NEW RESEARCH

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SCIENTIFIC INVESTIGATIONS

Adaptive Servoventilation for Treatment of Opioid-Associated Central Sleep Apnea

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Rationale: Opioids have become part of contemporary treatment in the management of chronic pain. Although severe daytime ventilatory depression is uncommon, chronic use of opioids could be associated with severe central and obstructive sleep apnea.

Objectives: To determine the acute efficacy, and prolonged use of adaptive servoventilation (ASV) to treat central sleep apnea in patients on chronic opioids.

Methods: Twenty patients on opioid therapy referred for evaluation of obstructive sleep apnea (OSA) were found to have central sleep apnea (CSA). The first 16 patients underwent continuous positive airway pressure (CPAP) titration, which showed persistent CSA. With the notion that CSA will be eliminated with continued use of CPAP, 4 weeks later, 9 of the 16 patients underwent a second CPAP titration which proved equally ineffective. Therefore, therapy with CPAP was abandoned. All patients underwent ASV titration.

Main Results: Diagnostic polysomnography showed an average apnea-hypopnea index (AHI) of 61/h and a central-apnea index (CAI) of 32/h. On CPAP 1, AHI was 34/h and CAI was 20/h. Respective indices on CPAP 2 were AHI 33/h and CAI 19/h. During titration with ASV, CAI was 0/h and the average HI was 11/h on final pressures. With a reduction in AHI, oxyhemoglobin saturation nadir increased from 83% to 90%, and arousal index decreased from 29/h of sleep to 12/h on final ASV pressures. Seventeen patients were followed for a minimum of 9 months and up to 6 years. The mean long-term adherence was 5.1 ± 2.5 hours.

Conclusions: Chronic use of opioids could be associated with severe CSA which remains resistant to CPAP therapy. ASV device is effective in the treatment of CSA and over the long run, most patients remain compliant with the device. Randomized long-term studies are necessary to determine if treatment of sleep apnea with ASV improves quality of life and the known mortality associated with opioids.

Keywords: morphine, oxycontin, ASV, CPAP, CSA

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Multiple studies have consistently demonstrated an association of opioids with sleep apnea.[1-6] Meanwhile, in the last decade, there has been a major change in the management of chronic pain with a marked increase in the therapeutic use of opioids.[7-9] Therefore, with widespread use of opioids for pain management, a large number of patients could suffer from sleep apnea. Because both obstructive and central sleep apnea may contribute to the mortality of patients with these breathing disorders,[10-12] sleep apnea may also be a risk factor for mortality of patients on opioids.[13,14] This speculation is supported by the excess mortality of young individuals on opioids who have been found dead in bed, with the cause in several of them remaining unknown.[15] It is, therefore, conceivable that the therapy of sleep apnea in patients on opioids could prevent sleep-related mortality.

Positive airway pressure therapy via adaptive servoventilation (ASV) and continuous positive airway pressure (CPAP) devices have been used to treat sleep apnea associated with opioids.[16,17] The present study represents our experience in patients on opioids with central sleep apnea that failed CPAP therapy and were switched to ASV. We report acute and prolonged effects of these devices. Some of the patients underwent two full-night CPAP titration studies few weeks apart and because considerable amount of disordered breathing including central apneas persisted, CPAP therapy was abandoned and therapy with an ASV was recommended. The sequence of events as occurred during management of the patients is described in the Methods. The preliminary results have been published in an abstract form.[18]

BRIEF SUMMARY

Current Knowledge/Study Rationale: The main aim of this study was to determine the efficacy of positive airway pressure devices for treatment of sleep apnea associated with the use of opioids.

Study Impact: The results of the study show that CPAP is ineffective in treatment of CSA due to opioids, whereas new adaptive servoventilation devices are quite helpful with acceptable long-term adherence and efficacy.

METHODS

Design

This is a report of 20 consecutive patients using chronic opioids who were referred for evaluation for obstructive sleep apnea (2006-2010). All of the patients were seen in consultation. All patients underwent full night attended polysomnography. Sixteen patients had CSA (CAI ≥ 5/h of sleep) and the remaining 4 patients were diagnosed with OSA. The management plan was for all patients to undergo CPAP titration;

however due to failure of CPAP to eliminate central apneas in sequential patients, treatment plan was modified. The 4 patients who had OSA on baseline PSG developed complex sleep apnea (CA ≥ 5/h) upon commencement of CPAP therapy. Of the 16 patients with CAI ≥ 5/h on baseline PSG, 12 underwent CPAP titration which showed persistent CSA. In a follow-up visit, the author explained that the central apneas were present during therapy with CPAP, but it is conceivable that with continued use of CPAP, disordered breathing events might improve.[19] Therefore, 9 of the 12 patients underwent a second CPAP titration 4-8 weeks later. Because, the second CPAP titration proved ineffective in these 9 patients, we abandoned further therapy with CPAP. At this time, there were 4 remaining patients with CAI ≥ 5/h on initial polysomnographic studies for whom CPAP titration was not recommended.

The operation of ASV devices was explained and all patients underwent ASV titration. Five of the 20 patients who were part of this management protocol have been previously reported.[16] The protocol of this retrospective study was approved by the Institutional Review Board of The Christ Hospital in Cincinnati.

Procedures

Polysomnography was performed using standard techniques as detailed previously.[15-17] For staging sleep, we recorded the electroencephalogram (2 channels), the chin electromyogram (one channel) and the electro-oculogram (2 channels). Airflow was qualitatively monitored using both an oral/nasal pressure transducer (PTAF 2, Mukilteo, WA) and a thermistor (Model 1459 Sleepmate Technologies, Midlothian, VA). While on PAP devices airflow was monitored by the pneumotach of the device. Thoraco-abdominal excursions were measured qualitatively by piezo crystal technology (Model 1314 Sleepmate Technologies, Midlothian, VA) or Z RIP adult Durabelt (Pro Tech, Murrysville, PA) placed over the rib cage and abdomen. Arterial blood oxyhemoglobin saturation was recorded using a finger pulse oximeter (Healthdyne Oximeter Model 930, Respironics Inc. Murrysville, PA). These variables were recorded on a multichannel computerized polysomnographic system (Alice sleepware systems, Respironics Inc. Murrysville, PA). An apnea was defined as cessation of inspiratory airflow for ≥ 10 sec. An obstructive apnea was defined as the absence of airflow in the presence of rib cage and abdominal excursions. A central apnea was defined as the absence of airflow with absence of rib cage and abdominal excursions (flat signals from these probes). Hypopnea was defined as a reduction of airflow (30%) and/or thoracoabdominal excursions lasting ≥ 10 sec and associated with ≥ 4% drop in arterial oxyhemoglobin saturation and/or an arousal, as defined previously.[20]

The number of apneas and hypopneas per hour of sleep is referred to as the apnea-hypopnea index. The number of arousals per hour of sleep is referred to as the arousal index. All polysomnograms were reviewed by one of the authors (SJ).

PAP Titration Studies:

CPAP (Respironics Inc., Murrysville, PA) titration was performed using a uniform approach: Titration began at pressure of 5 cm H_2O and every few minutes the pressure was increased to eliminate obstructive apneas, hypopneas, and eventually snoring. Patients were discharged at the final pressure. In the 9 patients who underwent a retitration with CPAP, a similar protocol was used (titration began at 5 cm H_2O). However, patients were fitted with a full face mask (ResMed Mirage Quattro [n = 15], Respironics Comfortfull [n = 3], and Fisher and Paykel 432 [n = 1]). All patients that underwent a second CPAP titration wore the same mask during titration with ASV. Titration with an ASV device (VPAP Adapt SV and VPAP Adapt SV Enhanced, ResMed Corp, San Diego, CA, n = 19, or BiPAP autoSV Advanced, Philips Respironics, Murrysville, PA, n = 1) was performed in 20 patients. With VPAP Adapt SV, the expiratory pressure was gradually increased to eliminate obstructive disordered breathing events. To begin with, the minimum inspiratory pressure support was set at 3 cm H_2O and the maximum pressure support at 8 cm H_2O. However, the pressure support was also increased gradually to eliminate hypopneas. The backup rate was automatic; in this manner the device algorithm follows the patient's breathing rate, but the device could increase the breath rate to 15 per minute if needed.

With BiPAP autoSV Advanced, the device algorithm was used. With this device the expiratory pressure is automatic, which behaves similarly to an auto PAP. The inspiratory support is variable.

Statistical Analysis

We used analysis of variance with repeated measures and Bonferroni correction factor for the 9 patients who underwent 4 nights of polysomnography including the baseline, 2 CPAP, and ASV studies. $p < 0.05$ was considered significant. We used two-tailed paired t-test for the 20 patients who underwent baseline and ASV studies. Means ± SD are reported. Calculations were performed using NCSS statistical software.

RESULTS

The patients were middle-aged subjects who presented with various symptoms of obstructive sleep apnea (**Table 1**). Patients were receiving opioids and morphine equivalents at doses ranging from 15 to 915 mg; some of the patients were taking more than one opioid medication (**Table 2**). Twelve were receiving medications for hypertension. Fifteen patients had history of depression and were on a serotonin reuptake inhibitor, and 13 were on a benzodiazepine receptor agonist (clonazepam, alprazolam, zolpidem, and temazepam). Two patients had previous history of congestive heart failure and one patient had history of stroke without any residual neurological findings.

Arterial blood gases and pH were available in 7 patients while breathing room air in a sitting position for 15 minutes. $PaCO_2$ varied from 42 to 48 mm Hg and in one patient $PaCO_2$ was 53 mm Hg. The mean PaO_2 was 80 mm Hg (range = 59-99 mm Hg). pH values ranged from 7.36 to 7.42.

Diagnostic polysomnography showed that all patients (except 3, AHI = 15/h, AHI = 15/h, and AHI = 21/h) had severe sleep apnea (range 34/h-124/h) with an average AHI of 61/h (n = 20, **Table 3**). The central apnea index was 32/h, which primarily occurred in NREM sleep (**Table 3**). Sleep apnea was associated with considerable number of arousals and significant desaturation.

Table 1—Historical and physical findings in 20 patients on opioids

Variables	n
Gender	
Male	13
Female	7
Habitual snoring	18
Witnessed apnea	14
Nocturia	14
Unrefreshing sleep	17
Falling asleep while	
Watching television	19
Reading	15
Driving	16
Hypertension	12
Depression	15
Variables	**Mean ± SD (range)**
Age, years	53 ± 10 (22–65)
Height, cm	174 ± 10 (150–191)
Weight, kg	99 ± 19 (72–152)
Body mass index, kg/m²	33 ± 7 (24–50)
Neck circumference	41 ± 2 (38–46)
Epworth Sleepiness Scale	12 ± 5 (4–20)

Figure 1 shows a recording of 5-min period of one patient in NREM sleep (N2). Characteristically breathing is ataxic with short episodes of central apneas of variable duration, obstructive apneas and hypopneas. Central apneas persisted on CPAP). With ASV, all central apneas were eliminated **(Figures 2**, **3)**, and the apnea-hypopnea index decreased significantly (**Table 3**). In association with reduction in sleep apneas and hypopneas, oxyhemoglobin desaturation, and arousal index due to respiratory disturbances decreased significantly (**Table 3**). **Figure 3** shows the individual values of CAI at baseline, CPAP 1, CPAP 2, and ASV studies.

Table 4 shows polysomnographic findings during the first and second CPAP titration studies. The latter titration study was performed after 8 weeks of therapy with CPAP. While at home CPAP levels were maintained as determined during titration study. The therapeutic compliance hours were 4.8 ± 2.2 h at 4 and 4.2 ± 2.5 (n = 9) h at 8 weeks. As noted AHI remained elevated and central apneas persisted in spite of "short-term" use of CPAP. The demographics, AHI, and CAI of those patients undergoing second CPAP titration were not significantly different from those who did not undergo a second CPAP titration.

One of 20 patients refused using ASV and two patients were lost to follow-up in less than a month. In the remaining 17 patients, follow up ranged from 9 months to 6 years (25 ± 5.2 months). The mean ASV adherence for these patients was 5.1 ± 2.5 h. One patient was able to discontinue use of opioids. The mean download home AHI was 3.3 ± 3.4 (range was 0 to 8.7) in 6 patients whose device had the related algorithm. The mean ESS was 12.4 ± 4.6 at baseline, 10.7 ± 5.8 on CPAP, and 10.4 ± 4.6 on ASV at final follow-up.

Table 2—Opioids and morphine equivalent dosage in 20 patients.

Opioid	n
Morphine	6
Oxycodone	13
Fentanyl transdermal	2
Methadone	3
Tramadol	1
Hydromorphone	3

Morphine equivalent: range = 15 mg–915 mg, median = 118 mg. Some patients were prescribed more than one opioid.

Table 3—Polysomnographic findings at baseline and ASV (n = 20)

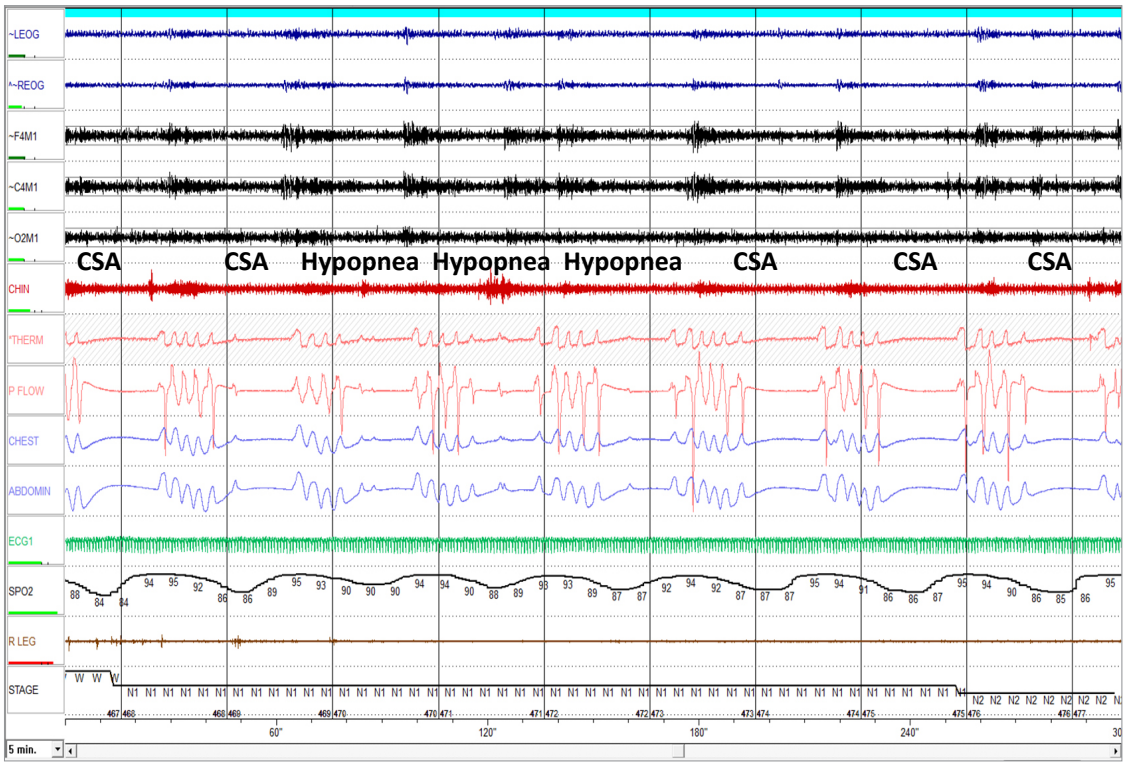
Variables	Baseline PSG	ASV	p value
Total recording time, h	6.8 ± 1	7 ± 1	0.9
Total sleep time, h	5.4 ± 1	5.4 ± 1	0.9
Sleep efficiency, %	80 ± 16	78 ± 11	1.0
N1, % TST	37 ± 21	12 ± 11	0.0001
N2, % TST	55 ± 20	77 ± 12	0.0002
N3, % TST	0 ± 0	1 ± 2	0.1
REM, % TST	8 ± 8	10 ± 7	0.3
AHI, n/h	61 ± 30	23 ± 18	0.0001
AHI, n/h	61 ± 30	11 ± 12 FP	0.0001
NREM AHI, n/h	66 ± 30	20 ± 16	0.0001
REM AHI, n/h	24 ± 20	9 ± 12	0.02
CAI, n/h	32 ± 31	0 ± 0	0.0004
Non-REM CAI, n/h	35 ± 33	0 ± 0	0.0002
REM CAI, n/h	5 ± 9	0 ± 0	0.03
OAI, n/h	5 ± 5	0 ± 1	0.001
ArI, n/h	29 ± 16	20 ± 15	0.03
ArI , n/h	29 ± 16	12 ± 12 FP	0.002
Baseline SpO_2	94 ± 3	95 ± 2	0.4
Minimum SpO_2	83 ± 8	90 ± 4 FP	0.001

Expiratory pressure, cm H_2O = 9 ± 3 (range 5–15). Minimum inspiratory support, cm/H_2O = 5 ± 1 (range 3–6). Maximum inspiratory support, cm/H_2O = 10 ± 1 (range 8–13). Values reported are mean ± SD. ASV, adaptive servoventilation; Baseline SpO_2, saturation in supine position during relaxed wakefulness; AHI, apnea hypopnea index; REM, rapid eye movement; OAI, obstructive apnea index; CAI, central apnea index; ArI-DB, arousal index associated with disordered breathing; FP, final ASV pressures.

DISCUSSION

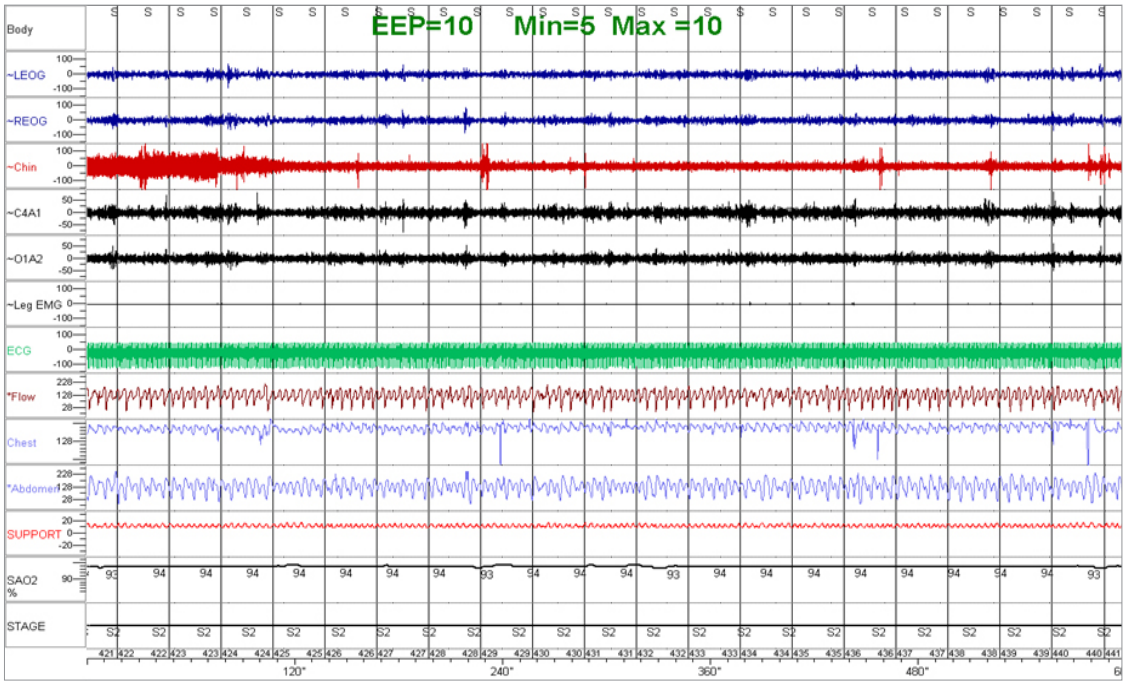
We report that CPAP therapy is ineffective in improving opioid-associated central sleep apnea, whereas overnight ASV titration is effective. The patients suffered from severe sleep apnea-hypopnea, with an average index of 61 per hour and a central apnea index of 32 per hour. In regard to accurate classification of apneas, we emphasize that we require flat lines of at least 10 seconds on thoracoabdominal excursions and both airflow signals, the pressure and the thermocouple probes, as the criteria for central apnea; these strict criteria should diminish cross contamination with any other respiratory event.

Figure 1—A 5-min epoch of a polysomnogram showing central (CSA) apneas, and hypopneas in stage N2.



Note fluctuations in SaO_2 which parallel apneas and hypopneas. The respiratory events are marked. Please note that with CSA airflow and thoraco-abdominal excursions are flat. With hypopneas there is air flow at least on one of the air flow channels Montage channels in descending order: body position, left electrooculogram (LEOG), right electrooculogram (REOG), chin electromyogram (EMG), central EEG, occipital EEG, leg EMG, pressure transducer, thermocouple, rib cage respiratory inductance plethysmography, abdomen respiratory inductance plethysmography, SaO_2, sleep stage.

Figure 2—A 10-min epoch of a patient on adaptive pressure support servoventilation.



Note uninterrupted breathing without any central or obstructive disordered breathing events. Montage channels as in Figure 1 except the flow channel in pink is from the ASV device. The values for end expiratory positive airway pressure (EEP), minimum (min) and maximum (max) inspiratory pressure support are noted on top of the epoch.

We are therefore confident that in the absence of an esophageal balloon, central apneas are classified as accurately as possible.

During laboratory titration, at final ASV pressures central and obstructive apneas were eliminated and the average hypopnea index was 11/h compared to baseline AHI of 61/h (**Table 4**). As a result of improvement in sleep-related breathing disorders, oxyhemoglobin desaturation and arousal index improved significantly with application of ASV. The arousal index decreased from 29 to 12/h, primarily due to reduction of arousals due to sleep related disordered breathing. There were no differences in response to ASV therapy in the patients with complex sleep apnea (n = 4) compared to the remaining 16 patients who had CSA on baseline PSG.

Sleep apnea associated with chronic use of opioids is highly prevalent.[1-6] In one study of 140 patients in a pain clinic, in which patients were enrolled independent of risk factors for sleep apnea, 36% had an AHI ≥ 30/h.[5] However, in our study, virtually all suffered from severe sleep apnea (average AHI = 64/h and 18 of 20 had AHI ≥ 30/h). This is not surprising as our patients were all referred to sleep laboratory with established risk factors for sleep apnea including habitual snoring, nocturia, unrefreshing sleep, excessive daytime sleepiness and hypertension.

As noted in the Methods, a second CPAP titration was initially recommended to nine patients but was later abandoned. Previous studies in patients with OSA[19,21,22] have shown emergence of CSA(CAI ≥ 5/h of sleep) during initial titration with CPAP. This has been termed complex sleep apnea.[21,23] In a previous study of a large number of OSA patients who had CSA (CAI ≥ 5/h) during first night CPAP titration, central apneas were eliminated in most patients with continued use of the device.[19] Therefore, we had hoped for a similar outcome in the present study; however, the results show that CSA associated with the use of opioids is an important exception, in that

Figure 3—Central-apnea index (CAI) on final PAP level as compared to baseline for the 20 patients.

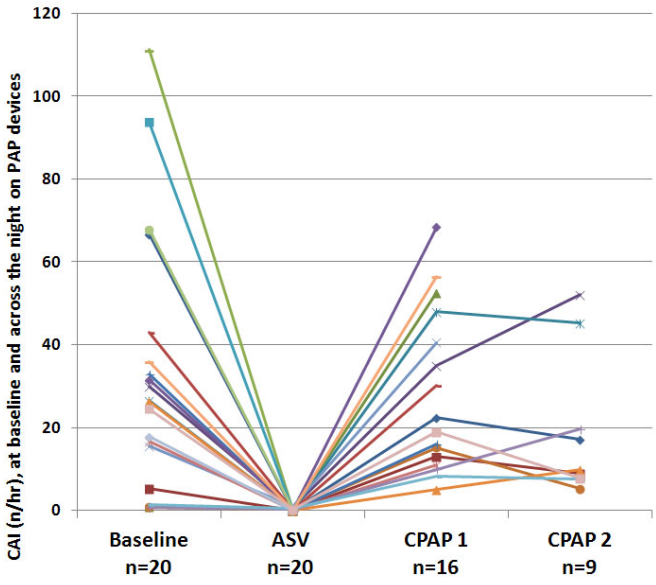


Table 4—Polysomnographic findings at baseline, CPAP 1, CPAP 2, and ASV (n = 9)

Variables	Baseline	CPAP 1	CPAP 2	ASV	p value
Total recording time, h	7 ± 1	6.9 ± 1	7 ± 1	7 ± 1	0.978
Total sleep time, h	5.5 ± 1	5.6 ± 1	5.4 ± 1	5.2 ± 1	0.905
Sleep efficiency, %	80 ± 19	82 ± 10	77 ± 14	74 ± 10	0.647
N1, % TST	28 ± 20	14 ± 12	25 ± 26	18 ± 12	0.191
N2, % TST	61 ± 16	81 ± 11	68 ± 26	72 ± 12	0.222
N3, % TST	0 ± 0	0 ± 1	0 ± 0	1 ± 3	0.439
REM, % TST	11 ± 9	5 ± 4	7 ± 5	8 ± 6	0.058
ArI, n/h	25 ± 16	24 ± 19	23 ± 13	17 ± 8	0.321
AHI, n/h	45 ± 22	34 ± 19	33 ± 18	21 ± 14	0.016
AHI final PAP level, n/h	n/a	42 ± 24	32 ± 20	12 ± 14*	0.006
CAI, n/h	20 ± 21	20 ± 14	19 ± 17	0 ± 0*	0.006
NREM CAI, n/h	23 ± 27	20 ± 15	21 ± 20	0 ± 0*	0.014
REM CAI, n/h	4 ± 7	6 ± 8	3 ± 3	0 ± 0*	0.211
OAI, n/h	4 ± 4	1 ± 2¶	1 ± 1	0 ± 0	0.002
ArI-DB, n/h	20 ± 14	17 ± 18	17 ± 13	14 ± 8	0.533
Baseline SpO_2	95 ± 2	95 ± 2	95 ± 2	94 ± 2	0.421
Minimum SpO_2	83 ± 10	87 ± 4	85 ± 5	86 ± 6	0.417
Oxygen desaturation index	30 ± 24	16 ± 16¶	15 ± 11	9 ± 15	0.0002
PLMSI, n/h	0 ± 1	0 ± 0	0 ± 1	1 ± 1	0.24
Expiratory pressure, cm H_2O	n/a	10 ± 4	11 ± 4	10 ± 3	0.031

Values reported are mean ± SD. ASV, adaptive servoventilation; Baseline SpO_2, saturation in supine position during relaxed wakefulness; PLMSI, periodic leg movements index during sleep; TST, total sleep time; AHI, apnea hypopnea index; REM, rapid eye movement; OAI, obstructive apnea index; CAI, central apnea index; ArI-DB, arousal index associated with disordered breathing. Analysis of variance with repeated measures and Bonferroni correction factor were used for comparisons of Baseline vs. CPAP 1, CPAP 1 vs. CPAP 2, and CPAP 2 vs. ASV. ¶Significant when comparing CPAP 1 to baseline. *Significant when comparing ASV to CPAP 2.

CSA persists in spite of continued use of CPAP. **Figure 3** shows the individual values for CAI in all patients who underwent PAP titration. Central apneas persisted in spite of several weeks use of CPAP with an average therapeutic use of 4 to 5 hours per night. With that observation we felt it was economically and medically futile to continue to recommend therapy with CPAP in the remaining patients with opioid-associated central apneas. Therefore, ASV treatment was initiated. The considerable reduction in CAI, AHI, and related arousals and desaturation with overnight acute ASV titration is remarkable. Most recently Ramar and colleagues reported their experience with ASV therapy for complex sleep apnea including patients with heart failure and those on chronic opioids.[24] They reported lack of efficacy of single night CPAP therapy and equal efficacy of ASV device for both groups of patients. We emphasize that our experience with opioid-induced CSA and CPAP therapy is different than CPAP therapy of CSA associated with heart failure. In the latter, almost 50% of patients respond to CPAP,[25] and these patients have improved survival.[26] Therefore, we do not recommend ASV therapy for heart failure patients whose CSA is suppressed by CPAP.

In our study of prolonged follow up (up to 6 years) in patients using ASV for opioid- induced CSA, adherence was satisfactory with an average of 5.1 hours. Unfortunately, only six of the devices had algorithms capable of downloading the AHI, with mean AHI of 3/hr. We note that home AHI is based on airflow only, and with device-specific airflow criteria. However, since our patients were doing well on ASV, as dictated by standard care, in-laboratory evaluation was not clinically indicated.

Although central apneas are commonly observed during initial polysomnography,[1-6] they may be absent initially and appear during CPAP titration referred to as complex sleep apnea.[21-24] In regard to the latter, Guilleminault and associates reported the presence of primarily obstructive sleep apnea in a large group of patients on opioids.[27] However, central apneas resulting in sleep fragmentation emerged and persisted with use of CPAP or bilevel devices, eventually necessitating use of bilevel device with backup rate. The persistence of central sleep apnea in the study of Guilleminault and associates[25] is consistent with our observation, except that most of our patients had large number of central apneas during initial polysomnography.

We also observed that opioids were associated with altered sleep architecture characterized by reduction in sleep efficiency, REM sleep, and absence of deep sleep (**Table 3**) consistent with previous studies showing adverse effects of opioid use on sleep infrastructure.[26,27] A large number of arousals were present, mostly due to sleep-related breathing disorders fragmenting sleep. Periodic limb movements (PLMs), which are common polysomnographic findings, were virtually absent in our patients (**Table 3**), consistent with efficacy of opioids in treatment of PLM.

Summary

Patients on opioids may suffer from severe central sleep apnea which persists in spite of continued use of CPAP for several weeks. However, adaptive pressure support servoventilation devices are effective in improving central apneas. Most patients remain adherent to ASV during long-term follow-up, and the limited data from this study suggest persistent suppression of home (flow) AHI with long-term use. Hopefully, future long-term studies will show that effective treatment of sleep apnea decreases the likelihood of the unexpected deaths of patients on chronic opioids.

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