33 (71)	36 (66)	.45
Dyslipidemia	77 (34)	48 (39)	13 (29)	20 (36)	.39
Ischemic heart disease	25 (11)	10 (8)	10 (21)	6 (10)	.22
Atrial fibrillation	17 (8)	2 (2)	8 (17) *	8 (14) †	.02
Compensated heart failure	31 (14)	10 (8)	8 (17)	15 (28) †	.04
Stroke	11 (5)	6 (5)	4 (8)	2 (4)	.73
Hypothyroidism	34 (15)	16 (13)	13 (29)	8 (14)	.16
PFT					
FEV_1, % predicted	84 ± 12	83 ± 11	78 ± 5	91 ± 19	.32
FVC, % predicted	85 ± 11	86 ± 12	80 ± 8	78 ± 8	.65
FEV_1/FVC	81 ± 6	82 ± 7	79 ± 5	81 ± 5	.72
ABG					
pH	7.39 ± 0.03	7.39 ± 0.03	7.39 ± 0.03	7.39 ± 0.04	.53
$PaCO_2$ (mmHg)	50 (47–55)	47 (46–49)	52 (51–53) *	61 (58–67) †,‡	< .001
PaO_2 (mmHg)	64.5 ± 11.3	68.9 ± 9.0	61.4 ± 11.5 *	56.3 ± 10.5 †	< .001
HCO_3^- (mmol/L)	30.8 ± 4.1	28.7 ± 2.0	31.4 ± 3.4 *	35.2 ± 4.9 †,‡	< .001
Resting oxygen saturation (%)	92 (90–94)	94 (91–95)	91 (88–94) *	89 (83–92) †	< .001

Data are presented as mean ± standard deviation, median (25th–75th percentile), or n (%) as indicated. * = *P* < .05 moderate versus mild OHS. † = *P* < .05 severe versus mild OHS. ‡ = *P* < .05 severe versus moderate OHS. ABG = arterial blood gas, BMI = body mass index, FEV_1 = forced expiratory volume in one second, FVC = forced vital capacity, OHS = obesity hypoventilation syndrome, PFT = pulmonary function test.

Figure 2—Changes in ABG at baseline and at the end of the follow-up period.



Values presented as mean ± standard deviation below graph. ABG = arterial blood gas.

measurements demonstrated significant improvements in median $PaCO_2$ values ($P < .001$), mean PaO_2 values ($P < .05$), and mean HCO_3^- values ($P < .005$) (see supplemental material).

In stepwise multiple linear regression models, the magnitude of change in $PaCO_2$ was associated only with PAP use (β = −1.5 mmHg per average hour of nightly PAP use [95% confidence interval (CI), −2.5, −0.5]; $P = .007$) and baseline $PaCO_2$ (β = −0.87 [95% CI, −1.2, −0.5]; $P < .001$) after controlling for the potential confounders (**Table S3** in the supplemental material). The change in PaO_2 was related only to baseline PaO_2 (β = −0.89

Table 2—Baseline PSG data and questionnaires scores of the final sample.

	Total (n = 225)	Mild OHS (n = 123)	Moderate OHS (n = 46)	Severe OHS (n = 55)	*P* Across All
Diagnostic PSG					
AHI (events/h)	58 (36–86)	74 (30–74)	43 (35–68)*	43 (8–83)	.04
REM AHI (events/h)	69 ± 27	72 ± 27	71 ± 23	58 ± 28	.07
AI (events/h)	52 ± 21	55 ± 21	48 ± 18	47 ± 22	.13
4% ODI (events/h)	70 ± 29	75 ± 28	63 ± 28	64 ± 32	.08
Mean SaO_2 (%)	87.0 (83–89)	87 (84–90)	86 (79–88)	86 (80–88)	.12
Minimum SaO_2 (%)	65 ± 10	65 ± 10	65 ± 9	65 ± 11	.97
TST90 (minutes)	151 (110–241)	154 (97–258)	152 (109–240)	141 (110–238)	.99
$PtcCO_2$ awake (mmHg)	51 (47–59)	49 (46–50)	53 (51–53)*	62 (59–62)†,‡	< .001
$PtcCO_2$ asleep (mmHg)	67.8 ± 9.6	61.9 ± 6.7	68.1 ± 5.1*	78.5 ± 7.3†,‡	< .001
After PAP Titration					
AHI (events/h)	4 (3–4)	4 (3–4)	4 (3–5)	4 (3–5)	.30
AI (events/h)	7 ± 2	7 ± 2	8 ± 3	7 ± 2	.70
4% ODI (events/h)	5 ± 2	5 ± 1	5 ± 2	5 ± 2	.05
Mean SpO_2 (%)	95 (94–95)	95 (94–95)	95 (93–95)	94 (94–95)	.06
Lowest SpO_2 (%)	89 ± 2	89 ± 1	88 ± 3*	88 ± 2	.008
TST90 (minutes)	1 (0–2)	1 (0–2)	3 (2–5)*	1 (0–5)	< .001
Questionnaire Score					
ESS	14 (11–16)	14 (10–17)	14 (12–16)	13 (10–16)	.89
BDI	15.5 ± 7.3	14.3 ± 7.0	17.4 ± 7.5	16.3 ± 8.1	.18
SF-36	74 (67–79)	76 (71–81)	71 (60–76)*	71 (62–75)†	< .001

Data are presented as mean ± standard deviation or median (25th–75th percentile). * = $P < .05$ moderate versus mild OHS. † = $P < .05$ severe versus mild OHS. ‡ = $P < .05$ severe versus moderate OHS. AHI = apnea-hypopnea index, AI = arousal index, BDI = Beck Depression Inventory, ESS = Epworth Sleepiness Scale, ODI = oxygen desaturation index, OHS = obesity hypoventilation syndrome, PAP = positive airway pressure, PSG = polysomnography, $PtcCO_2$ = transcutaneous CO_2, REM = rapid eye movement, SF-36 = Short Form 36 Health Survey, TST90 = total sleep time spent with SpO_2 < 90%.

Table 3—Comparison of ABG and questionnaire scores at baseline and at the end of the follow-up period for all patients.

	Baseline	End of Follow-Up Period	Difference	*P*
$PaCO_2$	50.0 (46.7–55.4)	43.0 (39.2–45.0)	−8.3 (−14.3, −4.9)	< .001
PaO_2	63.2 ± 10.6	72.7 ± 10.3	9.5 ± 13.9	< .001
HCO_3^-	31.4 ± 4.2	27.5 ± 3.2	−3.9 ± 4.7	< .001
ESS	14 (11–16)	7 (4–9)	−6 (−9, −3)	< .001
BDI	15.5 ± 7.3	8.8 ± 4.9	−6.7 ± 5.5	< .001
SF-36	74 (67–79)	82 (78–87)	8 (6–11)	< .001

Data are presented as mean ± standard deviation or median (25th–75th percentile). ABG = arterial blood gas, BDI = Beck Depression Inventory, ESS = Epworth Sleepiness Scale, SF-36 = Short Form 36 Health Survey.

[95% CI −1.2, −0.57]; $P < .001$) and HCO_3^- change only with baseline HCO_3^- (β = −0.77 [95% CI −1.1, −0.5]; $P < .001$).

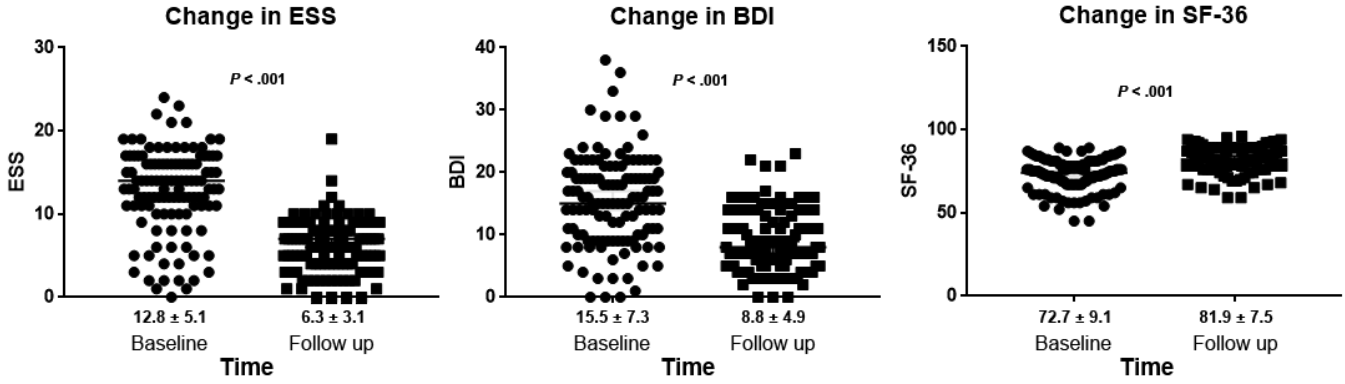
At the end of the study, 38 patients (18%) had daytime $PaCO_2 > 45$ mmHg (median $PaCO_2$ 46.9 mmHg [46.03–48.78]). These patients had higher baseline daytime $PaCO_2$ (54 versus 49 mmHg, $P = .03$), were categorized mostly as moderate to severe OHS at baseline (82%, $P = .02$) and were similar in age, sex, BMI, type of PAP therapy, spirometry tests, or presence of comorbidities ($P > .05$). Mean adherence to PAP therapy was 6.7 ± 1.5 h/night for patients who achieved normocapnia versus 5.7 ± 1.3 h/night for those who remained hypercapnic ($P = .038$). When we separately analyzed the clinical characteristics of the patients with persistent daytime $PaCO_2 > 45$ mmHg, most of them had a follow-up $PaCO_2$ of 45–49 mmHg, and 5 (2.3%) had a $PaCO_2$ above 50 mmHg. These patients had optimal nighttime SpO_2 correction and were clinically asymptomatic and consequently, PAP treatment was maintained.

Questionnaires Scores

PAP therapy also significantly improved ESS ($P < .001$), BDI ($P < .001$), and SF-36 ($P < .001$) scores in all patients in the three OHS groups and in the subgroup of patients who never smoked (**Table 3**, **Figure 3**, and **Table S2**).

Change in ESS was correlated only with baseline ESS (β = −0.78 [95% CI −0.89, −0.67]; $P < .001$). Change in BDI was associated with baseline BDI (β = −0.68 [95% CI −0.8, −0.6]; $P < .001$), baseline SF-36 (β = −0.16 [95% CI −0.25, −0.01]; $P = .004$), and awake $PtcCO_2$ (β = −0.097 [95% CI

Figure 3—Changes in questionnaires scores at baseline and at the end of the follow-up period.



Values presented as mean ± standard deviation below graph. BDI = Beck Depression Inventory, ESS = Epworth Sleepiness Scale, SF-36 = Short Form 36 Health Survey.

Table 4—Comparisons of changes in ABG and questionnaire scores over the follow-up according to PAP use per night.

	All Patients		Mild OHS	
	< 6 h/night (n = 97)	≥ 6 h/night (n = 128)	< 6 h/night (n = 67)	≥ 6 h/night (n = 56)
$PaCO_2$	−3.6 (−5.8, −2.5)	−10.8 (−16.6, −7.9)**	−3.6 (−5.8, −2.3)	−8.9 (−10.4, −5.7)**
PaO_2	0.5 ± 13.6	13.5 ± 12.2**	2.0 ± 9.5	12.0 ± 10.8**
HCO_3^-	−1.2 ± 2.4	−5.2 ± 5.0**	−1.2 ± 2.7	−2.5 ± 4.3
ESS	−6 (−9, −2)	−7 (−10, −5)	−6 (−9, −2)	−7 (−11, −5)
BDI	−6.1 ± 4.1	−7.1 ± 6.3	−6.5 ± 4.1	−6.4 ± 6.6
SF-36	7 (5–10)	9.5 (7–13)**	7 (5–10)	9 (7–11)
	Moderate OHS		Severe OHS	
	< 6 h/night (n = 10)	≥ 6 h/night (n = 36)	< 6 h/night (n = 21)	≥ 6 h/night (n = 34)
$PaCO_2$	−5.0 (−6.3, −3.1)	−8.9 (−12.3, −7.3)*	−3.2 (−5.7, −2.2)	−18 (−25.7, −15.6)**
PaO_2	−4.7 ± 31.5	13.4 ± 13.8**	−6.0 ± 2.5	15.0 ± 12.7**
HCO_3^-	−0.5 ± 0.8	−4.7 ± 4.3*	−1.2 ± 2.3	−8.5 ± 4.6*
ESS	−6 (−8, −4)	−6 (−9, −2)	−5 (−12, 0)	−8 (−10, −5)
BDI	−4.8 ± 1.5	−8.4 ± 5.2	−5.4 ± 4.9	−7.6 ± 7.0
SF-36	8 (7–11)	10 (7–13)	7 (6–9)	12 (9–14)*

Data are presented as mean ± standard deviation or median (25th–75th percentile). * = $P < .05$, patients with ≥ 6 h/night PAP use versus patients with < 6 h/night PAP use. ** = $P < .01$, patients with ≥ 6 h/night PAP use versus patients with < 6 h/night PAP use. ABG = arterial blood gas, BDI = Beck Depression Inventory, ESS = Epworth Sleepiness Scale, OHS = obesity hypoventilation syndrome, PAP = positive airway pressure, SF-36 = Short Form 36 Health Survey.

−0.26, −0.03]; $P = .041$). Change in SF-36 was correlated with PAP use (β = 0.8 [95% CI 0.12, 1.45]; $P = .007$) and baseline SF-36 (β = −0.27 [95% CI −0.45, −0.16]; $P < .001$) (**Table S4** in the supplemental material).

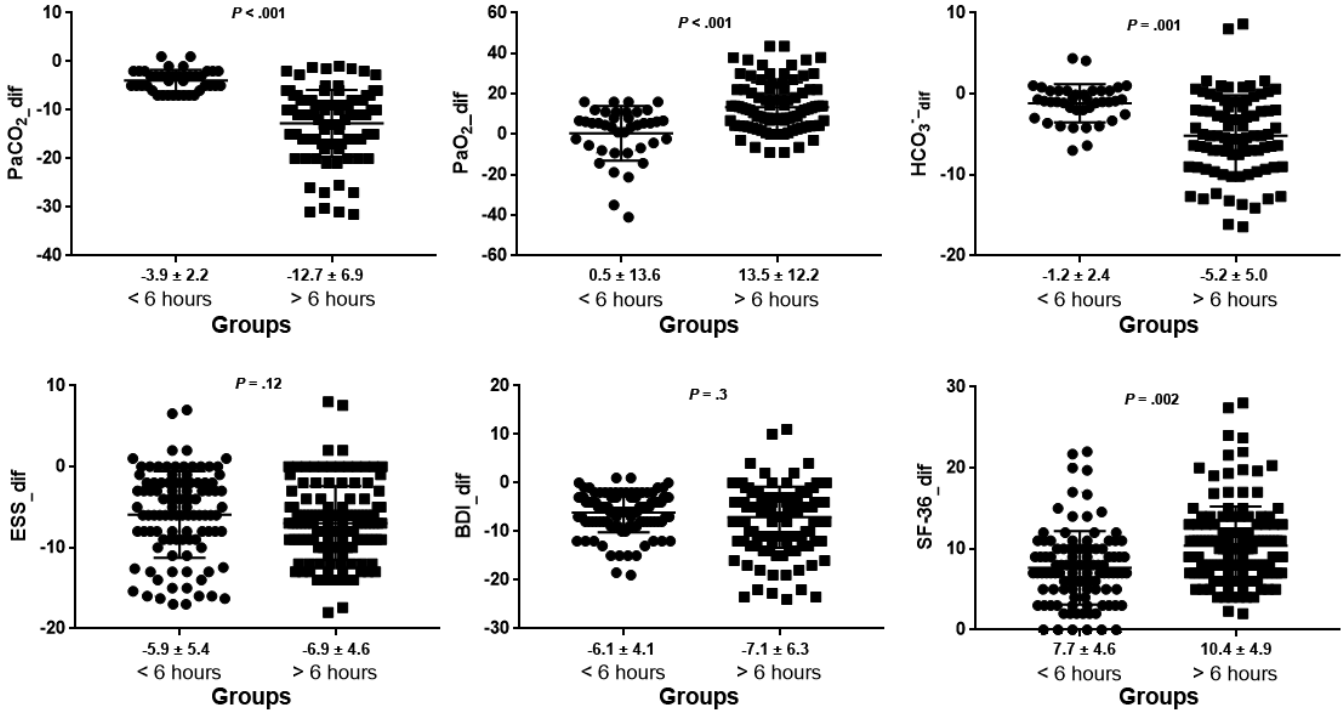
Subgroup Analysis by Hours of PAP Use

Because PAP use was among the strongest correlated factors in most of the aforementioned parameters, subgroup analysis was performed to compare changes in these parameters between patients with PAP use ≥ 6 and < 6 h/night. Baseline demographics, spirometric measurements, ABG analysis, and PSG parameters (**Table S5** and **Table S6** in the supplemental material) did not differ between these subgroups ($P > .05$). Patients who used PAP therapy ≥ 6 h/night had a considerably greater improvement in ABG and SF-36 score than patients who were less adherent (**Table 4**, **Figure 4**). Similar results were obtained in the subgroup of patients who never smoked (**Table S7** in the supplemental material). Furthermore, the benefit of PAP adherence on $PaCO_2$ and SF-36 seems to continue after 6 hours of PAP use (**Table S8** in the supplemental material). The final $PaCO_2$ normalized (< 45 mmHg) in 71% of patients with adherence below 6 h/night compared to 76% of patients with adherence equal or above 6 h/night ($P = .18$). In more adherent patients, the need for daytime home oxygen therapy decreased from 56% to 5% ($P < .001$), and in less adherent patients it decreased from 30% to 12% ($P = .003$). At least one serious cardiovascular event was diagnosed in 15.1% of the patients who used PAP therapy for < 6 h/night compared to none of the more adherent patients during follow-up ($P = .001$).

Mortality

The median follow-up was 30 months (24–52 months). During the entire observation period, a total of 11 deaths (5% of

Figure 4—Changes in ABG and in questionnaires scores according to PAP compliance.



Values presented as mean ± standard deviation below graph. ABG = arterial blood gas, BDI = Beck Depression Inventory, ESS = Epworth Sleepiness Scale, PAP = positive airway pressure, SF-36 = Short Form 36 Health Survey.

all patients) were recorded. The main cause of death (in 90%) was cardiovascular diseases (heart failure in two patients, sudden death in three patients, ischemic heart disease in three patients, and stroke in two patients). Other causes of death were cancer (10%).

With regard to diagnostic OHS subgroups, 2 patients (1.6%) in the mild OHS group died, whereas in the moderate-severe group, there were 9 deaths (9%). Baseline $PaCO_2$ ($r = -.2$, $P = .03$), total sleep time spent with $SaO_2 < 90\%$ ($r = .23$, $P = .02$), and hours of PAP use ($r = -.26$, $P = .003$) were found to predict mortality. The use of supplemental oxygen therapy was not associated with mortality. In a logistic regression model, after adjusting for important covariates, higher PAP adherence was independently associated with significantly reduced mortality (0.45; 95% CI 0.22, 0.92; $P = .029$). Patients who used PAP therapy for ≥ 6 h/night had a considerably lower mortality than less adherent patients (8.7% versus 2.5%, $P = .038$).

Impact of Type of PAP Therapy

Table 5 summarizes the baseline characteristics and outcomes of patients treated with CPAP (n = 84) or bilevel PAP (n = 141). Patients who used bilevel PAP therapy had a higher baseline $PaCO_2$ level ($P = .018$) as well as awake and asleep $PtcCO_2$ levels ($P < .001$). Baseline demographics, spirometric measurements, and PSG parameters did not differ between these subgroups ($P > .05$). Furthermore, patients who used bilevel PAP had greater PAP adherence ($P = .027$) and experienced a greater improvement in BDI score ($P = .004$). However, there was no difference in all the other outcomes as well as mortality between the two groups ($P = .90$).

DISCUSSION

This study investigated the effect of PAP treatment on clinical outcomes in a large number of clinically stable patients with OHS. The current results show that in patients with OHS, the use of PAP therapy for ≥ 6 h/night for a period of at least 2 years resulted in significant improvements in gas exchange, quality of life, and all-cause mortality.

A noteworthy aspect of the study was the diagnosis of OSA in most of the patients recruited, confirming the important role of obstructive events in the pathogenesis of hypoventilation in obese patients. Therefore, optimal therapy of chronic hypoventilation should not only focus on improvement of oxygen saturation and normalization of hypercapnia, but also in stabilizing the upper airway. Evidence supporting one mode of PAP therapy over another in patients with OHS and OSA is limited.[28] Both continuous and bilevel PAP therapy modes can successfully improve daytime gas exchange.[12,29–31] Importantly, adherence to PAP therapy is an important modifiable factor related to the response to treatment. Prior PAP trials have demonstrated that correction of OSA and nocturnal hypoventilation improves diurnal respiratory physiology, quality of life, and morbidity/mortality.[28,30,31,32] Several small studies with 1 night or up to 3-month follow-up periods have evaluated such PAP interventions.[29,30,33–35] The first prospective study on 23 patients was conducted by Banerjee et al., demonstrating the correction of obstructive events and improvement in sleep architecture during the first CPAP titration night, although a failure to correct nocturnal hypoxemia was noted in 43% of the patients.[33] An observational study of 29 patients with OHS treated with

Table 5—Baseline characteristic and outcomes at the end of the study based on mode of PAP therapy.

	CPAP (n = 84)	Bilevel PAP (n = 141)	*P*
Baseline Characteristics			
Age (years)	60 (45–67)	64 (54–72)	.08
Sex (male), n (%)	48 (57)	60 (43)	.14
BMI (kg/m^2)	44.3 (39.5–49.8)	42.8 (38.4–49.5)	.82
Baseline $PaCO_2$ (mmHg)	48 (46–52)	51 (47–57)	.018
Baseline PaO_2, (mmHg)	66.5 ± 10.8	63.3 ± 11.4	.14
PaO_2 ≤ 55 mmHg, n (%)	6 (7.1)	34 (24.1)	.023
Baseline resting SpO_2	92.7 (90.8–94.8)	91.4 (89.0–93.8)	.06
Need for daytime oxygen therapy, n (%)	16 (19)	66 (47)	.002
Need for oxygen therapy during sleep, n (%)*	17 (20)	83 (59)	< .001
Baseline FEV_1, % predicted	86.5 ± 13.2	79.7 ± 9.7	.10
Baseline FVC, % predicted	83.6 ± 13.3	86.6 ± 4.5	.63
AHI (events/h)	58 (36–86)	57 (37–86)	.99
TST90 (minutes)	147 (89–246)	152 (118–241)	.49
$PtcCO_2$ awake, mmHg	47 (46–50)	54 (50–62)	< .001
Mean $PtcCO_2$ asleep, mmHg	61.6 ± 6.3	71.7 ± 9.2	< .001
Pressures	10.5 ± 2.5	IPAP 13.9 ± 2.7 EPAP 9.2 ± 2.1	
Baseline ESS	14 (10–17)	13 (11–16)	.50
ESS > 10, n (%)	61 (72.6)	110 (78.0)	.51
Baseline BDI	13.1 ± 7.2	16.9 ± 7.0	.005
Baseline SF-36	76 (72–81)	72 (66–77)	.001
Outcomes at 2-Year Follow-Up			
Adherence, h/night	5.6 ± 1.6	6.3 ± 1.7	.027
$PaCO_2$ (mmHg)	43.4 (39.3–45.0)	43.0 (39.03–45.0)	.78
$PaCO_2$ < 45 mmHg, n (%)	70 (83)	114 (81)	.78
PaO_2 (mmHg)	71.5 ± 10.1	72.9 ± 10.7	.61
PaO_2 ≤ 55 mmHg, n (%)	0 (0)	4 (2.8)	.54
Resting SpO_2	93.8 (92.4–95.4)	94.4 (92.4–95.7)	.59
Need for daytime oxygen therapy, n (%)	4 (4.7)	17 (12.0)	.16
Need for oxygen therapy during sleep, n (%)*	4 (4.7)	20 (14.2)	.08
Change in ESS	−7 (−11, −4)	−6 (−9, −3)	.29
ESS > 10, n (%)	0 (0)	8 (6)	.13
Change in BDI	−4.8 ± 4.5	−7.7 ± 5.7	.004
Change in SF-36	8 (6–10)	9 (6.5–12)	.083
Death, n (%)	4 (4.7)	7 (4.9)	.90

Data are presented as mean ± standard deviation, median (25th–75th percentile), or n (%) where indicated. * = oxygen supplementation added to the PAP circuit during sleep. AHI = apnea-hypopnea index, BDI = Beck Depression Inventory, BMI = body mass index, ESS = Epworth Sleepiness Scale, FEV_1 = forced expiratory volume in one second, FVC = forced vital capacity, PAP = positive airway pressure, $PtcCO_2$ = transcutaneous CO_2, SF-36 = Short Form 36 Health Survey, TST90 = total sleep time spent with SpO_2 < 90%.

CPAP found progressive improvements in mean nocturnal SpO_2 and daytime CO_2 over a 3-month period.[34] Piper and coworkers[29] performed a randomized trial that compared CPAP to bilevel PAP in spontaneous mode (no backup respiratory rate) for treatment of selected patients with OHS and OSA. A similar degree of improvement in daytime $PaCO_2$, oxygen saturation, bicarbonate, and daytime sleepiness was noted at 3 months in both treatment groups. In a more recent clinical trial, Howard and colleagues[30] compared CPAP to bilevel PAP in ST mode (with a backup respiratory rate) in 60 patients with stable OHS over a 3-month period and found no difference between the two PAP modalities in terms of quality of life, adherence to therapy, or improvement in daytime hypercapnia. In the largest randomized clinical trial (the Pickwick trial), Masa and colleagues randomized 221 patients with stable OHS to bilevel PAP therapy in volume-targeted mode that included a backup respiratory rate, CPAP, or lifestyle modification over a 2-month period. The authors found that both volume-targeted bilevel PAP therapy and CPAP achieved greater improvements in awake $PaCO_2$ and bicarbonate when compared to lifestyle changes. However, there was no significant difference between the two PAP modalities.[31] It is worth noting that bicarbonate and $PaCO_2$ improvement with CPAP was dependent on treatment adherence.[31] Indeed, similar to prior studies,[36,37] we also

found that adherence to PAP treatment was essential to obtain clinical benefits such as improvement in ABG and quality of life, irrespective of the modality of PAP therapy (ie, CPAP or bilevel PAP). Although PAP adherence was higher in our clinical cohort than some of the prior studies,[30,31] it was similar to that in other studies.[33,34] A previous retrospective study by Mokhlesi and associates[12] found that the amount of improvement in daytime $PaCO_2$ level is critically dependent on adherence to PAP therapy, regardless of the PAP modality (ie, CPAP or bilevel PAP). There was considerable variability but the $PaCO_2$ level dropped on average by about 1.84 mmHg for every hour of nightly adherence and reached a plateau with longer than 7 hours of nightly use. In our study, the benefit of PAP adherence on $PaCO_2$ level (an average drop of 1.5 mmHg per average hour of nightly PAP use) and SF-36 seems also to continue after 6 hours of nightly PAP use. Furthermore, Carter and colleagues[35] in a substudy of a randomized controlled trial in OHS patients found that PAP adherence over a 6-week period had a marked effect on improving surges in nocturnal blood pressure control as well. Therefore, the importance of close clinical follow-up after PAP therapy is initiated should be stressed to ensure adequate adherence and confirm response to therapy, particularly because poor adherence to PAP therapy has also been associated with increased mortality.[12,38]

OHS has been associated with a fourfold increased mortality risk if untreated.[7] Moreover, previous studies showed that patients with OHS may experience higher morbidity and mortality than patients who have OSA without OHS.[38–40] Our study showed an even lower mortality rate among patients with OHS (5%) compared to previous studies,[10,41–43] probably because of less severe cases of OHS and higher overall PAP adherence. PAP adherence < 6 h/night independently predicted mortality, irrespective of PAP mode, which seems intuitive because good adherence to PAP can improve prognosis, as reported by others.[8,41] Surprisingly, mortality was not associated with ABG values, parameters related to obstructive respiratory events (ie, AHI), or gas exchange alterations during sleep, again emphasizing the effectiveness of nocturnal PAP use. Although supplemental oxygen therapy was the only independent predictor of mortality in the study by Priou et al.,[41] we did not find an association between supplemental oxygen prescription and increased mortality. This difference may be related to difference in patient population (40.8% with heart disease in the study by Priou et al. versus 25% in our study) and different sample sizes. It is important to note that supplemental oxygen was actively discontinued in a large percentage of our patients. However, the use of supplemental oxygen therapy to prevent nocturnal oxygen desaturation is still an open question, with a more recent study suggesting that low-flow supplemental oxygen is safe at 2 months in patients with OHS as long as they are closely monitored.[44] Further research is needed to examine whether long-term supplemental oxygen therapy increases the risk of cardiovascular morbidity and mortality in patients with OHS.

In line with prior studies, we also found improvements in subjective sleepiness (ESS score),[8,13,29–31,34,36,41,45] depressive symptoms (BDI score),[46] and quality of life (SF-36 score)[29–31,36,37,46] at the end of the follow-up period. We have previously reported that in patients with OSA, > 6 h/night of PAP use is associated with a greater improvement in ESS, BDI, and SF-36 scores.[25] In the current study, we only noted a significant association between PAP adherence and improvement in SF-36. The improvement in ESS and BDI scores were mostly related to the baseline values and not to PAP adherence. This may be in part related to the fact that we had high levels of adherence in most patients. This finding is also not surprising if we consider that sleepiness and depressive symptoms may be affected by many factors including socioeconomic status, occupation, and coexisting diseases.

Despite correction of these nocturnal obstructive events with PAP therapy, daytime $PaCO_2$ did not return to normal in 18% of the patients. These patients had higher baseline daytime $PaCO_2$, were categorized mostly as moderate to severe OHS at baseline (as assessed according to $PaCO_2$ values), and had lower hours of PAP use. Nevertheless, these patients had optimal nighttime SpO_2 correction and were clinically asymptomatic; consequently, PAP treatment was maintained. Furthermore, a significant proportion of patients will finally require supplemental oxygen in addition to PAP therapy, at least initially, in accordance with previous studies.[8,12,30] Our study suggests that patients with moderate to severe OHS may be more likely to require nocturnal oxygen supplementation in addition to PAP therapy. There was no association between comorbidities such as heart failure and need for nocturnal oxygen supplementation, probably because of lower prevalence of heart disease in our cohort. In those requiring long-term oxygen supplementation, close clinical monitoring is necessary, as PAP adherence seems to be a better predictor of mortality than baseline PaO_2 and $PaCO_2$. Moreover, as demonstrated in our cohort, a large proportion of patients who are adherent to PAP therapy can successfully discontinue supplemental oxygen therapy. Therefore, early follow-up is imperative and should include repeat measurement of ABG and objective assessment of PAP adherence in order to assess readiness to discontinue supplemental oxygen therapy.

Despite the significant morbidity and mortality associated with this syndrome, diagnosis and initiation of effective treatment usually occurs late in the course of the disease. Unfortunately, OHS is often misdiagnosed as asthma or chronic obstructive pulmonary disease, even in hospitalized patients, delaying or preventing initiation of effective PAP therapy.[7,47] Therefore, maintaining a high index of suspicion can lead to early recognition and treatment reducing the high burden of morbidity and mortality and related health care costs associated with undiagnosed and untreated OHS. Finally, separate from PAP treatment, successful management of OHS should consist of a multidisciplinary approach in order to effectively address the various facets of this complex condition including obesity, physical inactivity, and management of cardiometabolic comorbidities.[48]

Certain limitations of the current study must be addressed. A major limitation of this study is that the results are applicable mainly to the subset of stable patients with OHS with mild to moderate hypercapnia. This limits the applicability of the findings to patients with a higher degree of hypercapnia or those with clinical instability. Our findings may not be applicable to the 10% of patients with OHS who do not have concomitant

OSA given that these patients represented a small number of the cohort. Another limitation is that the study was limited by a wide range of follow-up period. Furthermore, although we excluded patients with lung disease, a confounding factor in the selection process of our patients is that age, BMI, and smoking may influence gas exchange.[49] However, our results were similar even when we only included never smokers. Last, the observational nature of our study precludes causal inferences. However, the findings from our longitudinal analyses strengthen our hypothesis that a higher level of adherence to PAP therapy is associated with better outcomes in patients with OHS.

In conclusion, higher level of adherence to PAP therapy is associated with better outcomes in patients with OHS. Clinicians should encourage adherence to PAP therapy in order to provide a significant improvement in clinical status and gas exchange in these patients.

ABBREVIATIONS

AASM, American Academy of Sleep Medicine
ABG, arterial blood gas
AHI, apnea-hypopnea index
BDI, Beck Depression Inventory
BMI, body mass index
ESS, Epworth Sleepiness Scale
OHS, obesity hypoventilation syndrome
OSA, obstructive sleep apnea
PAP, positive airway pressure
PSG, polysomnography
$PtcCO_2$, transcutaneous CO_2
SF-36, Short Form 36 Health Survey

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