Accepted Manuscript

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PII: S1389-9457(17)30406-9

DOI: 10.1016/j.sleep.2017.09.032

Reference: SLEEP 3543

To appear in: *Sleep Medicine*

Received Date: 2 August 2017

Revised Date: 7 September 2017

Accepted Date: 20 September 2017

Please cite this article as: Baratta F, Pastori D, Bucci T, Fabiani M, Fabiani V, Brunori M, Loffredo L, Lillo R, Pannitteri G, Angelico F, Del Ben M, Long-Term prediction of adherence to Continuous positive air pressure therapy for the treatment of moderate/severe obstructive sleep apnea syndrome, *Sleep Medicine* (2017), doi: 10.1016/j.sleep.2017.09.032.

LONG-TERM PREDICTION OF ADHERENCE TO CONTINUOUS POSITIVE AIR PRESSURE THERAPY FOR THE TREATMENT OF MODERATE/SEVERE OBSTRUCTIVE SLEEP APNEA SYNDROME.

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Running title: OSAS and adherence to CPAP

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Declarations

All the Authors have seen and approved the manuscript. All the Authors did not receive financial support and have no conflict of interest in relation to the manuscript

Number of tables: 2 **Number of figures:** 0 **Abstract word count:** 250

Manuscript word count: 2144

ABBREVIATIONS

OSAS: obstructive sleep apnoea syndrome; CPAP: continuous positive air pressure;

AHI: apnoea/hypopnoea index; MACCE: major cardiovascular and cerebrovascular event

SUMMARY

Background

Continuous positive airway pressure therapy (CPAP) is a highly effective treatment for obstructive sleep apnoea syndrome (OSAS). However, poor adherence is a limiting factor and a significant proportion of patients are unable to tolerate CPAP. Aim of this study was to determine predictors of long-term non-compliance with CPAP.

Methods

CPAP treatment was prescribed to all consecutive patients with moderate or severe OSAS (AHI ≥15 events/h) (n=295) who underwent a full-night CPAP titration study at home between February 1, 2002 and December 1, 2016. Adherence was defined as CPAP use for at least 4 hours per night and 5 days per week. Subjects had periodical follow-up visits including clinical and biochemical evaluation and assessment of adherence to CPAP.

Results

Median follow-up observation was 74.8 (24.2/110.9) months**.** The percentage of OSA patients adhering to CPAP was 41.4% (42.3% in males and 37.0% in females) and prevalence was significantly higher in severe OSAS as compared to moderate (51.8% vs 22.1%; p<0.001; respectively). At multivariate analysis, lower severity of OSAS (HR=0.66; CI95 0.46-0.94) p<0.023), cigarette smoking (HR=1.72; CI95 1.13-2.61); p=0.011) and previous cardiovascular events (HR=1.95; CI95 1.03-3.70; p=0.04) were the only independent predictors of long-term non-adherence to CPAP after controlling for age, gender and metabolic syndrome.

Conclusions

in our cohort of patients with moderate/severe OSAS who were prescribed CPAP therapy, long-term compliance to treatment was present in less than half of the patients. Adherence was positively associated with OSAS severity and negatively associated with cigarette smoking and previous cardiovascular events at baseline.

KEY WORDS

Obstructive sleep apnoea syndrome; continuous positive air pressure; adherence to treatment;

1. INTRODUCTION

Obstructive Sleep Apnoea (OSA) is a disorder characterized by daytime sleepiness and repeated breathing cessations during sleep, which can result in cycles of hypoxia, negative intrathoracic pressure and arousals with potentially serious cardiovascular consequences [1-5].

Continuous positive airway pressure therapy (CPAP) is a highly effective treatment for OSA and should be considered both first-line and gold-standard treatment for patients with all stages of OSAS [6-8]. CPAP improves quality of life and excessive daytime sleepiness and decreases sympathetic neural activity and blood pressure. Besides, the prescription of CPAP appears to reduce long-term CVD events[9] and total mortality, although negative results have been also reported and not all patients benefit from CPAP treatment even if they have a severe OSA [10, 11].

Adequate CPAP compliance is essential for achieving cardiovascular and metabolic benefits in patients with OSAS. However, poor adherence to CPAP is a significant limiting factor in treating OSA despite efforts to improve devices and educate patients especially during the early stages of treatment. In fact, failure to comply with CPAP therapy may occur in up to 25% to 50% patients with OSA and patient adherence to treatment frequently remains inadequate[12, 13]. A significant proportion of patients are unable to tolerate CPAP therapy, and frequently seek alternate treatment. A recent systematic literature review reported that the rate of CPAP adherence remained persistently low over twenty years of published data[14].

Various factors were evaluated in trying to predict compliance [15]. Some patients may refuse treatment without even initiating it, some eventually abandon therapy. Poor mask fit and discomfort, complaints of noise, interference with normal life and sexual functioning frequently induce low adherence. In fact, CPAP may induce nasal drying, congestion, rhinorrhea, sinusitis, and allergic reaction to the materials in the mask. Besides, the patient's age, gender, low socioeconomic status, overweight, obesity, comorbid conditions and smoking have been associated to poor compliance. By contrast, patients with a more severe OSA tend to be more compliant and their apnoea-hypopnea index (AHI) showed a relationship with improved compliance[16]. In particular, the balance between symptom severity pre-treatment and symptom relief with CPAP treatment is amongst the strongest predictors of CPAP compliance.

However, so far, no single factor has been consistently identified as predictive of adherence. Moreover, there are very few data on objectively assessed compliance with CPAP in large OSA cohorts and treatment adherence has been incompletely assessed in long-term follow-up studies.

Aim of this study was to determine predictors of long-term non-compliance with CPAP in a large cohort of moderate and severe newly diagnosed OSA patients during a six-year follow-up.

2. MATERIAL AND METHODS

2,1 Subjects

The initial population consisted of 483 patients who attended consecutively our outpatient metabolic clinic because of suspected metabolic disorders with heavy snoring and possible OSAS between February 1, 2002 and December 1, 2016. Patients had a complete clinical and biochemical work-up including unattended overnight home polysomnography. The device recorded nasal and oral airflow, chest and abdominal movement, pulse oximetry, body position and snoring noise. The sleep recordings were downloaded to a computer and scored by a principal investigator. OSAS severity was quantified as the number of apnea/hypopnea events/h during sleep study (AHI). Patients were categorized as follows; snorers without OSAS with AHI <5 events/h; mild OSA with AHI 5-14 events/h; moderate/severe OSA with AHI ≥15 events/h. Information on previous cardiovascular and cerebrovascular disease (MACCE) defined as history of physician-diagnosed heart failure, angina, myocardial infarction, stroke and coronary revascularization, was obtained for each participant. Finally, all the therapies and the number of tablets consumed every day were recorded. A detailed description of screening procedures was previously reported[17, 18].
CPAP treatment was prescribed to all consecutive patients with moderate or severe OSAS (AHI ≥15 events/h) (n=301) who underwent a full-night CPAP titration study at home using an automated pressure setting device. Written consent was obtained from all subjects before the study and the study conforms to the ethical guidelines of the 1975 Declaration of Helsinki. The research protocol was approved by the University Department of Experimental Medicine and Pathology scientific board in 2002.

2.2 Assessment of compliance to CPAP

Adherence to CPAP was arbitrarily defined as CPAP use for at least 4 hours per night and 5 days per week, although there is no definite agreement on frequency and duration of optimal CPAP treatment. Subjects had periodical follow up visits including clinical and biochemical evaluation and assessment of adherence to CPAP. Besides, patients were contacted by telephone by a single investigator who was not part of the clinical team between December 1, 2016 and May 31, 2017. First, they were questioned if they started treatment and were still using their CPAP device. Those adhering to therapy were asked to estimate the number of nights per week, and hours per night CPAP was being used. Those who abandoned therapy and those who never initiated treatment were questioned about their reasons for non-adherence.

2.3 Statistical analysis

Continuous variables are reported as mean $\pm$ standard deviation or median with interquartile range. Continuous variables were analyzed by Student's t-test or Mann-Whitney test depending on their

distribution. Dichotomous variables are reported as numbers and percentages. Differences were tested using the χ2 test for categorical variables. All tests were two-tailed and only *p* values <0.05 were considered as statistically significant. Univariate and multivariate Cox regression analyses using a forward selection was used to calculate the unadjusted and adjusted relative hazard ratios (HR) of predictors for discontinuation of CPAP therapy. Analyses were carried out with SPSS V.18.0 (Armonk, USA).

3. RESULTS

Complete information on CPAP compliance was available for 301 subjects with moderate or severe OSA. Median follow-up observation was 74.8 (24.2/110.9) months**.** The percentage of OSA patients adhering to CPAP was 41.4% (42.3% in males and 37.0% in females) and prevalence was significantly higher in severe OSAS as compared to moderate OSAS (51.8% vs 22.1%; p<0.001; respectively). Severe OSAS had a better compliance than moderate both in males (53.4% vs 20.0%; p<0.001; respectively) and females (43.3% vs 29.2%; p=0.39, respectively). Adherers and non-adherers had similar age at the time of diagnosis of OSA (57.1 $\pm$ 10.5 years vs 57.0 $\pm$ 10.9 years, respectively).

Clinical and biochemical characteristics of adherers and non-adherers are reported in Table 1. At baseline examination, the indices of OSA severity – AHI and ODI- were significantly increased, while $SatO_2$ was decreased in patients with good compliance. In the same group, the indexes of central obesity and serum triglycerides tended to be higher. Prevalence of cigarette smokers was about double in non-adherers as compared to adherers (20.8% vs 10.7%; p=0.026, respectively). No statistically significant differences were observed for the prevalence of diabetes, arterial hypertension, metabolic syndrome, statin use and previous MACCE at the basal examination.

Table 2 reports the results of univariate and multivariate Cox regression analyses of predictors of CPAP discontinuation. In the Cox analysis adjusted for possible confounders, lower severity of OSAS (HR=0.66; CI95 0.46-0.94) p<0.023), cigarette smoking (HR=1.72; CI95 1.13-2.61); p=0.011) and previous MACCE (HR=1.95; CI95 1.03-3.70; p=0.04) were the only independent predictors of long-term non-adherence to CPAP after controlling for age, gender and metabolic syndrome.

The main reasons for poor adherence were self-reported mask-related and pressure-related side effects, nasal symptoms, and psychological and social factors. Other frequent reasons for stopping treatment were surgical management or weight loss with consequent improvement of OSA.

4. DISCUSSION

There are few data on the long-term assessment of adherence to CPAP in OSAS patients and no single factor so far, has been consistently identified as predictive of long-term adherence. Moreover, studies on CPAP adherence in Mediterranean countries are limited.

In this study, about 40% of patients with moderate or severe OSAS, who were prescribed CPAP therapy, were still on treatment after an average six-year follow-up observation when non-adherence was defined as a mean of ≤4 hours of use per night and 5 days per week. This is in agreement with previous studies showing a compliance to treatment in about 30-80% of patients depending on the definition criteria for adherence and the duration of follow-up [12, 13].
Compliance was higher in patients with more severe OSAS, where half of those with AHI >30 events/hour were good adherers to CPAP treatment. Those with a higher AHI tended to be more compliant both in males and females and in all ages.

Our findings are in keeping with the results of some studies reporting a strong relationship between adherence to CPAP and the severity of sleep-disordered breathing. So, in a large prospective study performed in US, disease severity rather than patients' symptoms or complaints, seemed to play a role in the quality of compliance to treatment[19]. Moreover, in a large cohort of OSAS patients, severity of sleep-disorder breathing assessed as number of oxygen desaturation events, was the only clinical condition associated to long-term adherence[20]. Similar findings were reported in a retrospective chart review of 369 patients with moderate or severe OSAS who were recommended to receive CPAP: at one year, older male patients with higher AHI values were more adherent to CPAP[21]. In addition, a highly significant correlation of compliance with the initial AHI was found in a small study of OSA patients at 14 months on the average after starting treatment with CPAP[22]. Moreover, an association between compliance to treatment and severity of OSAS was also reported in a retrospective study evaluating 156 patients with OSAS were patients with a higher AHI were those who better adhered to long-term treatment with CPAP[23]. Finally, in a cross-sectional study of 138 OSA patients performed in Lebanon, higher oxygen desaturation index at baseline was associated with a better short-term CPAP adherence [24].

Based on these data, it could be speculated that patients with more severe OSAS have a better compliance. However, other studies showed that measures of OSA severity *per se* appear poorly associated with CPAP. In fact, in a short-term study of 59 patients (42 men) with metabolic syndrome and OSA, mask leak was the only independent predictor of CPAP compliance at the 8-week follow-up visit [25]. Moreover, in another study of 60 patients who were recommended CPAP therapy, one-year compliance was associated with higher body mass index, higher Epworth sleepiness scale score, history of witnessed apnea, and reduction in daytime sleepiness with CPAP therapy, while OSAS severity was not associated [26]. In conclusion, based on the above data, it is difficult to conclude that the severity of OSA at the initial sleep study always predicts long-term use of CPAP.

In our study, cigarette smoking was an independent predictor of non-compliance to CPAP. This is in keeping with the results of an 8-years retrospective chart review of older male patients prescribed CPAP therapy for OSA, where cigarette smoking was associated with non-compliance [27]. However, these findings are in contrast with data from a small prospective cohort study where cigarette smoking, alcohol intake, concurrent medication use and work patterns were not important predictors of short-term CPAP use [28].

Previous MACCE in our study were independent predictors of worse adherence to CPAP. Similar findings have been reported in previous studies on the compliance to CPAP in patients with concomitant OSAS and cardiovascular disease, where adherence decreased progressively over time [29, 30]. These findings raise the possibility that patients with OSAS and CVD may benefit less from CPAP therapy as they are more concerned with cardiovascular disease.

There are several strengths and limitations of this study that merit to be discussed. Major strength of this study is the duration of follow-up that is greater than that of most published studies. Unattended home polysomnography should be considered as a major limitation of this study, although an excellent correlation with the results of attended polysomnography has been reported [31]. A further limitation is that we used telephone survey to assess the compliance of CPAP therapy in half of the patients because almost all of the patients used CPAP units not capable to keep record of night use. This may have ended with a possible selection bias since patients lie a lot when asked about compliance and there may be discrepancies between what patients think they do at night and what they really do [32]. Moreover, the studied population was taken only from an outpatient metabolic clinic and non-snorers and patients without metabolic disorders were probably not included in the study. Finally, CPAP compliance was not assessed in patients with mild OSAS.

In summary, in our cohort of patients with moderate or severe OSAS who were prescribed CPAP therapy, long-term compliance to treatment was present in less than half of the patients. Adherence was positively associated with severity of OSAS and negatively associated with cigarette smoking and previous MACCE at the initial examination.

FUNDING This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgements

We would like to thank nurse Daniela Salzano for her skillful collaboration.

Author contributions:

F Angelico, M Del Ben, M Fabiani: study concept and design; interpretation of data; drafting of the manuscript; critical revision of the manuscript.

F Baratta, T Bucci, D Pastori: study concept and design; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript.

V Fabiani, M Brunori, G Pannitteri: acquisition and interpretation of data; drafting of the manuscript; critical revision of the manuscript.

R Lillo, L. Loffredo: acquisition of data; drafting of the manuscript; critical revision of the manuscript.

F Angelico is the guarantor of the paper. All authors read and approved the final version of the manuscript.

Table 1. Clinical and biochemical characteristics of adherers and non-adherers to CPAP therapy

	Non-adherers to CPAP (n=178)	**Adherers to CPAP** (n=123)	***p***
Age (yrs)	57.0 ± 10.5	57.1 ± 10.9	0.944
AHI (events/h)	37.6 ± 20.4	45.7 ± 17.6	0.001
ODI (events/h)	34.7 ± 22.4	45.6 ± 21.3	0.000
Average $SatO_2$ (%)	92.3 ± 3.6	90.3 ± 7.8	0.007
BMI (kg/m^2)	32.9 ± 6.0	34.4 ± 8.8	0.099
Waist circumference (cm)	113.0 ± 13.6	116.2 ± 12.9	0.052
Hip circumference (cm)	114.2 ± 12.1	117.7 ± 11.9	0.022
Systolic blood pressure (mmHg)	135 ± 15	135 ± 15	0.455
Diastolic blood pressure (mmHg)	84 ± 10	83 ± 10	0.562
Total Cholesterol (mg/dl)	206.2 ± 42.3	196.7 ± 42.5	0.067
HDL Cholesterol (mg/dl)	45.7 ± 12.0	42.2 ± 9.9	0.012
LDL Cholesterol (mg/dl)	129.0 ± 35.8	121.1 ± 40.5	0.088
Triglycerides (mg/dl)	130.0 (92.0/180.0)	148.0 (102.5/205.0)	0.107
Fasting blood glucose (mg/dl)	103.4 ± 27.0	104.0 ± 26.1	0.835
Insulin (μU/ml)	20.9 ± 17.5	21.7 ± 16.9	0.748
HOMA-IR	3.9 ± 4.8	4.0 ± 5.5	0.831
Diabetes (%)	18.1	20.3	0.648
Hypertension (%)	69.1	73.0	0.513
Metabolic syndrome (%)	61.3	71.2	0.099
Cigarette smoking (%)	20.8	10.7	0.026
Statin use (%)	38.6	45.7	0.262
Polypharmacy (n. of pills/day)	2.5 (1.0/5.0)	4.0 (2.0/6.0)	0.001
Previous MACCE (%)	13.0	10.1	0.274

Table 2. Univariate and multivariate Cox regression analysis of predictors of CPAP discontinuation

	Univariate Analysis		**Multivariate Analysis**	
	HR (C.I. for HR)	*p*	HR (C.I. for HR)	*p*
Age (yrs)	1.007 (0.993-1.021)	0.331	1.008 (0.992-1.025)	0.331
Female gender	1.123 (0.762-1.656)	0.558	1.050 (0.664-1.661)	0.835
AHI (events/h)	0.989 (0.981-0.997)	0.007		
ODI (events/h)	0.993 (0.986-1.001)	0.081		
Average $SatO_2$ (%)	1.014 (0.975-1.055)	0.480		
Severe OSAS (%)	0.630 (0.461-0.862)	0.004	0.661 (0.463-0.945)	0.023
BMI (kg/m^2)	0.989 (0.962-1.016)	0.428		
Waist circumference (cm)	0.994 (0.982-1.006)	0.322		
Hip circumference (cm)	0.995 (0.982-1.009)	0.501		
Systolic blood pressure (mmHg)	0.992 (0.982-1.002)	0.134		
Diastolic blood pressure (mmHg)	0.987 (0.971-1.002)	0.093		
Total Cholesterol (mg/dl)	1.001 (0.997-1.004)	0.770		
HDL Cholesterol (mg/dl)	1.016 (1.003-1.030)	0.019		
LDL Cholesterol (mg/dl)	0.999 (0.995-1.003)	0.557		
Triglycerides (mg/dl)	1.000 (0.998-1.002)	0.991		
Fasting blood glucose (mg/dl)	1.001 (0.994-1.007)	0.868		
Insulin (µU/ml)	0.999 (0.990-1.007)	0.757		
Diabetes (%)	0.913 (0.610-1.367)	0.659		
Hypertension (%)	1.153 (0.801-1.659)	0.443		
Metabolic Syndrome (%)	0.802 (0.581-1.109)	0.182	0.757 (0.531-1.080)	0.125
Cigarette smoking (%)	1.655 (1.119-2.447)	0.012	1.723(1.133-2.619)	0.011
Statin use (%)	0.979 (0.698-1.372)	0.901		
Polypharmacy (n. of pills/day)	1.000 (0.938-1.066)	0.995		
Previous MACCE (%)	1.889 (1.114-3.204)	0.018	1.954 (1.030-3.705)	0.040

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HIGHLIGHTS

- CPAP is an effective treatment for obstructive sleep apnoea.
- Poor adherence to CPAP is a significant limiting factor in treating OSA
- Aim of this study was to determine predictors of long-term non-compliance
- Less than half of the patients were compliant during a six-year follow-up
- Adherence was positively associated with OSA severity, smoking and previous CVD