

Comparative Evaluation of Therapeutic Approaches to Central Sleep Apnea

Abstract

Background: To date, there is no standard approach to manage and to improve central sleep apnea (CSA). The most applicable therapeutic approaches are positive airway pressure therapy (PAP), bi-level PAP therapy (BIPAP), supplemental O₂ and servo ventilation, or a combination of two approaches. Given the high prevalence of heart disease (HF) and/or concomitants of other diseases and opioid use worldwide; it seemingly requires evaluation of patients' conditions in response to each abovementioned approach to select the most effective approach. **Materials and Methods:** This longitudinal cross-sectional study included 64 CSA patients who had undergone continuous PAP (CPAP), CPAP + O₂, and BiPAP. Hence, if a patient was nonresponsive to a treatment, the next was applied. If the patient was nonresponsive to all approaches, oxygen alone was administered. The collected data were analyzed with SPSS. **Results:** The study of 64 CSA patients showed that frequencies of response to CPAP, CPAP + O₂, and BiPAP were 42.2%, 20.3%, and 28.1%, respectively. While 9.4% of patients with histories of congestive heart failure (CHF) and ischemic heart disease (IHD) who were older than others and with the highest apnea-hypopnea index, were nonresponsive to all approaches. CPAP therapy showed more appropriate results in patients with CHF and IHD. Furthermore, patients with the history of opioid use showed the most positive results in response to CPAP and BIPAP. **Conclusion:** The results suggest that CPAP and BIPAP are, respectively, the most effective therapeutic approaches to CSA in patients with the histories of HF and opioid use, but CPAP + O₂ could be reliable in some conditions as well. Therefore, it may require further studies to be clarified.

Keywords: Bi-level positive airway pressure, central sleep apnea, continuous positive airway pressure, supplemental O₂

Introduction

The sleep-disordered breathing which is generally classified into obstructive sleep apnea (OSA) and central sleep apnea (CSA), has been reported in 6.5%–9% of adults.^[1] CSA is uncommon, unlike the high prevalence of OSA, and may be presented as primary or secondary outcomes (due to disease or medication) or concomitant with OSA/hypopnea. The CSA outbreak is <1% in the general population.^[2]

Mostly, CSA is concomitant with obstructive episodes due to increased sensitivity to PCO₂. CSA can result in disordered gas exchange at night and accordingly insomnia or oversleeping. Congestive heart failure (CHF), opium, and hypoxia are some risk factors for CSA. The CSA prevalence rates have been reported 25%–40%, 10%,^[3] and 30%^[4] in

CHF patients, patients with stroke, and methadone users, respectively.

Therefore, the choice of therapy for CSA can be influenced by the variable etiologies of CSA and the presence of concomitant disorders.^[5]

There are various therapeutic options, for example, using positive airway pressure (PAP) devices, including continuous PAP (CPAP),^[6,7] bi-level PAP therapy (BIPAP),^[8,9] and adaptive servoventilation (ASV),^[10,11] or applying supplemental O₂,^[12,13] carbon dioxide,^[14,15] and/or pharmacologic agents.^[16-18]

There is limited evidence in previous studies evaluating the effectiveness and efficacy of various CSA therapies, each can lead to different consequences.^[17,19] Few studies have suggested decreased central apnea frequencies, particularly in patients with

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hypoxia as a result of using supplemental O₂.^[20] CPAP has been recommended for Cheyne–Stokes respiration (CSR) and more appropriate control of CHF in some patients with or without oxygen supplement.^[21] Furthermore, CSA therapy secondary to CHF has been focused in the majority of published studies.^[22–25]

Moreover, a few data are available in the case of CSA therapy-associated with opioid use and the concomitants of CSA and OSA.^[26,27]

In this respect, some studies indicated the effectiveness of titrating PAP alone or with O₂ for CSA therapy related to opioid or comorbidities.^[20,28]

Given increasing opioid use worldwide, the role of etiologies as well as concomitants in therapy choice and the lack of a global standard treatment; the current study aimed to evaluate some therapy options in CSA with respect to the histories of concomitants and opioid use in the patients.

Materials and Methods

This longitudinal cross-sectional study aimed to compare the therapeutic approaches to CSA. Taking into account, the low prevalence of CSA and accordingly the likelihood of small available sample, initially all 74 patients presented at the centers of sleep and breathing disorders in Isfahan during April 2017–January 2018 were included in the study by the census.

Using standard polysomnography (PSG) and/or during two-sectional diagnostic PSG for hours, these patients were diagnosed with a central apnea index (CAI) of >5 events/h.

After the code of ethics was obtained from the Ethics Committee of Isfahan University of Medical Sciences (396341), and the written consent was obtained from the parents of eligible children, the demographic and clinical characteristics in CSA and hypoxia including age, sex, weight, height, body mass index (BMI), blood pressure, neck circumference, apnea-hypopnea index (AHI), CAI, the histories of CHF, coronary heart disease, diabetes, stroke, use of opioid, and smoking were recorded in an encoded form to keep the privacy (ethical issues).

When OSA patient presented at the center, the patient underwent positive air pressure titration from a low pressure to the pressure of 15 cm H₂O. If the patient was nonresponsive to CPAP, BIPAP was used. It should be noted that CPAP and BIPAP titrations were performed based on the American Academy of Sleep Medicine (2008) guideline for adults^[23] [Figures 1 and 2].

Afterward, providing a CAI of >5 with the oxygen saturation of <93%, it was considered as nonresponsive case to therapeutic approaches and for the patient, only oxygen was administered and was discharged.

Finally, the collected data were analyzed with SPSS (version 22; SPSS Inc., Chicago, Ill., USA). Data shown were frequency (%) or mean ± standard deviation also, to compare the quantitative data of each therapeutic approach with others and the response to treatment two-by-two, the Fisher’s exact test was applied and to compare all four therapeutic approaches existing in the study protocol, the Chi-square test was used. Given that the Kolmogorov–Smirnov test indicated the normality of data distribution, for quantitative data and in order

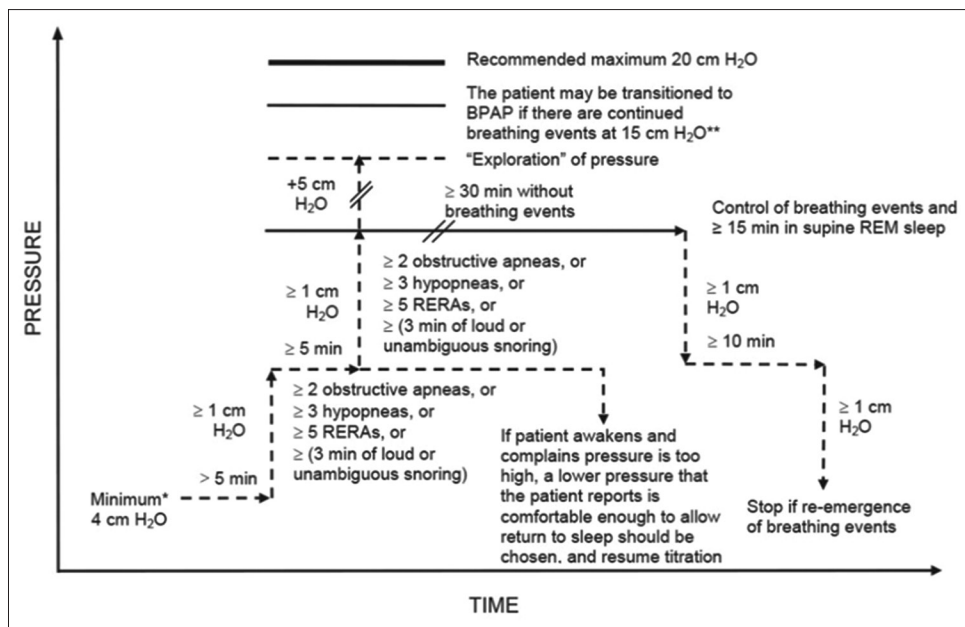


Figure 1: Continuous positive airway pressure titration algorithm for patients' ≥12 years during full- or split-night titration studies. Note: upward titration at ≥1-cm increments over ≥5-min periods is continued according to the breathing events observed until ≥30 min without breathing events is achieved. *A higher starting continuous positive airway pressure may be selected for patients with an elevated body mass index and for retitration studies. **The patient should also be tried on bi-level positive airway pressure if the patient is uncomfortable or intolerant of high continuous positive airway pressure

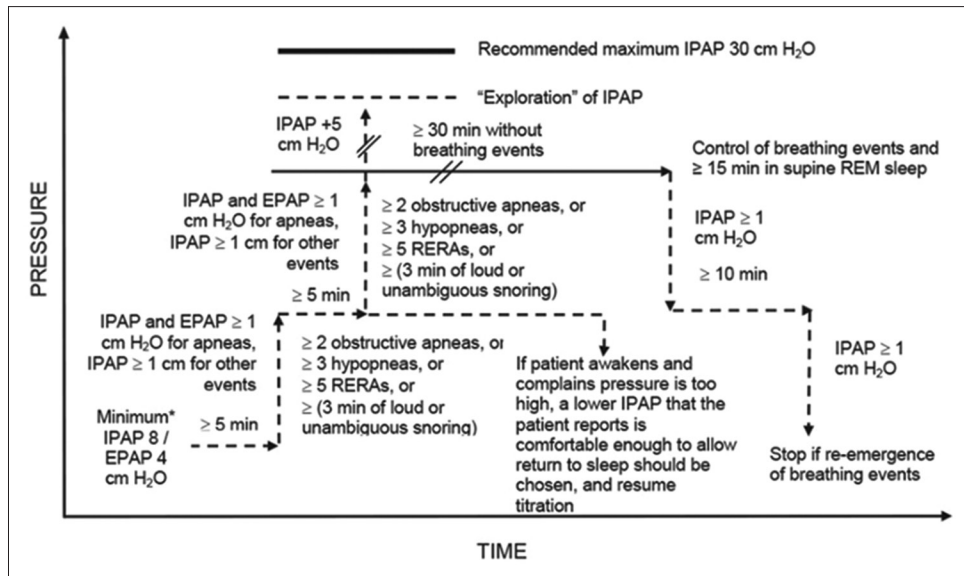


Figure 2: Bi-level positive airway pressure titration algorithm for patient's ≥ 12 years during full-or split-night titration studies. Note: upward titration of inspiratory positive airway pressure and expiratory positive airway pressure ≥ 1 cm H₂O for apneas and inspiratory positive airway pressure ≥ 1 cm for other events over ≥ 5 -min periods is continued until ≥ 30 min without breathing events is achieved. A decrease in inspiratory positive airway pressure or setting bi-level positive airway pressure in spontaneous-timed mode with backup rate may be helpful if treatment-emergent central apneas are observed. *A higher starting inspiratory positive airway pressure and expiratory positive airway pressure may be selected for patients with an elevated body mass index and for retitration studies. When transitioning from continuous positive airway pressure to bi-level positive airway pressure, the minimum starting expiratory positive airway pressure should be set at 4-cm H₂O or the continuous positive airway pressure level at which obstructive apneas were eliminated. An optimal minimum inspiratory positive airway pressure-expiratory positive airway pressure differential is 4-cm H₂O and an optimal maximum inspiratory positive airway pressure-expiratory positive airway pressure differential is 10-cm H₂O

to comparison of mean variables between responsive and nonresponsive patients to the treatment, we used independent samples *t*-test. To compare the mean variables of four therapeutic approaches, one-way ANOVA was used and the two-by-two comparison of therapeutic approaches was made by the *post hoc* Tukey test. In all analyses, we used a significance level of <0.05 .

Results

This study included 64 CSA patients (men = 60 [93.8%], women = 4 [6.3%]; mean age = 60.38 ± 13.98 y) with the mean AHI of 28.10 ± 29.64 events/h. Among these patients, the histories of diabetes mellitus (DM), hypertension (HTN), hyperlipidemia, CHF, and ischemic heart disease (IHD) were 42.2%, 37.5%, 21.9%, 42.2%, and 39.1%, respectively, and a half of patients (50%) recognized as opioid users [Table 1].

According to the results, 27 patients were responsive to CPAP therapy versus 37 nonresponsive patients, and these patients showed statistically significant differences in the histories of CHF and IHD ($P < 0.05$). The majority of patients with the histories of CHF and IHD were responsive to CPAP therapy [Table 2].

Furthermore, of 37 nonresponsive patients to CPAP, 13 patients were identified as responsive cases to CPAP + O₂ versus 24 nonresponsive patients. All responsive cases to CPAP + O₂ were males ($n = 24$), but nonresponsive cases were composed of one man (76.9%) and three

Table 1: Baseline and clinical characteristics of patients with central sleep apnea

| Characteristics | n (%) [†] or mean (SD) [*] |
|-----------------------------|--|
| Age, years | 60.38 (13.98)* |
| Sex | |
| Male | 60 (93.8) [†] |
| Female | 4 (6.3) [†] |
| BMI, kg/m ² | 31.02 (6.94)* |
| Height, cm | 170.58 (9.95)* |
| Weight, kg | 90.66 (25.41)* |
| Neck circumference, cm | 39.67 (2.06)* |
| AHI, n/h [‡] | 28.10 (29.64)* |
| Mild CSA | 25 (39.1) [†] |
| Moderate CSA | 27 (42.2) [†] |
| Severe CSA | 12 (18.8) [†] |
| History of clinical records | |
| History of DM | 27 (42.2) [†] |
| History of HTN | 24 (37.5) [†] |
| History of HLP | 14 (21.9) [†] |
| History of CHF | 27 (42.2) [†] |
| History of IHD | 25 (39.1) [†] |
| Smoking | 30 (46.9) [†] |
| Opioid users | 41 (64.1) [†] |

*: Data shown mean (SD), [†]: Data shown n(%), [‡]AHI group: Mild CSA ($5 \leq \text{AHI} < 15$ events/h); moderate CSA ($15 \leq \text{AHI} < 30$ events/h); and severe CSA ($\text{AHI} \geq 30$ events/h). SD: Standard deviation, AHI: Apnea-Hypopnea Index, BMI: Body mass index, CSA: Central sleep apnea, DM: Diabetes mellitus, HTN: Hypertension, CHF: Congestive heart failure, IHD: Ischemic heart disease, HLP: Hyperlipidemia

women (23.1%) ($P = 0.037$). Furthermore, the patients with the history of HTN showed a greater responsiveness (in percentages) to CPAP + O₂ ($P < 0.05$) [Table 3].

On the other hand, of 24 nonresponsive patients to CPAP + O₂, 18 patients with a mean age of 56.28 ± 15.50 y, were responsive to BIPAP compared to that of the six nonresponsive patients with a mean age of 71.50 ± 2.74 y ($P = 0.028$). All of these six nonresponsive patients to BIPAP had the histories of IHD and CHF were discharged with oxygen administration [Table 4].

It should be considered that the mean CPAP pressure used for the responsive patients to CPAP + O₂, was 10.29 ± 0.49 . Furthermore, mean inspiratory pressure (J), expiratory pressure, and respiratory rate were 19.33 ± 2.06 , 10.11 ± 1.45 , and 18.22 ± 2.36 times/m, respectively.

The evaluation of baseline and clinical characteristics of responsive patients to protocol showed that nonresponsive patients to all therapeutic approaches in the study, who were finally discharged with oxygen administration, were older than responsive patients to CPAP + O₂ and BIPAP therapies ($P < 0.05$). Furthermore, the BMI of nonresponsive patients to all therapies was significantly lower than others.

In addition, AHI of nonresponsive patients to all therapies (mean AHI = 33.67 ± 25.72 events/h) was the highest compared to that of the responsive patients to CPAP + O₂ with the lowest CAI (mean AHI = 26.20 ± 7.02 events/h) ($P < 0.05$). On the other hand, the risk factors including the histories of HTN, CHF, and IHD in CPAP therapy showed the highest frequency compared to that of the other therapies. In other words, patients with the histories of HTN, CHF, and IHD may show better results in response to CPAP ($P < 0.05$). The frequencies of responsiveness to CPAP and BIPAP among patients with the history of opioid use were 41.5% and 36.6%, respectively, but the lowest frequency of responsiveness to CPAP + O₂ was also observed in these patients ($P < 0.05$) [Table 5].

Discussion

According to the results, >90% of CSA patients were men with the age range of 28–82 years and the mean age of 60.38 ± 13.98 y. The majority of CSA patients had the histories of IHD and DM. Furthermore, unfortunately, more than half of patients were opioid users and also, 46.9% of patients had the history of smoking.

The prevalence of CSA is considerably higher in men and it increases with age. For example, a community cohort of 741 men showed that the CSA prevalence was estimated to be 0.4% overall among those aged 65 and older.^[29] Furthermore, afterward another cohort of 2,911 men reported that the CSA prevalence (CAI ≥ 5) was higher among those aged 65 and older.^[30] Some studies have noted the association between CSA and the histories of

Table 2: Demographics and baseline characteristics of responsive patients versus nonresponsive patients to continuous positive airway pressure

| Characteristics | Responsive (n=27) | Nonresponsive (n=37) | P |
|-----------------------------|-------------------|----------------------|-------|
| Age, years | 60.70±16.41 | 60.19±12.47 | 0.893 |
| Sex | | | |
| Male | 26 (96.3) | 34 (91.9) | 0.632 |
| Female | 1 (3.7) | 3 (8.1) | |
| BMI, kg/m ² | 30.18±4.84 | 31.63±8.15 | 0.416 |
| Height, cm | 173.00±6.50 | 168.81±11.62 | 0.096 |
| Weight, kg | 89.26±16.81 | 91.68±30.39 | 0.710 |
| Neck circumference, cm | 41.00±2.01 | 39.98±2.27 | 0.067 |
| AHI, n/h | 29.11±32.06 | 27.35±28.17 | 0.738 |
| History of clinical records | | | |
| History of DM | 11/27 (40.7) | 16/37 (43.2) | 0.841 |
| History of HTN | 8/27 (29.6) | 16/37 (43.2) | 0.306 |
| History of HLP | 5/27 (18.5) | 9/37 (24.3) | 0.761 |
| History of CHF | 16/27 (59.3) | 11/37 (31.4) | 0.040 |
| History of IHD | 16/27 (59.3) | 9/37 (24.3) | 0.009 |
| Smoking | 9/27 (33.3) | 21/37 (56.8) | 0.079 |
| Opioid use | 17/27 (63) | 24/37 (64.9) | 0.876 |

Data expressed as n/N (%) or mean±SD. SD: Standard deviation, AHI: Apnea-Hypopnea Index, BMI: Body mass index, DM: Diabetes mellitus, HTN: Hypertension, CHF: Congestive heart failure, IHD: Ischemic heart disease, HLP: Hyperlipidemia

Table 3: Demographics and baseline characteristics of responsive patients versus nonresponsive patients to continuous positive airway pressure + O₂

| Characteristics | Responsive (n=13) | Nonresponsive (n=24) | P |
|-----------------------------|-------------------|----------------------|-------|
| Age, years | 60.38±6.01 | 60.08±14.99 | 0.945 |
| Sex | | | |
| Male | 10 (76.9) | 24 (100) | 0.037 |
| Female | 3 (23.1) | 0 | |
| BMI, kg/m ² | 32.96±5.81 | 30.90±9.21 | 0.471 |
| Height, cm | 170.23±9.62 | 168.04±12.70 | 0.591 |
| Weight, kg | 96.38±23.90 | 89.13±33.58 | 0.496 |
| Neck circumference, cm | 41.01±2.56 | 39.60±2.19 | 0.086 |
| AHI, n/h | 26.20±7.02 | 33.40±33.29 | 0.020 |
| History of clinical records | | | |
| History of DM | 7/13 (53.8) | 9/24 (37.5) | 0.489 |
| History of HTN | 9/13 (69.2) | 7/24 (29.2) | 0.036 |
| History of HLP | 3/13 (23.1) | 6/24 (25) | 0.896 |
| History of CHF | 1/13 (7.7) | 10/24 (43.5) | 0.034 |
| History of IHD | 1/13 (7.7) | 8/24 (33.3) | 0.119 |
| Smoking | 8/13 (61.5) | 13/24 (54.2) | 0.739 |
| Opioid users | 6/13 (46.2) | 18/24 (75) | 0.148 |

Data expressed as n/N (%) or mean±SD. SD: Standard deviation, AHI: Apnea-Hypopnea Index, BMI: Body mass index, DM: Diabetes mellitus, HTN: Hypertension, CHF: Congestive heart failure, IHD: Ischemic heart disease, HLP: Hyperlipidemia

heart failure (HF), stroke (cerebrovascular accident), atrial fibrillation (AF), renal failure (chronic kidney disease), and taking medications (e. g., long-acting opiates).^[31,32]

Many studies have reported that opioid use is common in CSA patients and this group of patients is at risk of HF.^[33,34]

The results indicated that of 64 patients; CPAP, CPAP + O₂, and BIPAP therapies were effective in 42.2%, 20.3%, and 28.1% of patients, respectively. Ultimately, 9.2% of patients showed no response to any therapies in this study and were discharged with only oxygen administration.

Chowdhuri *et al.* suggested a 50% response to CPAP therapy as the most response to treatment using a staged protocol of CSA therapy. Hence, CPAP was considered as the first option for treatment. In addition, CPAP + O₂ were effective in 35% of cases.^[34]

Kasai *et al.* stated that ASV can result in more appropriate than CPAP in patients with concomitants of OSA and CSR-CSA.^[35]

On the other hand, evaluation of the condition of patients with respect to their response to therapies in this study showed that the majority of responsive patients to CPAP had the histories of CHF and IHD while patients with a history of HTN were responsive to CPAP + O₂. The younger patients with the histories of CHF and IHD were also responsive to BIPAP, although six nonresponsive patients to any therapies aged >70 years with a lower BMI and the highest AHI compared to others as well as the histories of CHF and IHD. Therefore, age accompanied by other risk factors such as CHF and IHD may reduce the effectiveness of the treatment.

In this regard, some studies have revealed that using supplemental O₂ can lead to decreased frequencies of CSA, especially in patients with hypoxia. Furthermore, for CSR, and the proper control of CHF in some patients; using CPAP with or without supplemental O₂ has been recommended.^[21]

In contrary to this study, other studies suggested that nonresponsive patients compared to that of the responsive patients to CPAP can show lower PaCO₂ but higher BNP levels longer CSR-CSA duration, more frequent incidence of AF as well as higher AHI. Accordingly, they believe that it is more likely that patients with more severe HF or CSR show no response to CPAP therapy.^[18,36]

Table 4: Demographics and baseline characteristics of responsive patients versus nonresponsive patients to bi-level positive airway pressure

| Characteristics | Responsive (n=18) | Nonresponsive (n=6) | P |
|-----------------------------|-------------------|---------------------|--------|
| Age, years | 56.28±15.50 | 71.50±2.74 | 0.028 |
| Sex | | | |
| Male | 18 (100) | 6 (100) | - |
| Female | 0 (0) | 0 (0) | |
| BMI, kg/m ² | 32.01±10.45 | 27.60±1.09 | 0.321 |
| Height, cm | 169.00±14.54 | 165.17±3.12 | 0.534 |
| Weight, kg | 93.83±30.84 | 75.00±21.08 | 0.243 |
| Neck circumference, cm | 40.81±2.34 | 39.02±2.25 | 0.116 |
| AHI, n/h | 33.64±36.12 | 32.67±25.72 | 0.378 |
| History of clinical records | | | |
| History of DM | 6/18 (33.3) | 3/6 (50) | 0.635 |
| History of HTN | 7/18 (38.9) | 0/6 (0) | 0.130 |
| History of HLP | 3/18 (16.7) | 3/6 (50) | 0.139 |
| History of CHF | 4/18 (23.5) | 6/6 (100) | 0.002 |
| History of IHD | 2/18 (11.1) | 6/6 (100) | <0.001 |
| Smoking | 10/18 (55.6) | 3/6 (50) | 0.813 |
| Opioid users | 15/18 (83.3) | 3/6 (50) | 0.140 |

Data expressed as n/N (%) or mean±SD. SD: Standard deviation, AHI: Apnea-Hypopnea Index, BMI: Body mass index, DM: Diabetes mellitus, HTN: Hypertension, CHF: Congestive heart failure, IHD: Ischemic heart disease, HLP: Hyperlipidemia

Table 5: Demographics and baseline characteristics of individuals with response to the protocol

| Characteristics | CPAP (n=27) | CPAP + O ₂ (n=13) | BIPAP (n=18) | O ₂ (n=6) |
|-----------------------------|-----------------------------|------------------------------|----------------------------|----------------------------|
| Age, years | 60.70±16.41 | 60.38±6.01 [‡] | 56.28±15.50 [‡] | 71.50±2.74 ^{‡,‡} |
| Sex, male (n=60) | 26/60 (43.3) | 10/60 (16.7) | 18/60 (30) | 6/60 (10) |
| BMI, kg/m ² | 30.18±4.84 [‡] | 32.96±5.81 [‡] | 32.01±10.45 | 27.60±1.09 ^{*,†} |
| Height, cm | 173.00±6.50 [‡] | 170.23±9.62 [‡] | 169.00±14.54 | 165.17±3.12 ^{*,†} |
| Weight, kg | 89.26±16.81 [‡] | 96.38±23.90 [‡] | 93.83±30.84 | 75.00±21.08 ^{*,†} |
| Neck circumference, cm | 41.00±2.01 | 41.01±2.56 | 40.81±2.34 | 39.02±2.25 |
| AHI, n/h | 29.11±32.06 | 26.20±7.02 [‡] | 32.64±36.12 | 33.67±25.72 [‡] |
| History of clinical records | | | | |
| History of DM (n=27) | 11/27 (40.8) | 7/27 (25.9) | 6/27 (22.2) | 3/27 (11.1) |
| History of HTN (n=24) | 8/24 (33.3) [†] | 9/24 (37.5) ^{*,‡} | 7/24 (29.2) | 0/24 (0) [†] |
| History of HLP (n=14) | 5/14 (35.8) | 3/14 (21.4) | 3/14 (21.4) | 3/14 (21.4) |
| History of CHF (n=27) | 16/27 (59.3) ^{‡,‡} | 1/27 (3.7) ^{*,‡} | 4/27 (14.8) ^{*,‡} | 6/27 (22.2) ^{‡,‡} |
| History of IHD (n=25) | 16/25 (64) ^{‡,‡} | 1/25 (4) ^{*,‡} | 2/25 (8) ^{*,‡} | 6/25 (24) ^{‡,‡} |
| Smoking (n=30) | 9/30 (30) | 8/30 (26.7) | 10/30 (33.3) | 3/30 (10) |
| Opioid users (n=41) | 17/41 (41.5) | 6/41 (14.6) [#] | 15/41 (36.6) [†] | 3/41 (7.3) |

*Significant level of comparison versus CPAP, [†]Significant level of comparison versus CPAP + O₂, [‡]Significant level of comparison versus BIPAP, [#]Significant level of comparison versus O₂. Data expressed as n/N (%) or mean±SD. SD: Standard deviation, AHI: Apnea-Hypopnea Index, BMI: Body mass index, DM: Diabetes mellitus, HTN: Hypertension, CHF: Congestive heart failure, IHD: Ischemic heart disease, HLP: Hyperlipidemia, BIPAP: Bi-level positive airway pressure, CPAP: Continuous positive airway pressure

While the effect of CPAP on CSA was supported by many studies,^[6,37,38] the strongest effect of CPAP was identified in CSA patients related to HF.^[23] The CPAP therapy could result in restoration of upper airway patency as well as stabilization of the respiratory control system. CSA usually as cycles of apnea/hypopnea in association with obstructive episodes.

The instability after apnea can be a multifactorial phenomenon.^[39] CSA may lead to narrowing or occlusion of pharyngeal airway.^[39,40] Therefore, opening on the airway, overcoming tissue adhesion force and gravitational forces may be required to spontaneous breathing resumption.^[41]

Moreover, comparison of baseline and clinical characteristics among the responsive patients to CPAP, CPAP + O₂, and BIPAP clarified the higher responsiveness to CPAP in CSA patients with the histories of HTN, CHF, and IHD compared to that of the other therapies (CPAP + O₂, BIPAP). In addition, using supplemental oxygen with CPAP could be more effective in patients with the history of HTN, compared to CPAP alone but overall, about other factors, no significant difference was observed compared to CPAP. In addition, most responsive patients to BIPAP were of younger patients with least risk factors of CSA.

In line with this study, Krachman *et al.* showed the equal effectiveness of oxygen therapy and nasal CPAP therapy in decreasing the AHI among CHF patients with CSR.^[42]

Furthermore, Dohi *et al.* suggested that the effectiveness of BIPAP in nonresponsive patients to CPAP equals to the effectiveness of CPAP in responsive patients to CPAP and BIPAP led to immediate decrease in CSR with CSA (CSR-CSA) and improvement of long-term LV function. Hence, BIPAP can be as an effective option for patients with HF and CSR-CSA, particularly when they are nonresponsive to CPAP.^[8]

As mentioned above, the effects of CPAP on CSA follows a sequence. First, restoring upper airway patency leads to ventilator overshoot damping and subsequent hypocapnia migration followed by the increased nocturnal PaCO₂ maybe with ventilator overshoot dampening as well as hypocapnia^[43] and increased lung volume.^[44]

In the newborn lamb, Naughton *et al.* have suggested stabilized chemoreflex control of the respiratory system with increased lung volume and decreased loop gain due to CPAP.^[45]

Furthermore, improved cardiac output,^[46] as well as circulation time, can play an important role in stabilizing the breath in patients with CHF. Among non-CHF patients, the response to PAP demonstrated that reduced propensity to CSA can be as a result of the restoration of upper airway patency, increased lung volume, unloading of respiratory muscles, improved oxygenation, and mitigation of intermittent hypoxia.

Among patients with the history of opioid use, the highest rates of desired response to the treatment were related to the therapies of CPAP and BIPAP with 41.5% and 36.6%, respectively, and the lowest rate was for CPAP + O₂.

In addition, some previous studies pointed out the highest prevalence of using opioids among CSA patients while narcotic was very common among them. These findings can be practical for patients and related professionals. Another study suggested narcotic use as the more common risk factor than HF.^[4] PAP with oxygen therapy was identified as an effective therapy in CSA with opioid use and if CPAP alone was ineffective to eliminate CSA, it can be useful as an alternative option.

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. They found that narcotic use was a more common risk factor for CSA than HF.^[37] 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.

Finally, it should be noted that the validity as well as generalizing of study will be proved by the larger population. Therefore, one of the limitations of this study was using a small sample. In addition, lack of follow-up of patients for the next 1–6 months after the treatment was another limitation. Hence, it is recommended that further studies with similar protocol take into the account of long-term follow-up and two-by-two comparisons of therapeutic approaches separately to achieve the stronger evidence with a sufficient sample size.

Conclusion

According to the results of this study CPAP and BIPAP are the therapeutic approaches that are mostly effective to CSA in patients having the histories of HF and opioid use, but it could be also reliable in some conditions to use CPAP + O₂, but it requires further studies to be more clarified.

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Conflicts of interest

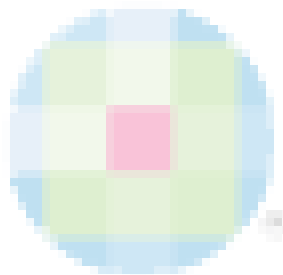
There are no conflicts of interest.

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