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CASE REPORTS

CPAP titration failure is not equivalent to long-term CPAP treatment failure in patients with obesity hypoventilation syndrome: a case series

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Study Objectives: Medium and long-term trials comparing continuous positive airway pressure (CPAP) with noninvasive ventilation in patients with obesity hypoventilation syndrome have shown no differences in outcomes. However, it remains unclear whether CPAP therapy should be prescribed if significant hypoxemia persists during CPAP titration, despite optimization of upper airway obstructive events or if maximum CPAP pressure is reached. We aimed to examine the effects of 6 weeks of home CPAP therapy on gas exchange in patients with obesity hypoventilation syndrome who failed CPAP titration due to persistent hypoxemia.

Methods: This case series is a substudy of a randomized-controlled trial evaluating efficacy of 3 different PAP modalities in obesity hypoventilation syndrome. Patients randomized to CPAP who failed titration and were prescribed CPAP are included. CPAP failure was defined as spending more than 20% of total sleep time with oxygen saturation below 90% despite adequate resolution of apneas and hypopneas. Follow-up data included in-laboratory polysomnogram on prescribed CPAP after 6 weeks of home CPAP therapy.

Results: Three of seven participants (43%) randomized to CPAP failed CPAP titration. All were morbidly obese, had severe OSA (apnea-hypopnea index > 90 events/h) and severe sleep hypoxemia (percentage of total sleep time with oxygen saturation < 90% [T90] = 60–89%). Hypoxemia (T90: 43–67%, T80: 0–31%, and T70: 0–11%) and hypercapnia (transcutaneous pressure of CO_2 levels > 50 mm Hg) persisted during CPAP titration polysomnogram. The final polysomnogram after 6 weeks of adherent home CPAP therapy showed effective control of obstructive sleep apnea. Hypoventilation and hypoxemia severity decreased significantly in all 3 participants.

Conclusions: Our data suggest that CPAP titration failure does not equal CPAP treatment failure.

Clinical Trial Registration: Registry: ClinicalTrials.gov; Name: AVAPS-AE Efficacy Study; URL: https://clinicaltrials.gov/ct2/show/NCT01368614; Identifier: NCT01368614.

Keywords: obesity hypoventilation syndrome, obstructive sleep apnea, continuous positive airway pressure failure, hypoxemia

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Clinical trials in patients with obesity hypoventilation syndrome have demonstrated no difference in patient-centric outcomes between continuous positive airway pressure (CPAP) and noninvasive ventilation. However, studies have not addressed or provided guidance to clinicians on what to do when hypoxemia persists during CPAP titration (ie, CPAP titration failure). Given that persistent hypoxemia during CPAP titration is common, there is a need for additional studies to examine CPAP treatment effectiveness in the setting of CPAP titration failure.

Study Impact: In patients with obesity hypoventilation syndrome and coexistent severe obstructive sleep apnea, 6 weeks of CPAP therapy led to marked improvements in gas exchange during sleep despite persistent hypoxemia during CPAP titration. Our findings may result in changes in positive airway pressure titration protocols and clinical practice and lower health care utilization costs.

INTRODUCTION

Obesity hypoventilation syndrome (OHS) is defined by obesity (body mass index ≥ 30 kg/m^2), awake daytime hypercapnia (awake, resting partial pressure of carbon dioxide in the arterial blood [$Paco_2$] ≥ 45 mm Hg at sea level), and sleep-disordered breathing after excluding other causes for hypoventilation.[1] With increasing prevalence of severe obesity among the adult US population,[2] the prevalence of OHS is bound to increase. Given that several clinical trials have reported similar medium-term and long-term outcomes between continuous positive airway pressure (CPAP) and noninvasive ventilation (NIV),[3–6] current clinical practice guidelines recommend treating patients with OHS and coexistent severe obstructive sleep apnea (OSA) with CPAP rather than NIV.[7] This recommendation applies to a large proportion of patients with OHS since comorbid severe OSA is present in approximately 70% of patients with OHS.[8]

Currently there is no consensus on the definition of CPAP titration failure in patients with OHS.[9] A prior study arbitrarily defined CPAP titration failure if the oxygen saturation remained below 90% for 20% of the total sleep time (TST) despite resolution of apneas and hypopneas. Using this definition, CPAP

titration failure occurred in 43% of patients with OHS.[10] Another study defined CPAP titration failure if oxygen saturation remained below 80% continuously for 10 minutes or longer in the absence of frank apneas. Based on this more stringent definition, CPAP titration failure occurred in 20% of patients with OHS.[5] These studies suggest that CPAP titration failure is not uncommon. Therefore, sleep clinicians will occasionally have to decide how to proceed when hypoxemia persists during CPAP titration, even after obstructive apneas and hypopneas are resolved or the maximum CPAP pressure of 20 cm H_2O has been reached. Should these patients be considered CPAP titration failure and titrated with other positive airway pressure (PAP) modalities such as NIV or should supplemental oxygen be added to the CPAP circuit? From a physiological standpoint, it stands to reason that in such circumstances, NIV is advantageous because it provides ventilatory support that CPAP is not designed to deliver. In fact, the American Academy of Sleep Medicine (AASM) recommends adding oxygen or switching to NIV in such circumstances.[11,12] However, the largest long-term clinical trial to date did not show any difference in patient outcomes between NIV and CPAP.[4] Moreover, NIV is significantly costlier than CPAP.[13]

It is not surprising that clinicians consider additional interventions when persistent hypoxemia is observed during CPAP titration. What remains unanswered is whether persistent hypoxemia during CPAP titration improves with time.[9] It is more challenging to address this question outside of a clinical research protocol because, in clinical practice, patients with OHS who have comorbid severe OSA typically undergo a split night polysomnogram (PSG), and if hypoxemia persists on CPAP, the patients are switched to NIV or supplemental oxygen is added to CPAP. However, in a research protocol, patients who are randomized to CPAP will have to receive CPAP, even if hypoxemia persists during titration. In this case series, we describe 3 patients who were randomized to CPAP therapy, failed CPAP titration based on persistent hypoxemia, and returned for an in-laboratory PSG after 6 weeks of home CPAP therapy.

METHODS

This case series is a substudy of a randomized controlled trial evaluating the efficacy of 3 different PAP modalities in patients with OHS. The purpose of the primary study was to evaluate the feasibility and benefit in daytime gas exchange at 6 weeks of using average volume assured pressure support with auto-expiratory positive airway pressure mode vs CPAP vs bilevel positive airway pressure therapy in spontaneous mode in patients with untreated newly-diagnosed OHS.

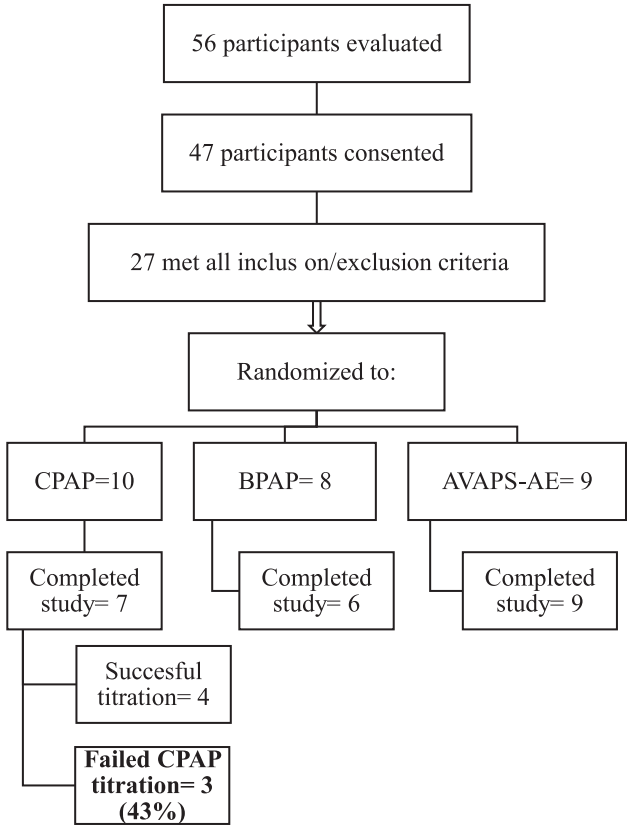
Participants

The study was completed at 2 different centers between November 2011 and February 2014; only patients enrolled at the University of Chicago were included in this study (clinical trial registration NCT01368614). Patients were eligible for enrollment if they were between 18 and 75 years old, with a new diagnosis of OHS (previous 3 months), naive to PAP therapy, daytime pH > 7.35 on arterial blood gases, comorbid OSA (AHI ≥ 5 events/h) and no evidence of obstructive lung disease by spirometric criteria (forced expiratory volume in the first 1 second [FEV_1]/forced vital capacity [FVC] > 70%). Patients were excluded if acutely ill, if hospitalized for respiratory exacerbation in the 6 weeks prior to the screening visit, had alkalosis (pH > 7.45) on arterial blood gases, impaired upper airway function, or anatomic abnormalities interfering with mask fit. For this case series, only patients randomized to CPAP were included (**Figure 1**). Of note, there were a total of 8 participants in the CPAP arm who completed the study. Of these, 7 participants were recruited at the University of Chicago. We did not have access to the raw polysomnography data for the only patient recruited at the other center. The main protocol was approved by the University of Chicago Institutional Board Review, and all participants provided written informed consent.

Polysomnography

Each participant underwent three in-laboratory polysomnograms (PSG): the initial baseline PSG, a full night PAP titration in the sleep laboratory within 7 days of the baseline PSG after being randomly assigned to 1 of the 3 PAP modes, and a full night PAP PSG on home PAP settings without additional titration after 6 weeks of home PAP therapy. These technician-attended, all-night

Figure 1—Flow diagram outlining screening and participants selection.



AVAPS-AE = average volume assured pressure support with auto expiratory positive airway pressure, BPAP = bilevel positive airway pressure therapy, CPAP = continuous positive airway pressure.

laboratory recordings were collected, scored, and interpreted in accordance with the 2007 edition of *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications*.[14] Recordings included 6 channels of electroencephalogram (F4/M1, C4/M1, O2/M1, F3/M2, C3/M2, O1/M2), 2 channels of electrooculogram (ROC/M1, LOC/M2), electromyogram (chin and anterior tibialis), electrocardiogram, 2 channels of airflow (oronasal thermocouples for apneas, nasal pressure transducer for hypopneas on the baseline PSG or PAP flow and mask leak for PAP studies), 2 channels of respiratory effort (thorax and abdomen inductance plethysmography belts), and 1 channel oxygen saturation by finger pulse oximeter. Transcutaneous capnography monitoring was performed during baseline, titration, and at the 6-week PSG. Apneas were defined as a reduction of airflow of at least 90% of the oronasal thermistor for at least 10 seconds with respiratory effort present. Hypopneas were scored once the peak signal excursions decreased by at least 30% of the baseline amplitude of the nasal pressure transducer for at least 10 seconds and were associated with a 4% or greater drop in oxygen saturation, as measured by finger pulse oximetry. The total AHI was defined as the number of apneas and hypopneas per hour of sleep. Severity of OSA was measured by the AHI: mild OSA = AHI 5–14 events/h, moderate = AHI 15–29 events/h, severe = AHI ≥ 30 events/h. The oxygen desaturation index was defined as the number of oxygen desaturations of at least 4% per hour of sleep. Severity of hypoxemia was further quantified using percent of TST with Spo_2 below 90%, 80%, and 70%. Severity of nocturnal hypoventilation was assessed using the percentage of total recording time with transcutaneous pco_2 above 50 and 60 mm Hg.

CPAP titration (Respironics OmniLab Advanced CPAP mode) was performed following AASM recommendations.[11] If Spo_2 remained persistently below 90% despite resolution of apneas, hypopneas, and flow limitation, CPAP pressure was increased by an additional 2–3 cm H_2O to assess impact on oxygenation. CPAP could be titrated up to 20 cm H_2O to control sleep-disordered breathing. Supplemental oxygen was not added and PAP mode was not switched if suboptimal response to CPAP therapy was noted. For the purposes of this analysis, we measured the various indices of hypoxemia and hypercapnia on the ideal or final CPAP pressure settings during the CPAP titration PSG, defined as the pressure that resolved obstructive apneas, hypopneas, and flow limitation, or if the maximum pressure of 20 cm H_2O was reached.

Follow up and PAP adherence monitoring

All 3 patients had objective CPAP adherence monitoring. Patients were contacted weekly to troubleshoot difficulties with CPAP use and encouraged to continue compliance. Patients had 2 visits, 1 at week 2 of CPAP initiation when compliance and mask fit were readdressed, and 1 final visit after 6 weeks of home CPAP therapy. Objective data were downloaded during these visits to determine percent of nights with PAP usage > 4 hours and mean hours of use per night.

Other measurements

For each patient, spirometry was obtained at baseline. Awake Spo_2 on room air, body mass index, and arterial blood gases were obtained at baseline and at 6-week follow up. Arterial blood gases were obtained during wakefulness, with the participants seated and breathing room air after resting for 20 minutes. Spot-check end-tidal pco_2 was obtained at baseline, week 2, and week 6 follow up. Epworth Sleepiness Scale score was recorded at baseline and at the week 6 follow up.[15]

RESULTS

Participants characteristics

Three out of seven patients (43%) randomized to CPAP met the criteria for CPAP titration failure based on persistent hypoxemia for 20% or more of the TST below 90% oxygen saturation despite resolution of most obstructive apneas and hypopneas. **Table 1** summarizes baseline characteristics of these 3 patients. All 3 were morbidly obese and had restrictive physiology on spirometric testing. There was a variable degree of improvement in baseline compensated hypercapnia after 6 weeks of adherent CPAP therapy. $Paco_2$ improved significantly in 2 patients who became eucapnic (reduction of 17.7 and 9.2 mm Hg in patients 2 and 3, respectively) and to a lesser degree in patient 1 (reduction of 2.4 mm Hg), despite no clinically significant changes in body mass index. There was also a progressive decrease in awake end-tidal pco_2 in all patients from baseline to week 2 to week 6 of follow up. Similarly, the improvements in awake hypoxemia was variable. Patient 2, who had the largest improvement in $Paco_2$ also had the largest improvement in Pao_2 (an increase of 12.9 mm Hg). In contrast, patient 3, who had a 9.2 mm Hg reduction in $Paco_2$, had only a 2 mm Hg improvement in partial pressure of oxygen in the arterial blood (Pao_2). Patient 1 had no change in Pao_2, despite a 2.4 mm Hg reduction in $Paco_2$. Oxygen saturation during wakefulness at baseline and week 6 remained ≥ 90% in all 3 patients.

Polysomnographic features

Polysomnographic data are summarized in **Table 2**. At baseline, rapid eye movement (stage R) sleep was decreased in all patients (0–9% of TST). All 3 patients had severe OSA, with AHI between 90 and 118 events/h. Significant hypoxemia was noted: oxygen desaturation index-4% was elevated between 98 and 160 events/h, the percentage of TST time with $Spo_2 < 90\%$ (T90) ranged from 60 to 89%, with 2 of the patients having about half of TST with $Spo_2 < 70\%$ (T70). Significant sleep hypoventilation at baseline was also evident, with 2 patients maintaining transcutaneous pco_2 levels > 50 mm Hg during the entire study and above 60 mm Hg for nearly half the study, while patient 1 maintained levels between 50 and 60 mm Hg during most of the recording (67% of the time).

During the initial CPAP titration study, sleep efficiency improved and stage R sleep increased significantly in all 3 patients. AHI normalized in 2 patients at the final CPAP titrated pressure, including in stage R sleep, and decreased from 90 to 25 events/h in 1 patient at the maximum titrated pressure of 20 cm H_2O. Significant hypoxemia persisted on therapeutic CPAP pressures, with T90 ranging between 43 and 67%, T80 between 0 and 31%, and T70 between 0 and 11% (**Figure 2**).

Table 1—Participant characteristics.

	Patient 1	Patient 2	Patient 3
Age, years	60	33	49
Sex	Female	Male	Female
Race	Black	White Hispanic	Black
BMI, kg/m^2	48.1	40.1	55.6
BMI at 6 weeks, kg/m^2	46.2	41.1	55.9
FVC, % predicted	57	72	56
FEV_1, % predicted	65	90	62
FEV_1/FVC	85	100	84
pH baseline	7.42	7.35	7.41
$Paco_2$ baseline, mm Hg	49.3	62.4	50.5
Pao_2 baseline, mm Hg	63.8	49	60.9
pH at 6 weeks	7.40	7.40	7.35
$Paco_2$ 6 weeks, mm Hg	46.9	44.7	41.3
Pao_2 at 6 weeks, mm Hg	63.9	61.9	63.9
Awake $Petco_2$ baseline, mm Hg	50	55	63
Awake $Petco_2$ 2 weeks post-CPAP, mm Hg	47	42	62
Awake $Petco_2$ 6 weeks post-CPAP, mm Hg	39	41	56
Awake Spo_2 baseline	95	90	92
Awake Spo_2 at 6 weeks	95	95	95
ESS score at baseline	9	18	12
ESS score at 6 weeks	5	0	13

BMI = body mass index, ESS = Epworth Sleepiness Scale, FEV_1 = forced expiratory volume in the first 1 second, FVC = forced vital capacity, $Paco_2$ = partial pressure of arterial CO_2, Pao_2 = partial pressure of arterial O_2, $Petco_2$ = end-tidal pco_2, Spo_2 = oxyhemoglobin saturation.

Transcutaneous pCO_2 levels remained elevated above 50 mmHg in all patients during the titration PSG (**Table 2**).

The final PAP study at week 6 (without titration and on the prescribed CPAP pressure for home use) showed that the OSA remained effectively treated (highest AHI recorded was 11 events/h), the oxygen desaturation index-4% was 10 events/h or fewer, and there was an improvement in gas exchange. Hypoxemia severity by T90, T80, and T70 decreased significantly in all patients (**Figure 2**). Transcutaneous pco_2 > 60 mm Hg improved in all 3 patients.

CPAP adherence data

Two of the patients were prescribed 20 cm H_2O and one 17 cm H_2O. Mean nightly use was > 6 h, and all patients met current recommended minimum adherence of ≥ 70% of the days ≥ 4 h (83–97%). OSA was controlled with residual AHI estimated by the CPAP devices between 2 and 6 events/h.

DISCUSSION

This is the first case series to demonstrate medium-term CPAP treatment effectiveness in patients with OHS and concomitant severe OSA who "failed CPAP" titration on the basis of significant oxygen desaturation on the initial CPAP titration study. In this case series, 3 out of 7 (43%) patients randomized to the CPAP arm had failed CPAP titration based on residual significant hypoxemia (> 20% of TST < 90% Spo_2), which is in keeping with the prevalence of CPAP titration failure previously reported.[10] Our patients, like the patients in the prior study, were morbidly obese and had severe comorbid OSA. In our study, all 3 patients were titrated to CPAP pressures that are higher than what has been described in prior studies, because our protocol allowed for CPAP pressure to be increased by an additional 2–3 cm H_2O after resolution of obstructive apneas, hypopneas, and flow limitation to assess impact on oxygenation. All 3 patients were highly adherent to CPAP therapy. At the final PSG study, after 6 weeks of home CPAP therapy, gas exchange improved in all patients, as evidenced by oxygen saturation (T90, T80, and T70) and transcutaneous pco_2 levels, despite no major changes in body weight. In fact, T90 was close to zero in all 3 patients. Sleep hypoventilation improved in all, although it did not entirely normalize, despite resolution or near resolution of daytime hypercapnia at 6 weeks. One could argue that it may take longer to demonstrate improvements in sleep hypoventilation by transcutaneous pco_2 or hypothesize that some degree of hypoventilation without associated significant hypoxemia persists long term. Many sleep laboratories use oxygen saturation to guide PAP titration as transcutaneous pco_2 is resource intensive and costly and may not be readily available in all sleep laboratories. This makes the routine use of transcutaneous pco_2 to guide PAP titration less generalizable. However, transcutaneous pco_2 monitoring is the optimal method of monitoring ventilation during polysomnography in

Table 2—Polysomnographic and objective CPAP data.

	Patient 1			Patient 2			Patient 3		
	Baseline	Titration	6 weeks	Baseline	Titration	6 weeks	Baseline	Titration	6 weeks
TRT, min	494	514	488	487	465	470	424	534	465
TST, min	291	450*	250	487	457‡	457	336	489‡‡	405
Stage R, min	9	95	58	0	118	91	30.5	220	117
AHI, events/h	118	5*	3	90	25‡	11	110	4‡‡	10
Obstructive apnea index	52	0*	0	32	0‡	8	28	0‡‡	2
ODI	118	3%*	5	98	31‡	3	160	22‡‡	10
Spo_2 nadir	64%	86%*	83%	50%	52%‡	89%	50%	70%‡‡	64%
T90, min (%TST)	258 (89%)	141* (67%)	20 (8%)	292 (60%)	110‡ (43%)	1 (0%)	257 (76%)	213‡‡ (60%)	26 (6%)
T80, min (%TST)	112 (38%)	0* (0%)	0 (0%)	369 (76%)	78‡ (31%)	0 (0%)	261 (78%)	43‡‡ (12%)	3 (0.01%)
T70, min (%TST)	10 (3%)	0* (0%)	0 (0%)	286 (59%)	28‡ (11%)	0 (0%)	160 (48%)	0‡‡ (0%)	0 (0%)
Transcutaneous $PCO_2 \geq 50$, % of time	67%	100%*	0%	100%	100%‡	82%	100%	100%‡‡	41%
Transcutaneous $PCO_2 \geq 60$, % of time	0%	55%*	0%	100%	94%‡	4%	41%	11%‡‡	0%
Mean CPAP adherence, hours/night	—	—	6.4	—	—	6.8	—	—	6.2
% days > 4 h CPAP use	—	—	97%	—	—	86%	—	—	83%
AHI on CPAP, events/h	—	—	2	—	—	6	—	—	4
Home CPAP pressure, cm H_2O	—	—	17	—	—	20	—	—	20

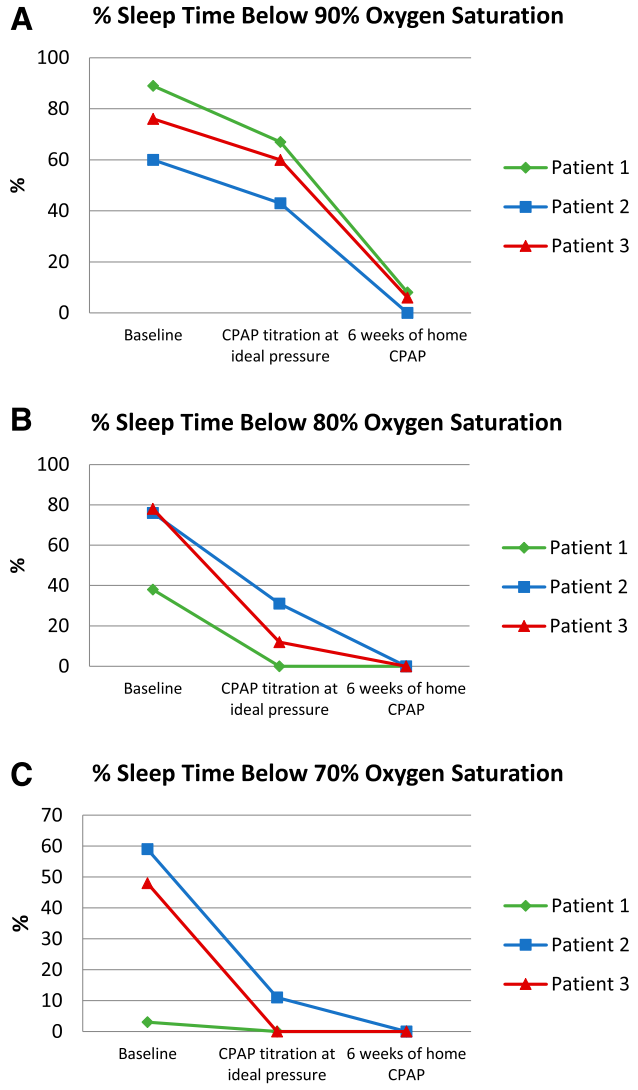
*At final CPAP pressures of 14–17 cm H_2O there were 210 minutes of sleep (including 46 minutes of Stage R sleep). ‡At final CPAP pressure of 20 cmH_2O there were 253 minutes of sleep (including 82 minutes of Stage R sleep). ‡‡ At final CPAP pressures of 19-20 cmH_2O there were 354 minutes of sleep (including 174 minutes of Stage R sleep). AHI = apnea-hypopnea index, CPAP = continuous positive airway pressure, ODI = oxygen desaturation index, Spo_2 = oxyhemoglobin saturation, Stage R = the stage of rapid eye movement sleep, as defined by the AASM scoring manual, $TcCO_2$ = transcutaneous partial pressure of carbon dioxide, TRT = total recording time, TST = total sleep time.

such patients, and the routine use of oximetry without pco_2 monitoring in patients with OHS should be discouraged.

We believe that in many sleep laboratories, patients with severe obesity with OHS may reach maximal CPAP pressure, and switching CPAP to NIV is viewed as the only remaining option to improve persistent hypoxemia and/or hypercapnia. However, this step-up PAP titration approach has not been demonstrated to provide clinical benefit or be cost effective in the long term. Traditionally, sleep technologists and sleep medicine experts seek to achieve normalization of hypoxemia (and hypercapnia if transcutaneous pco_2 is available) during PAP titration PSG. We acknowledge the challenge of prescribing long-term home CPAP therapy when important gas exchange perturbation during sleep persists during CPAP titration. Moreover, there are challenges in implementing our approach in clinical practice, because most insurers will reimburse health care systems for a split night PSG, not multiple PSGs. However, our small case series clearly demonstrates that, in patients with OHS and concomitant severe OSA, sleep hypoxemia and hypercapnia that persisted during CPAP titration improved dramatically after 6 weeks of home CPAP therapy. Our finding is in line with the medium-term clinical trials[5,6,8] and a long-term clinical trial[4] that have reported no difference in a variety of outcomes when patients are randomized to CPAP or NIV. To minimize health care resource utilization, one approach could be to prescribe CPAP therapy, despite persistent hypoxemia during CPAP titration and have the patient undergo home nocturnal oximetry while wearing CPAP after a few weeks of demonstrated adherent CPAP therapy. If nocturnal hypoxemia is resolved, the residual AHI estimated by the CPAP device remains low and daytime gas exchange improves, the patient should continue long-term CPAP therapy. Alternatively, oxygen can be added to the CPAP circuit in those who do not normalize their oxyhemoglobin saturation on CPAP during the titration study. In this scenario, clinicians should strongly consider discontinuing supplemental oxygen after a few weeks of home CPAP therapy if nocturnal hypoxemia is resolved on nocturnal oximetry study on CPAP, but without the oxygen supplementation.

Although CPAP does not provide ventilatory support, it has been postulated that CPAP improves gas exchange by decreasing upper airway resistance, improving lung mechanics, reducing the work of breathing, and recruiting dependent atelectatic lung areas.[16,17] If hypoxemia persists during CPAP titration due to hypoventilation, NIV is viewed as the logical "step-up" needed to provide additional ventilatory support. However, it is important to consider that it takes a few weeks of CPAP therapy during sleep for the blunted central respiratory drive to improve. Indeed, improvements in hypercapnic and hypoxemic ventilatory responses are noted as early as 2 weeks after initiating CPAP therapy and reach normal levels after 6 weeks of home CPAP therapy with demonstrated objective adherence in patients with OHS.[18–20] In this context, our results as well as the findings from the medium-term and long-term clinical trials showing no difference between CPAP and NIV are not surprising. It is important to recognize that in several clinical trials, patients who were randomized to CPAP and had persistent hypoxemia during

Figure 2—Oxygen saturation at baseline polysomnography, CPAP titration, and CPAP study at the home prescribed pressure after 6 weeks of CPAP use.



Percentage of sleep time with oxygen saturation under 90% (**A**), under 80% (**B**) and under 70% (**C**). Data are reported from total sleep time (TST) on baseline polysomnography, TST at the ideal titrated continuous positive airway pressure (CPAP) pressure on the CPAP titration study, and TST for the polysomnography performed on CPAP, at the home prescribed CPAP pressure, after 6 weeks of home CPAP use.

CPAP titration (ie, CPAP titration failure) remained on the allocated home CPAP therapy arm.[4,6,8] Importantly, both CPAP and NIV were equally effective in reducing the need for daytime supplemental oxygen therapy in patients with OHS,[4] with CPAP being significantly less costly.[13]

Based on the abbreviated alveolar air equation while breathing ambient room air, for every 1 mm Hg reduction in $Paco_2$, the Pao_2 should increase by 1.25 mm Hg.[21] In our case series, the improvement in awake $Paco_2$ did not lead to the expected degree of improvement in awake Pao_2. One possibility is that the degree of physiologic ventilation/perfusion mismatch was different between the baseline blood gas and the one obtained after 6 weeks of home CPAP therapy. In fact, the residual hypoxemia in our 3 patients, despite significant improvement in hypoventilation (particularly in patient 2 and patient 3), is most likely related to the known ventilation/perfusion mismatch related to morbid obesity.[22–25] This highlights the multifactorial component governing gas exchange in these patients.

We acknowledge several limitations to this study. First and foremost, the sample size is small. However, these data are difficult to obtain from clinical repositories because patients do not routinely undergo multiple PSGs outside of a research protocol. For the purpose of this study, we only included the 3 patients who failed CPAP titration. This is in keeping with our study aim: to ascertain whether persistent hypoxemia during CPAP titration improves with time in patients with OHS that optimally adhere to CPAP treatment. Second, we do not have long-term clinical data on these 3 patients. Nonetheless, data from medium-term and long-term clinical trials reporting similar clinical effectiveness between CPAP and NIV agree with our findings.

CONCLUSIONS

We provide evidence that in patents with OHS and severe concomitant OSA, 6 weeks of CPAP therapy leads to marked improvements in gas exchange despite evidence of CPAP failure during the titration study. Our data suggest that CPAP titration failure does not equal CPAP treatment failure. These findings have significant clinical implications that may result in changes in PAP titration protocols and clinical practice and ultimately promote more CPAP prescription in OHS, leading to lower health care utilization costs compared to NIV therapy. Larger, prospective, randomized clinical trials are needed to corroborate these findings.

ABBREVIATIONS

AASM, American Academy of Sleep Medicine
AHI, apnea-hypopnea index
CPAP, continuous positive airway pressure
NIV, noninvasive ventilation
OHS, obesity hypoventilation syndrome
OSA, obstructive sleep apnea
$Paco_2$, partial pressure of arterial carbon dioxide
Pao_2, partial pressure of arterial oxygen
PAP, positive airway pressure
PSG, polysomnography
RCT, randomized controlled trial
SpO_2, oxyhemoglobin saturation
Stage R sleep, the stage of rapid eye movement sleep, as defined by the AASM scoring manual

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