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ORIGINAL ARTICLE

Obstructive sleep apnea symptoms beyond sleepiness and snoring: effects of nasal APAP therapy

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Abstract
Objective The purpose of this study was to evaluate the prevalence and assess the response to nasal automatic positive airway pressure (APAP) therapy of less typical symptoms in patients diagnosed with obstructive sleep apnea (OSA), like fatigue, gasping, nocturia, nocturnal sweating, morning headaches, heartburn, and erectile dysfunction.
Methods Ninety-eight male patients with moderate to severe OSA were included in the study (n=98). In the beginning of the study, an overnight sleep study was performed to all subjects using a five-channel recording device. Patients started APAP therapy with pre-determined minimum and maximum pressures of 4 and 15 cmH_20, respectively. The total Sleep Disorders Questionnaire was answered by all subjects before and 6 months after APAP therapy. Questions 4, 18, 23, 25, 58, 88, and 148 were used in this study. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) 17.0 software.
Results Subjects had a mean (SD) age of 55.1 (10.8) years and an average of 52.2 (21.4) apnea–hypopnea events per hour of sleep. At baseline, nocturia was the most prevalent symptom (38%), followed by nocturnal sweating (34%), gasping (30%), erectile dysfunction (25%), fatigue (23%), heartburn (15%), and morning headaches (10%). After 6 months of APAP therapy, a statistically significant reduction on the prevalence of all symptoms was observed, except for erectile dysfunction and morning headaches.
Conclusion The findings suggest that APAP therapy is effective in controlling the majority of OSA symptoms beyond sleepiness and snoring.

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Introduction

Obstructive sleep apnea (OSA) is the most prevalent sleep disorder [1] affecting 2.2–4.8% of men and 0.7–2.2% of women from 20 to 100 years [2–4]. It is characterized by periods of functional obstruction of the upper airway during sleep, resulting in decreases in arterial oxygen saturation (SpO_2) and transient arousals. The major symptoms associated with OSA are excessive daytime sleepiness and loud snoring [5–8]. Nasal continuous positive airway pressure (CPAP) has demonstrated to be a cost-effective treatment for these symptoms as well as for cardiovascular complications of OSA [6–10]. Recent studies report that nasal automatic positive airway pressure (APAP) has similar efficacy to CPAP in improving sleep quality and reducing daytime sleepiness, snoring, number of arousals, and apnea–hypopnea index (AHI) [11–16], while it may be more accepted by patients, increasing its compliance [14–16].

In OSA, other symptoms are also described, such as fatigue [17, 18], gasping [19], nocturia [20], nocturnal sweating [21, 22], morning headaches [23–26], heartburn [27–31], and erectile dysfunction [32–35]. Although these symptoms hold a great impact on the quality of life of patients with OSA, there are few studies on the prevalence and outcomes with CPAP therapy [36, 37]. Regarding the available studies, most of them have a follow-up period lower than 6 months or a small sample of OSA patients. To

our knowledge, reports on the effect of APAP therapy on such a variety of symptoms have not been published.

Therefore, the purpose of this study was to evaluate the prevalence of the symptoms described above and assess its response to 6 months of APAP therapy in patients diagnosed with OSA.

Methods

Study design

This trial was designed as a prospective study. All patients gave written informed consent to participate in the trial. The study protocol was approved by the Hospital Ethics Committee, and the study was performed in accordance with the guidelines of the Declaration of Helsinki and its current revision.

Subjects

One hundred and two male patients referred for suspected sleep disordered breathing to our Sleep Disordered Breathing outpatient clinic were included in the study. No patient with COPD, other sleep disorders, psychiatric or oncologic diseases was included. All patients presented moderate to severe OSA (AHI>20/h) confirmed by a domiciliary sleep study. All but four patients concluded the study (n=98). Those who failed to conclude the protocol complained of nocturnal APAP intolerance as the reason to quit.

Sleep study

An overnight sleep study was performed using a five-channel recording device (Alphascreen; Viasys, Yorba Linda, CA, USA). This device produces a computerized recording of variations in oronasal airflow (measured by nasal cannula), body position, wrist actimetry, pulse rate, and arterial oxygen saturation (measured by finger pulse oximetry). The device estimates the total sleep time from the wrist actimetry registry, eliminating those periods with high activity. It automatically calculates the number of apneas plus hypopneas per hour of estimated sleep time (automatic respiratory disturbance index), and it also provides information of desaturations >4% per hour of estimated sleep time and the cumulative percentages of sleep time under 90% oxygen saturation. In all cases, sleep technicians carried out a manual analysis of the recordings, by counting apnea (episodes of ≤20% of previous airflow with at least 10 s of duration) and hypopnea episodes (episodes showing 20% to 50% of the previous airflow, with at least 10 s of duration joined with a 4% dip in oxygen saturation), dividing the total number of these episodes by the sleep time in hours, thus obtaining the manual respiratory disturbance index according to established criteria [38].

Patients received APAP therapy through a nasal mask, by REMstar™ Auto (Respironics, Inc., Murrysville, PA, USA) device with pre-determined minimum and maximum pressures of 4 and 15 cmH_20, respectively. No humidifier was used during the study period.

Sleep disorders questionnaire

All patients answered the total Sleep Disorders Questionnaire [39] before and 6 months after APAP therapy. We used the answers to the questions number 4 (nocturia), 18 (heartburn), 23 (gasping), 25 (nocturnal sweating), 58 (fatigue), 88 (morning headaches), and 148 (erectile dysfunction) to perform this study. Answers were measured on a 5-point Likert scale (1, never; 2, rarely; 3, sometimes; 4, usually; 5, always). A patient was considered to be symptomatic if the response was 4 or 5.

Statistical analysis

Data analysis was performed with the Statistical Package for the Social Sciences (SPSS, Inc., Chicago, IL, USA) 17.0 software. Baseline characteristics were described using mean, standard deviation, minimum and maximum values. Differences between symptomatic and asymptomatic patients were compared for each symptom using independent t test and Mann–Whitney test. The evolution with APAP therapy was tested by the McNemar test for symptoms and paired t test for Epworth sleepiness score (ESS), weight, body mass index (BMI), and waist-to-hip ratio. A comparison of baseline characteristics and compliance data was made for each symptom between patients whose symptom resolved and those whose symptom persisted using independent t test and Mann–Whitney test. Statistical significance was set at $p<0.05$.

Results

Ninety-eight male patients (n=98) with a mean age of 55.1 years were included in the statistical analysis, 16 (16.3%) with moderate and 82 (83.7%) with severe OSA. The subjects had an average of 52.2 apnea–hypopnea events per hour of sleep with a minimum nocturnal SpO_2 of 70.8%, an oxygen desaturation index of 47.3 per hour, and an ESS of 12.3 (Table 1).

From the seven studied symptoms, nocturia was the most prevalent, affecting 38% of patients, followed by nocturnal sweating (34%), gasping (30%), erectile dysfunction (25%),

Table 1 Baseline characteristics of patients

	Number	Mean ± SD	Range
Age (years)	98	55.1±10.8	22.0–74.0
Weight (Kg)	98	94.4±15.0	67.0–140.0
BMI (Kg/m^2)	98	33.3±4.9	24.5–50.2
Waist-to-hip ratio	98	0.996±0.063	0.840–1.140
AHI (events/hour)	98	52.2±21.4	20.2–105.8
Epworth sleepiness score	96	12.3±5.5	1.0–24.0
Minimum nocturnal SpO_2 (%)	95	70.8±9.3	46.0–89.0
Nocturnal ODI (events/hour)	92	47.3±23.5	7.2–102.0

BMI body mass index, *AHI* apnea–hypopnea index, *SpO_2* saturation of peripheral oxygen, *ODI* oxygen desaturation index

fatigue (23%), heartburn (15%), and morning headaches (10%).

Patients with fatigue at baseline were younger ($p<0.001$) and had an average of 5.2 more points on the ESS ($p<0.001$) and less weight ($p=0.019$) than patients with no fatigue complaints. On the other hand, patients with morning headaches had lower minimum nocturnal SpO_2 ($p=0.026$) and higher weight ($p=0.036$) and BMI ($p=0.015$). No significant differences at baseline characteristics were observed between groups for the other five symptoms.

APAP compliance was good with an average use of 5.9 h per night during 171.2 days which represents 88.5% of usage (Table 2).

After APAP therapy, a significant reduction was observed on the prevalence of all symptoms, except for erectile dysfunction and morning headaches, in which the reduction was not statistically significant (Table 3). Regarding the patients that were symptomatic at baseline, only 13 (13.7%) remained with nocturia, 8 (8.2%) with nocturnal sweating, 2 (2.1%) with fatigue, 1 (1.0%) with gasping and morning headaches, and none with heartburn after APAP therapy (Table 4).

Patients whose nocturia persisted were heavier ($p=0.033$) than those in whom the symptom resolved, while patients whose nocturnal sweating persisted were younger ($p=0.044$) and had a higher AHI ($p=0.009$) than those that showed a nocturnal sweating resolution.

A significant mean reduction of the ESS on more than 7 points ($p<0.001$) was also verified (Table 5). During the 6 months of treatment, body weight and BMI did not change significantly, though waist-to-hip ratio decreased ($p=0.021$) (Table 6).

Table 2 Nasal automatic positive airway pressure data

	Number	Mean ± SD	Range
Total days of use (days)	95	171.2±44.9	20.0–325.0
Total days of use (%)	95	88.5±17.4	12.2–100.0
Hours per night of use (hours/night)	96	5.9±1.4	1.5–8.5
Non-compliant (<4 h/night)	9	3.0±0.7	1.5–3.6
90th percentile of airway pressure (cmH_20)	89	10.1±2.3	5.9–17.6

Discussion

Our findings indicate that other symptoms besides excessive daytime sleepiness and loud snoring are present in OSA patients and can also benefit from APAP therapy. It is recognized that the present study has some limitations. Firstly, the study design does not include a control group, but it was considered that to withhold APAP therapy to previously diagnosed OSA patients would raise ethical issues. Secondly, the evaluation of the presence or absence of a symptom was based on a subjective answer to a questionnaire. However, an objective measure could not be applied to all symptoms, the used questionnaire being a uniform and internationally validated approach. Nevertheless, the homogeneity of the symptomatic and asymptomatic groups, the good APAP compliance, and the follow-up length contribute to the strength of our findings. Another limitation of our study was that we could not confirm objectively the degree of correction of AHI after APAP therapy and so cannot exclude that residual AHI could explain symptom maintenance in some patients.

Table 3 Prevalence of symptoms before and after nasal automatic positive airway pressure therapy

	Number	Pre (%)	Post (%)	McNemar test(p value)
Fatigue	97	23	2	<0.001
Gasping	97	30	2	<0.001
Nocturia	95	38	24	0.024
Nocturnal sweating	97	34	12	<0.001
Morning headaches	97	10	3	0.065
Heartburn	96	15	1	0.001
Erectile dysfunction	97	25	18	0.143

Table 4 Patients' condition after nasal automatic positive airway pressure therapy

	Symptomatic, *n* (%)		Asymptomatic, *n* (%)	
	Symptomatic at baseline	Asymptomatic at baseline	Symptomatic at baseline	Asymptomatic at baseline
Fatigue	2 (2.1)	0 (0.0)	20 (20.6)	75 (77.3)
Gasping	1 (1.0)	1 (1.0)	28 (28.9)	67 (69.1)
Nocturia	13 (13.7)	10 (10.5)	24 (25.3)	48 (50.5)
Nocturnal sweating	8 (8.2)	4 (4.1)	25 (25.8)	60 (61.9)
Morning headaches	1 (1.0)	2 (2.1)	9 (9.3)	85 (87.6)
Heartburn	0 (0.0)	1 (1.0)	14 (14.6)	81 (84.4)
Erectile dysfunction	12 (12.4)	5 (5.2)	12 (12.4)	68 (70.1)

Nocturia was the most prevalent studied symptom with 38% affected patients, similar to previous studies [20]. Although a significant reduction was observed, it was not as strong as expected [37, 40] since 13 (13.7%) patients remained symptomatic, and 10 (10.5%) reported nocturia as a new symptom at follow-up. Other concomitant pathologic processes, not assessed in this study, such as prostatic hyperplasia or other urologic diseases, or the simultaneous use of diuretics could explain this evolution.

Another frequent symptom was nocturnal sweating (34%). This finding was expected as it is known that OSA patients have an autonomic dysfunction with an altered sudomotor function [21, 22]. It was observed that APAP therapy had a positive effect, reducing the affected patients to 12%.

Gasping is also a common reported symptom [19, 37] that affected 30% of patients. After the 6-month treatment, only one (1.0%) patient kept the symptom, and another one (1.0%) newly developed it. The patient who remained with gasping could have another sleep disorder, and a polysomnographic (PSG) study could be indicated. The new manifestation of the symptom in the second patient may be due to arousals in result of high pressures of the APAP device [11], and so, a PSG study could also clarify it.

The prevalence of fatigue (23%) was lower than previously reported [17, 18], but a significant symptomatic improvement was also found with only two (2.1%) patients complaining of fatigue at follow-up.

Although the exact relationship between OSA and gastroesophageal reflux (GER) is not completely clear, it is thought that the increase of the intrathoracic pressure that occurs in each apnea event contributes to GER [27–31]. Moreover, it is reported that CPAP therapy reduces GER symptoms [29–31, 37]. Our study confirmed these findings as none of the patients who initially reported heartburn remained symptomatic at follow-up.

Headache seems to be another prevalent symptom found in OSA patients, particularly morning headaches [23–26]. It appears that these are correlated with nocturnal oxygen desaturation [24, 26] which can explain that in our sample, symptomatic patients had lower minimum nocturnal SpO_2 than asymptomatic ones. In this study, 10% of patients initially reported morning headaches, with only three patients remaining symptomatic at the end of the study, one (1.0%) previously symptomatic and two (2.1%) with new complaints. The symptomatic patients at follow-up could be due to migraine or other neurologic or psychiatric diseases that were not investigated in this study.

Although a decrease in the prevalence of erectile dysfunction and morning headaches (from 25% to 18% and 10% to 3%, respectively) was observed, these were the only studied symptoms where a statistically significant change was not found. Previous studies reported a higher prevalence of sexual dysfunctions on OSA patients, particularly in severe OSA [32–34]. Some concluded that CPAP therapy alone may improve erectile function in selected patients [33], while a randomized control trial could not establish a significant effect [34]. Other studies

Table 5 Epworth sleepiness score before and after nasal automatic positive airway pressure therapy

	Number	Pre (mean ± SD)	Post (mean ± SD)	Paired *t* test (*p* value)
Epworth sleepiness score	95	12.3±5.4	5.0±4.1	<0.001

Table 6 Weight, body mass index, and waist-to-hip ratio before and after nasal automatic positive airway pressure therapy

	Number	Pre (mean ± SD)	Post (mean ± SD)	Paired *t* test (*p* value)
Weight (Kg)	98	94.4±15.0	94.1±14.5	0.545
BMI (Kg/m^2)	97	33.3±4.9	33.2±4.8	0.529
Waist-to-hip ratio	98	0.996±0.063	0.986±0.060	0.021

BMI body mass index

reported that these patients may benefit from a combination treatment of CPAP and sildenafil [41, 42].

Differences of baseline characteristics and compliance data between patients whose symptom resolved and those whose symptom persisted were only studied for nocturia and nocturnal sweating. The same test was not performed for each of the other symptoms because of the low number of subjects who remained symptomatic. It was not possible to perform a regression analysis for any symptom in order to study baseline characteristics and compliance data of patients who better responded to APAP therapy in comparison to those who did not. The size of each group did not allow such statistical analysis.

In summary, our findings indicate that OSA patients can benefit from APAP therapy in the treatment of a wide range of symptoms besides excessive daytime sleepiness and loud snoring. In this study, the symptoms where APAP was more effective were fatigue, gasping, and heartburn with only four patients affected with these symptoms 6 months after therapy. We suggest that even in the absence of excessive daytime sleepiness, APAP therapy should be considered as it can the improve quality of life of non-sleepy OSA patients.

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Conflict of interest The authors declare that they have no conflict of interest.

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