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Treatment of Central Sleep Apnea in US Veterans

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SCIENTIFIC INVESTIGATIONS

Background: There are no standard therapies for the management of central sleep apnea (CSA). Either positive pressure therapy (PAP) or supplemental oxygen (O_2) may stabilize respiration in CSA by reducing ventilatory chemoresponsiveness. Additionally, increasing opioid use and the presence of comorbid conditions in US veterans necessitates investigations into alternative titration protocols to treat CSA. The goal was to report on the effectiveness of titration with PAP, used alone or in conjunction with O_2, for the management of CSA associated with varying comorbidities and opioid use.

Methods: This was a retrospective chart review over 3 years, performed at a VA sleep disorders center. The effects of CPAP, CPAP+O_2, and BPAP+O_2, used in a step-wise titration protocol, on consecutive patients diagnosed with CSA were studied.

Results: CSA was diagnosed in 162 patients. The protocol was effective in eliminating CSA (CAI ≤ 5/h) in 84% of patients. CPAP was effective in 48%, while CPAP+O_2 combination was effective in an additional 25%, and BPAP+O_2 in 11%. The remaining 16% were non-responders. Forty-seven patients (29%) were on prescribed opioid therapy for chronic pain, in whom CPAP, CPAP+O_2, or BPAP+O_2 eliminated CSA in 54%, 28%, and 10% cases,, respectively. CPAP, CPAP+O_2, and BPAP+O_2 each produced significant declines in the AHI, CAI, and arousal index, and an increase in the SpO_2.

Conclusion: The data demonstrate that using a titration protocol with CPAP and then PAP with O_2 effectively eliminates CSA in individuals with underlying comorbid conditions and prescription opioid use. Comparative studies with other therapeutic modalities are required.

Keywords: Sleep, central sleep apnea, obstructive sleep apnea, oxygen, continuous positive airway pressure, bilevel positive airway pressure, opioid drugs, periodic breathing

Commentary: A commentary on this article appears in this issue on page 565.

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The treatment of central sleep apnea (CSA) continues to lack a universally recognized standard of care.[1] Variable etiologies of CSA and the presence of concomitant disorders influence the choice of therapy. Thus, therapeutic options have varied markedly from positive airway pressure (PAP) devices, including continuous positive airway pressure (CPAP),[2-6] bilevel positive airway pressure therapy (BPAP),[7-9] and adaptive servoventilation,[10-13,20] to supplemental O_2,[14-17] carbon dioxide,[21,22] and/or pharmacologic agents.[23-25,29,30] The outcomes of therapy have also varied considerably, with limited evidence to establish the effectiveness of any therapy for CSA.[26-29,31,32] The majority of published literature has focused on the treatment of CSA secondary to congestive heart failure (CHF),[2-11,15-22,26-29] with very little data on patients with "primary" CSA[23,24] or CSA secondary to causes other than CHF.[33] In addition, there is very little data on the treatment of CSA related to opioid use and CSA that is concomitant with OSA.[13,35] The latter entities are of increasing importance in the US veteran population due to the increased use of prescription opioid drugs for chronic pain control and the risk for opioid related deaths.[34]

Central apnea (CA), defined as the cessation of breathing with an absence of respiratory effort, occurs as cycles of apnea alternating with hyperpnea. The ventilatory overshoot in the recovery period leads to hypocapnia and recurrent apneas. Treatment strategies primarily focus on preventing the "overshoot."

BRIEF SUMMARY

Current Knowledge/Study Rationale: Standard positive airway pressure (PAP) titration protocols for central sleep apnea (CSA) are poorly defined. Our goal was to determine the impact of a step-wise titration protocol using PAP therapy and supplemental oxygen, on CSA, in a sleep clinic population of patients with multiple co-morbid conditions and, particularly, with prescription opioid drug use.

Study Impact: The results confirm that CPAP eliminates central apneas in 50% of CSA cases, while CPAP in combination with oxygen is effective in an additional 25%. CSA related to prescription narcotic used is very common in the veteran population and PAP alone and in combination with oxygen are effective alternative therapies in this subpopulation of patients.

Positive pressure therapy, in the form of CPAP, BPAP, or ASV, and supplemental O_2 are two potential modalities that could stabilize respiration by dampening post-apneic hyperventilation and breathing instability.[14,36] Evidence in the literature supports the potential utility of each approach, but neither, separately or in combination, has been studied in large unselected patient populations.

In 2006, we initiated a stepwise protocol to standardize the initial management of central sleep apnea during PAP titration. Nasal CPAP was applied initially, followed by oxygen supplementation, aiming to stabilize breathing during sleep via

reduced chemoresponsiveness.[36] We are reporting our experience using a chart-based retrospective analysis that investigated whether instituting the above protocol during attended PAP titrations eliminated CSA in the veteran population.

METHODS

The site of the study was the Detroit Sleep-Wake Disorders Center, an AASM accredited sleep center at John D. Dingell VA Medical Center in Detroit, MI. The Human Investigation Committees of Wayne State University School of Medicine and Detroit Veterans Affairs Medical Center approved the retrospective research project.

Definitions

Polysomnographic (PSG) studies were performed using a digital polygraph (SomnoStar 8.5, Yorba Linda, CA, USA or Compumedics E-series, Abbotsford, Victoria, Australia) in a standard fashion, as per the AASM manual.[1] Electroencephalogram (EEG) was recorded using the international 10-20 system of electrode placement (EEG: C3-A2 and C4-A1; EOG, O-A2); electrooculograms (EOG), and chin electromyograms (EMG) were recorded using standard methodology. Airflow was monitored by nasal pressure transducer (PTAF 2, Philips Respironics, Murrysville, PA, USA) and thermistor during the diagnostic phase, or by the flow channel from the PAP (OmniLab Advanced, Phillips Respironics, Murrysville, PA, USA) pneumotachometer during the PAP titration phase. Respiratory effort was determined via the respiratory impedance plethysmography (RIP, Philips Respironics, Murrysville, PA, USA). Pulse oximetry oxygen saturation (SpO_2), was measured by the pulse oximeter incorporated in the digital polygraph systems. The device algorithm followed AASM guidelines for averaging SpO_2.[37] Sleep staging and arousals were scored according to standard methods; and obstructive apneas, central apneas, and hypopneas were scored based on current published AASM guidelines. The "alternate" scoring criterion provided by the 2007 AASM manual was used to score hypopneas: 50% reduction in flow associated with a 3% oxygen desaturation or an arousal.[37] Patients were diagnosed with OSA if the sum of the obstructive apneas and hypopneas per hour of sleep (the apnea-hypopnea index [AHI]), was ≥ 5/h. Patients were diagnosed with CSA if the number of CA per hour of sleep (central apnea index [CAI]) was > 5/h during a baseline PSG or the diagnostic portion of a split-night PSG. When the majority of the respiratory events were obstructive apneas or hypopneas, the sleep technologists followed the usual laboratory PAP titration protocol, starting at CPAP 4-5 cm H_2O and increasing by 2 cm H_2O with a goal of eliminating respiratory events,[65] with AHI < 10/h and CAI ≤ 5/h. The presence of frequent central apneas (corresponding with CAI > 5/h) during the baseline full-night PSG or the diagnostic portion of a split-night PSG was an indication to activate the *CSA titration protocol* (described below). The laboratory titration protocol is to titrate PAP to eliminate snoring, snore arousals, and REPRs (respiratory effort related arousals) and markers of flow limitation.

Central Sleep Apnea Titration Protocol

The CSA treatment protocol was designed as a technologist-driven protocol that was utilized in all patients with CSA, regardless of its etiology or the presence of concomitant OSA. The protocol was developed prior to the wide availability of ASV, which was not attempted if the above protocol was successful. Positive pressure titration was initiated at CPAP 4-5 cm H_2O and titrated upward to 10-14 cm H_2O. If frequent central apneas persisted at CPAP pressures of 10-14 cm H_2O, then CPAP was not increased further, in order to avoid further hyperinflation and hypocapnia. Instead, supplemental O_2 was added at 2 liters per minute (L/min) to dampen the post-apneic ventilatory overshoot,[36] and increased by 1 L/min to maintain oxygen saturation ≥ 93%, keeping CPAP at the same level. Oxygen saturation was maintained at ≥ 93%, to ensure that it was consistently > 90% even if apnea occurred, and allowing for a 2% device error. Supplemental oxygen at above goal was continued for ≥ 20 minutes. If central apneas persisted despite the addition of adequate supplemental O_2 for ≥ 20 min, CPAP was switched to BPAP while maintaining oxygen saturation ≥ 93%. Initial BPAP setting was adjusted to keep the inspiratory positive airway pressure setting (IPAP) 2-3 cm H_2O higher, and the expiratory positive airway pressure setting (EPAP) 2 cm H_2O lower than the previous CPAP setting. These were adjusted upward if hypopneas and obstructive apneas in addition to CA appeared, but keeping the IPAP-EPAP difference low (4-6 cm H_2O) to prevent further hypocapnia and central apneas. The usual laboratory protocol was to achieve optimal titration[65] in both supine and lateral positions. Eighty-four patients underwent a second or third night study for an initial or repeat PAP titration according to the above treatment protocol.

Data Analysis

A cross-sectional analysis of the data was performed on consecutive patients identified as having CSA by chart review for the period between January 2006 and June 2009, who received the diagnosis of CSA during an overnight baseline PSG or the diagnostic portion of a split-night PSG study. Patients with CPAP-emergent CSA (CAI < 5/h on the diagnostic portion of the PSG but ≥ 5/h during the titration phase of full-night PAP titration study or a split-night study) were not included in this analysis, as this was not the objective of the study. Moreover, the natural history of PAP-emergent CSA is that these resolve spontaneously over time.[60,61] Demographics and medical history data that could influence the presence of CSA and hypoxia were extracted, including age, gender, body mass index (BMI), Epworth Sleepiness Scale (ESS) score, medical history of heart failure (CHF), coronary artery disease (CAD), atrial fibrillation, hypertension (HTN), diabetes (DM), stroke, chronic obstructive pulmonary disease (COPD), and the use of opioid drugs. In addition, from the sleep study reports and charts we recorded the type of sleep study (baseline full-night or split-night PSG study), AHI, CAI, minimum oxygen saturation, the presence or absence of Cheyne-Stokes breathing/periodic breathing, and when available, transthoracic cardiac echocardiogram (ECHO) reports for ejection fraction (EF) and the presence or absence of diastolic dysfunction. Following initial variations in protocol implementation during the technologist training period, the protocol was followed more consistently and patients underwent titrations using the protocol on either the first night or a repeat study night. For the purpose of data analysis, an *optimal response* was defined as CAI ≤ 5/h and an AHI < 10/h. If the

Table 1—Demographics and baseline characteristics

Group characteristics	Entire group (n = 162)	CPAP (n = 72)	CPAP+O_2 (n = 38)	BPAP+O_2 (n = 17)
Age, years	59.0 ± 11.5	56.4 ± 11.8*	62.5 ± 8.9	62.0 ± 9.1
Males	159 (98)	72	37	16
BMI	33.5 ± 7.1	34.0 ± 7.1	32.9 ± 7.5	35.0 ± 6.2
ESS	11 ± 6	11 ± 6	11 ± 6	12 ± 6
Opioid use	47 (29)	25 (35)	16 (42)	7 (41)
History of CHF	32 (20)	9 (13)	8 (21)	6 (35)
Systolic dysfunction€	23 (14)	10 (14)	9 (24)	4 (24)
Diastolic dysfunction§	25 (15)	11 (15)	8 (21)	6 (35)¶
CAD	39 (24)	12 (17)	13 (34)	4 (24)
HTN	115 (71)	44 (61)	28 (74)	16 (94)*
Atrial fibrillation	20 (12)	3 (4)	10 (26)*	3 (18)
Stroke/TIA	10 (6)	4 (6)	0 (0)	4 (24)¶†
Hypothyroidism	8 (5)	4 (6)	2 (5)	0 (0)
DM	60 (37)	26 (36)	15 (39)	8 (47)
COPD	21 (13)	5 (7)¶	5 (13)*	5 (29)*
Baseline AHI	68.9 ± 29.8	66.8 ± 30.4	64.8 ± 28.8	70.7 ± 20.3
Baseline CAI	28.0 ± 25.6	23.8 ± 21.9	31.0 ± 32.6	21.6 ± 19.1
Baseline minimum SpO_2	82.0 ± 6.2	82.3 ± 5.2	82.7 ± 7.7	80.2 ± 7.0

Numbers in parenthesis are percentages of the number of patients in that group, rounded to the nearest integer. €Systolic cardiac dysfunction with estimated left ventricular ejection fraction < 55% (by 2-D echocardiogram, ECHO). §Diastolic cardiac dysfunction with normal systolic function of ejection fraction > 55% (2-D ECHO). The treatment groups were overall similar in characteristics to the entire "parent" group and to one another, except for the ones annotated; ¶p < 0.05 vs. entire group, *p < 0.05 vs CPAP, †p < 0.05 vs CPAP+O_2.

CAI remained > 5/h after undergoing ≥ 2 treatment options per the above protocol, these individuals were described as *non-responders*. The sleep stage percentages of total sleep time (TST) were calculated at baseline and during the entire titration period of the study. Arousal index was calculated as the number of AASM-defined arousals per hour of sleep and included arousals related to all respiratory events-including RERAs (respiratory effort related arousals).[37] In order to clarify the effect of optimal therapy on sleep continuity, the arousal index was calculated during the baseline study period and, specifically, for the period of PAP or PAP+O_2 therapy that produced an optimal response (as described above).

Two patterns of central apneas were noted: one, with a distinct oscillatory crescendo-decrescendo breathing pattern, and second, with repetitive apneas but without the oscillatory pattern. Periodic breathing (or Cheyne-Stokes respiration pattern) has been defined as repetitive crescendo-decrescendo pattern of central apneas and hypopneas lasting ≥ 10 min.[37] To ascertain if periodic breathing produced an optimal response with PAP or PAP+O_2 therapy in each patient, a *periodic breathing index* was calculated. The *highest* peak in the sine-wave crescendo-decrescendo oscillatory breathing pattern was first identified, then the number of peaks were summed and divided by the corresponding total sleep time to arrive at the index. The periodic breathing index was calculated at baseline and during optimal response in each of the 3 therapy groups.

A subgroup analysis for opioid users was completed. In 17 of 47 individuals with PRN opioid prescription, we were unable to determine the actual ingested dose even though the chart review indicated that the majority were using the prescribed dosing on a regular basis. To assess the impact of prescription opioid use, dosing was converted to a 24-h equipotent dose of oral morphine sulphate using the online *Hopkins Opioid Conversion Program.*[63] Morphine equipotency for tramadol, propoxyphene, and buprenorphine could not be determined due to unavailability of a reliable dose conversion factor.

Statistical Analysis

Descriptive statistics of the study population were evaluated (**Table 1**). One-way ANOVA or ANOVA on ranks with the Dunn test of multiple comparisons and the z test of proportions were used to compare the baseline characteristics among the groups: entire group, CPAP alone, CPAP+O_2, and BPAP+O_2. The pre-therapy AHI, CAI, and minimum oxygen saturation on the baseline diagnostic PSG were compared with the values obtained on optimal PAP alone or on optimal PAP plus O_2 using paired *t*-tests (AHI) for each intervention group. For nonparametric data (CAI and minimum SpO_2), the Wilcoxon signed rank test was used for comparison. All results are presented as mean ± standard deviation (SD). The level of statistical significance was set at $p < 0.05$. A commercially available computer statistical package was used to analyze the data (Sigma Stat 3.11.0, SPSS).

RESULTS

CSA was diagnosed in 162 patients following 41 full-night diagnostic/baseline and 121 split-night overnight attended PSG studies. The protocol was completed appropriately in 151 patients. Concomitant OSA was present in 149 of the 151 patients. The baseline characteristics of the patients are given on **Table 1**. Prescription opioid drug use was the most com-

Table 2—Numbers of individuals with optimal response to the protocol

	Total	CPAP	CPAP+O_2	BPAP+O_2
All patients, n = 151	127 (84)	72 (48)	38 (25)*	18 (11)*#
Opioid users, n = 41	36 (89)	22 (54)	11 (27)¶	4 (10)*

Optimal response was defined as CAI < 5/h and AHI < 10/h (responders). Numbers in parenthesis are percentages rounded to the nearest integer. No significant differences in outcomes between the entire vs. opioid user groups. Among the 3 interventions, significantly higher number of responders was noted with CPAP alone. *p < 0.01 vs CPAP, ¶p = 0.02 vs CPAP, #p < 0.01 vs CPAP+O_2.

Table 3—Comparison of sleep parameters for all patients at baseline and on therapy

	(1) Baseline	(2) CPAP therapy	(3) CPAP+O_2 therapy	(4) BPAP+O_2 therapy
TST, minutes	131.7 ± 90.3	273.6 ± 61.9*	274.8 ± 92.0*	215.2 ± 114.8*
SE %	63.4 ± 18.4	77.4 ± 15.1*	74.5 ± 19.4*	72.1 ± 21.0
Stage N1, %	52.9 ± 25.7	23.6 ± 12.8*§	27.6 ± 13.4*	36.6 ± 23.1
Stage N2, %	37.9 ± 21.4	53.0 ± 14.8*	52.7 ± 11.2*	47.8 ± 18.2
Stage N3, %	5.5 ± 10.5	8.3 ± 10.7*	5.7 ± 8.5	4.2 ± 5.9
Stage R, %	4.1 ± 7.2	14.6 ± 9.1*	14.1 ± 11.3*	11.4 ± 10.4*
Total arousal index, per hr at baseline and on *optimal therapy*#	63.2 ± 27.1	3.8 ± 5.1¶	3.6 ± 4.5¶	4.2 ± 6.3¶

Treatment group vs. baseline values, *p < 0.05, ¶p < 0.001; §CPAP vs. BPAP+O_2, p < 0.05. Remaining group comparisons were not significantly different. Lower baseline TST values are due the fact that both full-night and the diagnostic portion of split night studies are included in the analysis. TST, total sleep time; SE, sleep efficiency; N1, N2, N3 are stages of NREM sleep; stage R, REM sleep. The sleep stages percentages are given for the entire study duration for the baseline diagnostic period and for the entire PAP/PAP+O_2 titration periods, respectively. #The arousal index was averaged for the baseline period and for the final PAP/PAP+O_2 therapy setting that produced an *optimal response*. See text for a definition of *optimal response*.

mon risk factor for CSA (29%, 47 of 162 patients), even more common than the history of CHF (20%) or stroke (6%). All patients were naïve to CPAP at the time of titration, except one individual who had returned for a repeat split-night study and had CSA on the baseline portion of the study that resolved on CPAP alone. There was an optimal response in 127 of the 151 (84.1%) patients following the protocol (**Table 2**). In addition, the most common therapeutic modality that was effective was CPAP in 48% of individuals (**Table 2**). Significant reduction in AHI and CAI to AHI < 10/h and CAI < 5/h, respectively (**Figure 1A-C**), was achieved on final optimal settings with a concomitant significant increase in minimum oxygen saturation noted in each therapeutic group, thus establishing the presence of an optimal response to therapy. The time interval between the initiation of supplemental oxygen and the resolution of CSA in the CPAP+O_2 group was 97.8 ± 79 min (median 78 min, range 0 to 285 min; **Figure 2**). Finally, in 12 patients, the addition of oxygen did not eliminate CA adequately (CAI > 5/h) despite attaining adequate oxygen saturation. A significantly higher percent of this non-responder group compared to the entire sample had underlying systolic cardiac dysfunction (25% vs 10%, p < 0.01), while other baseline characteristics were similar. **Table 3** provides an assessment of sleep architecture on each therapeutic modality that produced an optimal response. The overall sleep architecture was improved compared with baseline but was not significantly different among the 3 therapy groups. The arousal index was elevated at baseline. Compared to baseline values, the arousal index was markedly reduced on the PAP/PAP+O_2 therapy settings that produced an optimal response in all 3 groups (**Table 3**). The percentage of stage 1 was markedly reduced, but not in the "normal" range for the *overall* titration duration which included an initial titration period when apneas and hypopneas still persisted, prior to optimal response; however, on optimal PAP/PAP+O_2 therapy, stage 1 was only 13%, with 87% of time with optimal response being stage N2/N3 and REM sleep (also see **Figure 2** as example). This along with the improvement in the arousal index indicates an improvement in sleep continuity with optimal CPAP or optimal PAP+O_2 combination therapy.

Periodic breathing pattern was observed in 41 patients during their respective baseline study periods. The remaining patients experienced repetitive central apneas but without a crescendo-decrescendo periodic breathing pattern. Of the individuals with oscillatory periodic breathing pattern, echocardiography was available in 28 and showed that 14 (50%) had diastolic (in the absence of systolic) cardiac dysfunction, 10 (36%) had systolic left ventricular dysfunction, and 4 had normal cardiac function by echocardiography. The periodic breathing index (see *Data Analysis*) decreased significantly with CPAP (n = 25, 30.9 ± 24.9/h vs. 0.4 ± 1.4/h, p < 0.001), CPAP+O_2 (n = 16, 27.2 ± 17.3 vs. 1.1 ± 3.5/h, p < 0.001) and BPAP+O_2 (n = 5, 42.2 ± 31.5 vs. 1.0 ± 2.3/h, p = 0.04), respectively.

Subgroup of Opioid Users with Optimal Response

Forty-seven patients (29%) were on prescribed opioid therapy for chronic pain control. The prescribed opioid drugs included hydrocodone (n = 19), oxycodone (n = 10), morphine (n = 7), methadone (n = 6), codeine (n = 3), oxymorphone (n = 1), propoxyphene (n = 1), buprenorphine (n = 1), and tramadol (n = 7). The exact dosing of opioid therapy was available from the medical record in 44 patients. The 24-h morphine sulfate equipotency dosing for the group was 93 ± 102 mg, with a median dose of 40 mg and maximum dose of 363 mg. The characteristics of the opioid users were not significantly differ-

ent from the parent group: 94% males, BMI 33.9 ± 7.4 kg/m^2, AHI 77.4 ± 33.1/h, CAI 37.6 ± 28.9/h, minimum O_2 saturation 80.5% ± 5.5%, ESS score 13 ± 5. However, the opioid user subgroup was younger, 53.7 ± 11.5 vs 59.0 ± 11.5 yrs, $p < 0.01$; only 6 individuals had a concomitant history of CHF, with 5 patients with EF < 55%; the proportion of individuals with CHF in opioid users was similar to that in the entire group, (13% vs 20%, p = ns). The titration protocol was fully implemented in 41 patients, with optimal response noted in 36 (89%). CPAP was the most effective treatment (**Table 2**) followed by PAP with oxygen supplementation. There were also significant improvements in AHI, CAI, and oxygen saturation, compared with baseline values in this subgroup (**Figure 3**) with the titration protocol.

DISCUSSION

To date, only small studies[15-19] conducted mostly in patients with underlying CHF, have demonstrated the effectiveness of adding O_2 for the management of CSA. However, no study has evaluated the effectiveness of a combination therapy of PAP and supplemental oxygen on the evolution of central apneas in an unselected population of patients with a mix of etiologies for CSA.

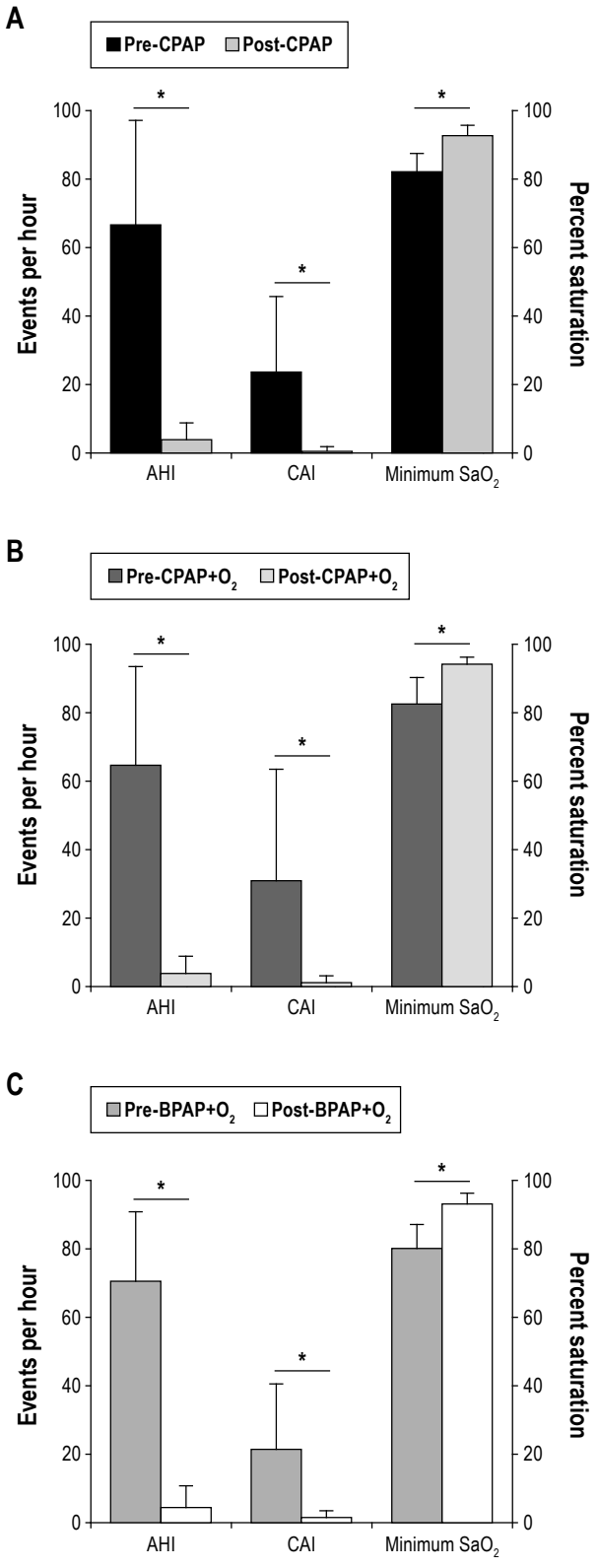
Summary of Findings

This study revealed several important findings: (1) CPAP therapy was effective in 50% of the study population, affirming that CPAP remains the initial therapeutic option when CSA is observed on a sleep study. (2) Supplemental O_2 therapy with PAP was effective in an additional 35% of cases, regardless of the etiology of CSA. These therapies reduced CSA with an improvement in sleep continuity and periodic breathing. (3) Narcotic use is very common in patients with CSA, and these results may be applicable to patients and of importance to practitioners outside of the VA system. We found that narcotic use was a more common risk factor for CSA than heart failure. (4) PAP with adjunctive oxygen therapy was effective in CSA with opioid drug use and may be considered as alternative therapy when central apneas are not eliminated by CPAP alone.

Potential Mechanisms of Action

Evidence supports the salutary effect of nasal CPAP in the treatment of central sleep apnea,[2,4,6,39,40] with the strongest evidence obtained from studies of patients with central apnea in relation to heart failure.[66] The therapeutic effects of nasal CPAP could be due to restoring upper airway patency and stabilization of the respiratory control system. Central apnea rarely occurs as a single event, but as cycles of apnea/hypopnea alternating with hyperpnea, often in association with obstructive events. Once apnea occurs, several factors promote further instability.[41] Central apnea results in pharyngeal airway narrowing or occlusion[41-43]; therefore, resumption of spontaneous breathing requires opening an occluded airway, overcoming tissue adhesion force and perhaps gravitational forces.[44] Furthermore, based on prior data, there is an "inherent inertia of the ventilatory control system"[45] that prolongs a central apnea and only allows resumption of respiratory activity after the arterial PCO_2

Figure 1



This figure demonstrates a significant decline in AHI and CAI associated with a significant increase in minimum oxygen saturation during titration with each of the 3 interventions as per the CSA titration protocol in the entire group. **(A)** CPAP, **(B)** CPAP plus oxygen, and **(C)** BPAP plus oxygen. AHI, apnea hypopnea index; CAI, central apnea index; CSA, central sleep apnea; CPAP, continuous positive airway pressure; BPAP, bilevel positive airway pressure; *p < 0.05.

Figure 2—The hypnogram from an individual patient undergoing a night study demonstrates an "optimal response" upon adding supplemental O_2 to CPAP

Position channel: B, back; R, right; L, left; S, side. Therapy channel: numbers indicate CPAP (cm H_2O) while the horizontal dark blue line indicates time period when supplemental O_2 was added to the circuit, starting from the arrow (↓), initially at 2 Lpm and then increased to 3 Lpm. On the respiratory event channel, the light blue, red, pink, and green bars represent central apneas, obstructive apneas, mixed apneas, and hypopneas, respectively. Respiratory events channel: numbers indicate duration of event in seconds; LM, leg movements. The clock time is indicated on the top border of the figure. Both obstructive and central events were at present at baseline and were *partially resolved with CPAP,* whereas the residual central apneas were completely eliminated by the addition of supplemental oxygen; (↓) denotes addition of O_2. Following an increase in the supplemental O_2 to 3 Lpm there was an *optimal response* (see text for definition). The sleep architecture also improved significantly on the optimal setting of CPAP plus oxygen at 3 Lpm, with maximum percentage of TST on this setting being stage N2 followed by stage R sleep. The salutary effect of supplementary O_2 was noted 25 min after adding supplemental O_2, or approximately 10 min (horizontal arrow, ←→), after reaching 93% SpO_2, represented by the elimination of central apneas.

is 4-6 mm Hg above eupnea. The prolongation of apnea leads to variable asphyxia (hypoxia and hypercapnia) and transient arousals, resulting in ventilatory overshoot, subsequent hypocapnia, and further apnea/hypopnea.

The aforementioned sequence may explain the reported therapeutic effects of nasal CPAP in the treatment of central apnea. First, nasal CPAP restores upper airway patency, resulting in dampening of ventilatory overshoot, and mitigation of subsequent hypocapnia. CPAP increases nocturnal $PaCO_2$, perhaps by dampening ventilatory overshoot and hypocapnia,[46] as well as by increased lung volume.[52] Edwards et al. have shown that CPAP stabilizes chemoreflex control of the respiratory system in the newborn lamb, via increased lung volume and decreased loop gain.[47] In addition, improvement in the cardiac output[59] with improved circulation time may contribute to stable breathing in individuals with CHF. However, the response to PAP in non-CHF patients indicates that the decreased propensity to central apnea may also be due to improved oxygenation, mitigation of intermittent hypoxia, increased lung volume, restoration of upper airway patency, and unloading of respiratory muscles. Our data do not allow us to ascertain the relative contribution of each potential mechanism.

We noted that the timeline for resolution of central apnea after initiation of supplemental oxygen was inconsistent with a peripheral chemoreceptor inhibition. While the duration of time required to reach SpO_2 of 93% may determine the time taken to eliminate the central apneas, in majority of the patients, resolution of central apnea required more than 5 minutes after reaching the goal SpO_2 level, indicating that the response was a central phenomenon and not a peripheral chemoreceptor response, since a peripheral chemoreceptor response would have occurred within a few breaths of adding oxygen. Therefore, we interpret our findings as a consequence of central stimulatory effect rather than peripheral inhibitory effect of hyperoxia. The present study corroborates our previous study demonstrating that sustained levels of oxygen at FiO_2 0.40 to 0.70 mitigates the susceptibility to hypocapnic central apnea in healthy adults during sleep.[36] Likewise, there is evidence that adding oxygen at FiO_2 as low as 30% for 30 minutes resulted in increasing minute ventilation by 21% above room air levels.[48] Thus, sustained hyperoxia is a ventilatory stimulant. Specific

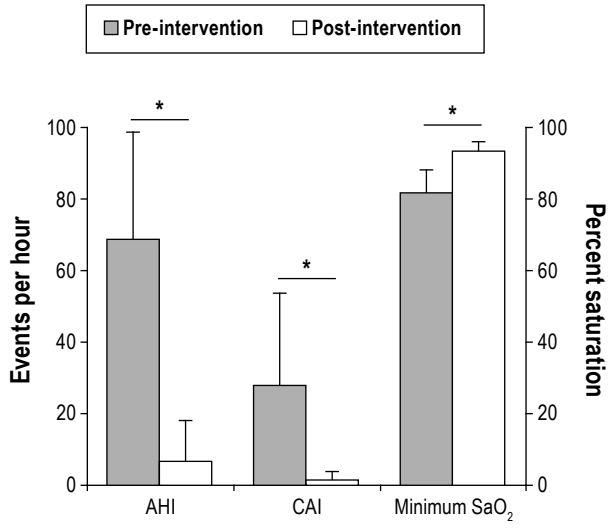
mechanisms of hyperoxic hyperventilation include increased brain tissue PCO_2 via cerebral vasoconstriction,[49] the Haldane effect,[50] or a direct stimulatory effect on chemosensitive respiratory neurons[51] via production of reactive oxygen species. The net effect of hyperoxia is alveolar hyperventilation, decreased plant gain, and increased CO_2 reserve, thus stabilizing respiration[36] during sleep.

The aforementioned discussion is applicable to post-hyperventilation central apnea. Nevertheless, it is unclear if the same mechanisms apply to CSA due to opioid use, given the uncertainty regarding the underlying mechanisms. It is possible that increased oxygen level increases chemoreceptor output[56] in this scenario too, while increased upper airway collapsibility may be countered by PAP; however, the latter explanation is speculative and needs further exploration in experimental settings.

Methodological Considerations

Several methodological issues should be considered for proper interpretation of our findings. First, our protocol does not allow us to test the effects of adaptive servo-ventilation (ASV) on central apnea, which was not included in the main pathway, as it was not available when this protocol was initiated in our facility. ASV may contain features that combine the mechanical effects of CPAP with dampening of ventilatory overshoot. A small study in patients with CSR compared the effects of CPAP vs. BPAP vs. ASV vs. O_2 alone, however CPAP plus O_2 was not included as a comparison group.[20] Another study[13] that included CPAP plus O_2 in a small group patients (n = 7) noted a decline in CSA; however, the majority (> 60%) had CPAP-emergent or "complex-CSA," unlike the population described in our study. A randomized study with direct comparisons of CPAP plus O_2 with ASV is required to assess the relative effects of each approach as well as relative cost-effectiveness. While BPAP with oxygen did produce an optimal response, a spontaneous mode of BPAP without a back-up rate was used, which is a limitation of this study. We recommend that future studies compare the efficacy of BPAP and oxygen, both in the spontaneous and spontaneous-timed modes. Second, our study was limited by the retrospective design, the predominance of males (because of the study location in a VA medical center), and the lack of longitudinal comparisons among different treatment arms. Third, the presence of REM sleep could have eliminated the central events during the latter portion of the PAP titration; however, the majority of sleep time was in NREM sleep with REM occupying only 8% to 14% of the TST. Fourth, we referred to the AASM scoring manual[37] for a qualitative definition of Cheyne-Stokes/periodic breathing pattern. However, proper quantification of periodic breathing cycles requires concomitant measurement of esophageal or supraglottic pressure for accurate classification of central and obstructive events, especially hypopnea. Finally, given the retrospective nature of the study we were unable to confirm the actual ingested dose of opioid medications. However, we expect that the patients were regularly ingesting the prescribed dosing of opioid for treatment of chronic pain. In addition, it was not possible to retrospectively determine the exact etiology triggering CSA in each patient. However, our primary goal at the outset of the study was to simulate real clinical situations where CSA coexists with comorbid conditions and to determine the role of O_2 supplementation as a simple and easily accessible measure in this patient group.

Figure 3



This figure demonstrates that in a sub-group of opioid users, the AHI and the CAI declined significantly, with a significant increase in the minimum oxygen saturation, using the CSA titration protocol; *p < 0.05.

Significance

Our study included a population of patients referred from multiple VA medical centers, with many underlying etiologies of CSA, and not just limited to patients with CSA due to heart failure or "primary" CSA. The recently published AASM Practice Parameters[64] provide guidance for the treatment of CSA in several clinical settings, and supports the use of CPAP alone or supplemental oxygen alone for the treatment of CSA. However, the document does not address the use of combination therapy of PAP plus supplemental oxygen because such studies are lacking. Moreover, there is very limited evidence for the management of CSA due to opioid use[53], as noted in the practice parameter[64]. The practice parameter also highlighted the absence of a large series evaluating the role of "dead space" and recognized that carbon dioxide is not universally available and is difficult to administer.[64] While ASV is now available, the cost of these devices is much greater than the cost of CPAP, and the latter may be sufficient in half of the patients with CSA. Additionally, ASV is not used as first line treatment for CSA, and alternative therapies are required for the management of CSA that persists on CPAP. The current study contributes to the available literature by providing a real-life scenario where OSA frequently coexists with CSA in both patients with CHF *and prescription opioid medication users*. To our knowledge, this is also the largest series of patients with CSA associated with prescription opioid use that describes the effect of the three different therapeutic modalities, in contrast to prior studies.[53] These results are of great relevance in the US veteran popula-

tion given the increasing trend for prescription opioid drug use for pain control.[34,58,62]

CONCLUSION

This study purports to simplify the management of CSA in a step-wise fashion in a sleep clinic-based population with underlying co-morbidities and prescription opioid use. The results shows that in individuals who fail initial CPAP during a titration study, a majority of residual CSA can be eliminated effectively by using oxygen adjunctively with PAP. Prospective comparative efficacy and cost-effectiveness trials using different treatment modalities are needed to expand on these findings.

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