ORIGINAL ARTICLE

The impact of continuous positive airway pressure on cardiac arrhythmias in patients with sleep apnea

Paula Cornelia Varga (Gocan)[1,2], Horia Stefan Rosianu[1,2], Ştefan Cristian Vesa[3], Bianca Gergely Domokos Hancu[4,5], Ruxandra Beyer[1,2], Carmen Monica Pop[4,5]

[1]Department of Cardiology, "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, România, [2]Department of Cardiology, Heart Institute "Niculae Stancioiu," Cluj-Napoca, Romania, [3]Department of Pharmacology, Toxicology and Clinical Pharmacology, "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, România, [4]Department of Pulmonology, "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, România, [5]Pulmonology Clinic "Leon Daniello", Cluj-Napoca, Romania

Background: Obstructive sleep apnea (OSA) can lead to cardiac complications: brady and tachyarrhythmias and sudden cardiac death. Continuous positive airway pressure (CPAP) is the gold standard for the treatment of OSA. The present study aims to demonstrate the efficiency of CPAP in the treatment of cardiac arrhythmias in patients with OSA. The study also recorded the frequency of arrhythmias in patients with untreated OSA and assessed the association between the severity of OSA and the occurrence of arrhythmias. **Materials and Methods:** This is a prospective cohort study. Ninety-three patients with OSA were included, aged 60 (58–64) years, with female/male sex ratio of 1:4. They were subjected simultaneously to home respiratory polygraphy examination and Holter electrocardiogram monitoring, in two different stages: at diagnosis and at the 3-month checkup after CPAP treatment. The presence of supraventricular and ventricular arrythmias was noted. Respiratory parameter values were also recorded. **Results:** Statistically significant decrease in the occurrence of supraventricular ($P < 0.001$) and ventricular extrasystoles ($P < 0.001$), atrial fibrillation (AF) ($P = 0.03$), nonsustained ventricular tachycardia (NSVT) ($P = 0.03$), and sinus pauses ($P < 0.001$) was observed 3 months after treatment with CPAP, compared with baseline. The apnea–hypopnea index (AHI) was correlated with the ventricular extrasystoles ($r = 0.273$; $P = 0.008$). The ejection fraction of the left ventricle was inversely correlated with the episodes of NSVT ($r = -0.425$; $P < 0.001$). AF was associated with the longest apnea ($r = 0.215$; $P = 0.04$). Cardiac activity pauses were correlated with AHI ($r = 0.320$; $P = 0.002$), longest apnea ($r = 0.345$; $P = 0.01$), and oxygen desaturation index ($r = 0.325$; $P = 0.04$). **Conclusion:** The prevalence of cardiac arrhythmias in patients with OSA was reduced after 3 months of CPAP therapy. Cardiac arrhythmias were correlated with the severity of OSA.

Key words: Ambulatory, arrhythmias, cardiac, continuous positive airway pressure, electrocardiography, sleep apnea syndromes

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INTRODUCTION

There is a growing prevalence of obstructive sleep apnea (OSA) in the world, and data from the United States and Europe suggest that between 14% and 49% of middle-aged men suffer from clinically significant sleep apnea.[1] If left untreated, it can lead to very serious complications: brady and tachyarrhythmias and sudden cardiac death.

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Patients with sleep-related breathing disorders are prone to arrhythmias: sinus pauses, atrial fibrillation (AF), and ventricular disorders[2] due to an autonomic nervous system imbalance associated with hypoxemia, respiratory acidosis, and sleep apnea.[3]

OSA has acute and chronic effects on the cardiovascular system. The occurrence of systemic hypoxia and hypercapnia, the increase in negative intrathoracic pressure, and repeated awakenings during night are

Address for correspondence: Dr. Stefan Cristian Vesa, Department of Pharmacology, Toxicology and Clinical Pharmacology, "Iuliu Hatieganu" University of Medicine and Pharmacy, 23 Gheorghe Marinescu Street, 40033 Cluj-Napoca, România. E-mail: stefanvesa@gmail.com
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physiological mechanisms responsible for acute adverse cardiovascular consequences. Chronic effects of untreated sleep apnea are represented by disruption of the autonomic nervous system, activation of inflammation and oxidative stress with pro-atherogenic effects, vascular and endothelial dysfunction, and the onset of metabolic disorders. OSA then can contribute to the onset of cardiac arrhythmia, high blood pressure, heart failure, shock, myocardial ischemia, stroke, and pulmonary hypertension.[4]

Continuous positive airway pressure (CPAP) is the gold standard for the treatment of sleep apnea[5] and improves patient quality of life.[6] Treatment with CPAP abolishes episodes of sleep apnea and reduces sympathetic activity.[7] This decreases daytime sleepiness and augments cognitive function. A minimum of 3–4 h of treatment each night is required to achieve long-term benefits.[8]

The presence and complexity of tachycardia and bradycardia may influence morbidity, mortality, and quality of life for patients with OSA.[9]

The present study aims to demonstrate the efficacy of CPAP in the treatment of cardiac arrhythmias. The study also recorded the frequency of arrhythmias in patients with untreated sleep apnea and assessed the association between the severity of sleep apnea and the occurrence of cardiac arrhythmias.

MATERIALS AND METHODS

Study design and participants

This is a prospective cohort study. It was conducted from January 2016 to August 2016 at "Leon Daniello" Clinical Hospital of Pulmonology in Cluj-Napoca. The study included 93 patients diagnosed with OSA. The inclusion criteria were diagnosis of sleep apnea established by home sleep apnea testing with respiratory polygraphy; Epworth Sleepiness Scale (ESS) >10; age >18 years; signature of the informed consent; and patients had to undergo all the necessary investigations, to carry out the treatment (at least 6 h CPAP/night), and to return for the checkup after 3 months. Exclusion criteria were the following: inconsistent participation or study abandonment, refusal to undergo treatment, cardiac or pulmonary severe disease, and presence of cardiac pacemaker.

The approval of the Ethics Committee of the University of Medicine and Pharmacy "Iuliu Hatieganu" Cluj-Napoca as well as the informed consent of each patient was obtained in order to carry out the study.

Procedures for assessment of variables

The following data were collected: demographic data (age, gender, and urban/rural residence), social data (employed and retired), clinical data (body mass index [BMI], abdominal circumference, neck circumference, blood pressure, and pulse rate). Detailed patient history assessment was conducted to observe aspects related to hypertension, dyslipidemia, diabetes, sleep position, toxic working environment, consumption of alcohol, coffee, tobacco (for smokers, we noted the number of packs/year of smoking history), and medication. The following examinations were performed: biological samples (blood count, blood sugar, and lipid profile); pulmonary function tests; and electrocardiogram (ECG), echocardiography, and otorhinolaryngology examination. Echocardiography was performed using the Acuson X 300 Siemens device (Siemens AG, Germany). The following parameters were observed: left ventricle (LV), interventricular septum, posterior wall, left atrium, right ventricle; ejection fraction; diastolic function; the presence of kinetic disorders of valvular heart disease (a defect in one of the four heart valves: mitral, aortic, tricuspid, or pulmonary), of pulmonary hypertension and pericardial effusion.

Patients were diagnosed based on medical history and a specific questionnaire completed by each patient – ESS.[10] A certain score was given depending on each response. A total score ≥10 indicated mild sleepiness, whereas a total score >18 indicated severe daytime sleepiness.

Patients were subjected to home respiratory polygraphy examination simultaneously with Holter ECG monitoring (for 7 h – between 11 p.m. and 6 a.m.). Patients with an apnea–hypopnea index (AHI) >5 were included in the study. Depending on the AHI values, patients were divided based on the severity of sleep apnea into mild (AHI between 5 and 15/h), moderate (AHI between 15 and 30/h), and severe (AHI over 30/h).

The NOX T3 portable sleep monitor device (produced by Nox Medical USA) was used in the study. The following respiratory parameters were observed: the AHI, the total number of events (apnea and hypopnea), minimum oxygen saturation, average oxygen saturation, the longest apnea, and oxygen desaturation index/h (ODI).

Holter ECG monitoring was performed using the three-channel BTL CardioPoint H100 Holter device (BTL Industries Limited, United Kingdom). As concerning the monitored parameters, they were as follows: resting pulse rate, minimum pulse rate, maximum pulse rate, total number of ventricular and supraventricular extrasystoles (isolated, ventricular bigeminy – the occurrence of a premature ventricular contraction every other beat, trigeminy – every third beat, and quadrigeminy – every fourth beat), the occurrence of AF, atrial flutter, nonsustained ventricular tachycardia (NSVT) (three or more consecutive beats

lasting <30 s), SVT, and cardiac activity pauses. It should be mentioned that the parameters derived from home sleep respiratory polygraphy examination and ECG Holter monitoring were observed in the following two different stages: while diagnosing sleep apnea and at the 3-month checkup.

The diagnosis and treatment of cardiac arrhythmias were carried out according to the guidelines of the European Society of Cardiology from 2013 regarding cardiac stimulation,[11] from 2012 concerning AF,[12] from 2015 regarding ventricular arrhythmias,[13] and from 2003 concerning supraventricular arrhythmias.[14]

After being diagnosed with sleep apnea, an individualized treatment strategy was chosen for each patient. Follow-up was set for 3 months. After this period, patients returned for checkup and completed a new ESS form and underwent home sleep respiratory polygraphy recording and Holter ECG monitoring. No interventions were made on the medication followed by patients.

Statistical analysis

Statistical analysis was performed using MedCalc statistical software version 16.8 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2016). The normality of distribution for quantitative variables was assessed using the Shapiro–Wilk test. Quantitative data were expressed as median and 25th–75th percentiles (nonnormal distribution), and qualitative data were expressed as frequency and percentage. The difference between two repeated measurements was checked with the Wilcoxon signed-rank test. The association between two continuous variables was assessed using the Spearman's rho coefficient. $P < 0.05$ was considered statistically significant.

RESULTS

Table 1 describes the characteristics of the study group. Of the 93 patients, 72 (77.4%) were male, 49.4% were with arterial hypertension Stage 2, and 39.8% were smokers. A number of 67 (72%) patients suffered from dyslipidemia and 28 (30.1%) patients suffered from diabetes.

The characteristics derived from home respiratory polygraphy at baseline and during the 3-month checkup are shown in Table 2. There was a highly statistically significant correlation between all these variables obtained as a result of home respiratory polygraphy at baseline and during the 3 month checkup ($P < 0.001$).

Holter ECG recording observed more parameters at baseline and during the 3-month checkup [Table 3]. A significant decrease in the occurrence of supraventricular extrasystoles was observed during the 3-month checkup,

Table 1: The characteristics of the study group

Variable	Value
Age (years)	60 (52; 64)
Men, *n* (%)	72 (77.4)
Urban residence, *n* (%)	81 (87.1)
BMI (kg/m^2)	34 (30.25; 38)
Waist circumference (mm)	123 (112; 130)
Neck circumference (mm)	44 (42; 46)
ESS	11 (7.5; 15)
Sleep apnea, *n* (%)	
Mild form	14 (15.9)
Moderate form	23 (23.2)
Severe form	56 (60.9)
Arterial hypertension, *n* (%)	
Stage 1	12 (12.9)
Stage 2	46 (49.4)
Stage 3	23 (24.7)
Pack-years (%)	15 (12.5; 18)
Alcohol, *n* (%)	31 (33.3)
Coffee, *n* (%)	59 (63.4)
Type 2 diabetes, *n* (%)	28 (30.1)
Dyslipidemia, *n* (%)	67 (72)
Snoring, *n* (%)	83 (89.2)

BMI: Body mass index, ESS: Epworth Sleepiness Scale

Table 2: Patient characteristics derived from home respiratory polygraphy observed at baseline and during the 3-month checkup

	Baseline	3 months	*P**
ESS	11 (7.5; 15)	7 (4; 10)	<0.001
AHI	47 (25; 70)	12 (7.5; 22)	<0.001
Events	273 (147.5; 429)	77 (55; 129)	<0.001
Minimum oxygen saturation (%)	76 (68; 83.5)	90 (85; 95)	<0.001
Average oxygen saturation (%)	88 (84; 93)	92 (90.5; 94)	<0.001
Longest apnea (s)	71 (52; 98)	35 (25; 55)	<0.001
Desaturation index/h	43 (20,5; 67.5)	15 (6; 22)	<0.001

*Comparisons between baseline and 3 months were performed using the Wilcoxon test. AHI: Apnea–hypopnea index, ESS: Epworth Sleepiness Scale

Table 3: Patient characteristics derived from Holter electrocardiogram monitoring observed at baseline and during the 3-month checkup

	Baseline	3 months	*P**
Minimum pulse rate	50 (45.5; 59)	50 (46; 58)	0.152
Maximum pulse rate	110 (99; 121)	108 (97; 115)	<0.001
Supraventricular extrasystoles	54 (10; 602.5)	25 (0; 141)	<0.001
Ventricular extrasystoles	36 (5; 220)	18 (4; 60.5)	<0.001
AF, *n* (%)	17 (18.3)	8 (8.6)	0.03
Atrial flutter, *n* (%)	4 (4.3)	1 (1.1)	0.083
Nonsustained VT, *n* (%)	10 (10.8)	1 (1.1)	0.03
Sustained VT, *n* (%)	1 (1.1)	0 (0)	0.317
Sinus pauses (s)	1.6 (1.3; 1.9)	1.2 (1; 1.4)	<0.001

*Comparisons between baseline and 3 months were performed using the Wilcoxon test. VT: Ventricular tachycardia, AF: Atrial fibrillation

and the frequency of ventricular extrasystoles was reduced by >50% ($P < 0.001$). In our study, the AHI correlated with the total number of ventricular premature beats ($r = 0.273$; $P = 0.008$).

As regarding AF, of the total patients, 17 patients (18.3%) had this rhythm disorder at baseline and only 8 patients during checkup. Therefore, there was a statistically significant correlation ($P = 0.03$). In our research, AF correlated with the longest apnea ($r = 0.215$; $P = 0.04$).

Of all the patients included in the study, ten patients (10.8%) had NSVT at baseline and only one patient during the 3-month checkup, with a statistically significant P value ($P = 0.03$). The ejection fraction of the LV correlated inversely with the episodes of NSVT ($r = -0.425$; $P < 0.001$).

Pauses in the normal activity of the heart had a median value at baseline of 1.6 and 1.2 during the checkup, with a highly statistically significant correlation ($P < 0.001$). Cardiac activity pauses correlated with AHI ($r = 0.320$; $P = 0.002$), with the longest apnea ($r = 0.345$; $P = 0.01$) and with ODI ($r = 0.325$; $P = 0.04$).

DISCUSSION

Patients with OSA were prone to arrhythmias, of which the most common were AF, ventricular extrasystoles, NSVT, and sinus arrest. We demonstrated that CPAP therapy is effective in the treatment of both sleep disorders and cardiac arrhythmias.

There has been a considerable improvement in all respiratory parameters (AHI, respiratory events, minimum oxygen saturation, average oxygen saturation, longest apnea, and ODI) during the 3-month check-up, which confirmed Walia's observations according to which CPAP is the mainstay for the treatment of sleep apnea.[15]

Fluctuations in sympathetic and parasympathetic activity in patients with sleep apnea may lead to the occurrence of atrial and ventricular arrhythmias.[16]

Atrial arrhythmias frequently occur in patients with moderate or severe sleep apnea, identified as an independent risk factor for both tachyarrhythmia and bradyarrhythmia.[4] CPAP therapy determines a significant improvement with an essential role in preventing and even abolishing these arrhythmias.[17]

As regarding the parameters reported by Holter ECG monitoring, there was a significant decrease in the frequency of supraventricular extrasystoles 3 months after CPAP therapy: from a median value of 54–25.

Given the increased prevalence of paroxysmal AF in patients with untreated sleep apnea and the lower risk of recurrence in patients treated with CPAP, it is important to identify patients likely to suffer from OSA, in order to allow them to benefit from such a treatment.[3] In an uncontrolled study, including 316 patients with newly diagnosed OSA, CPAP therapy significantly reduced the amount of nocturnal paroxysmal AF and supraventricular extrasystoles from 14% to 4%.[17] In our study, 18.3% of patients had AF at baseline and their number decreased significantly to 8.6% during the checkup, after adequate CPAP therapy. Treatment with CPAP improves hypoxia, decreases diurnal and nocturnal sympathetic tone, and decreases the recurrence rate of AF.[3] More studies focused on controlling AF with the use of CPAP device. General improvements of AF parameters (mean heart rate, frequency, and recurrence of AF episodes) have been reported, from baseline to follow-up.[17-20] The risk of this tachyarrhythmia in patients with sleep apnea has been described by several authors – Mehra *et al*.,[21] Gami *et al*.[22] in patients aged below 65 years, and Tanigawa *et al*.[23] in patients with severe sleep apnea. The guideline for the management of AF, of the European Society of Cardiology, also highlighted the association between AF and sleep apnea, mentioning the fact that CPAP can reduce the recurrence of AF.[24] There is a recommendation on Class II, level of evidence A, regarding the clinical signs of sleep apnea that should be considered in all patients with AF.

Seyis described that in patients with heart failure and sleep apnea, there was a significant decrease in the frequency of ventricular extrasystoles during sleep after treatment with CPAP, characterized by a reduced sympathetic nervous system activity.[25] CPAP therapy significantly reduced the occurrences of premature ventricular contractions ($P = 0.016$).[17] This fact is confirmed in our study that we observed a statistically significant decrease in ventricular extrasystoles from a median value of 36–18 ($P < 0.001$).

Ventricular arrhythmias and ventricular extrasystoles were reported in up to 66% of the patients with sleep apnea, which is significantly higher than in people without sleep apnea (0%–12%). They typically occur in patients with severe apnea and cardiovascular comorbidities. Initially, episodes of NSVT occurred in ten patients (10.8%) and then in only one patient (1.1%) 3 months after treatment with CPAP ($P < 0.03$). CPAP decreases the occurrence and recurrence of ventricular extrasystoles; this mechanism is possible by providing more homogeneous conduction and improving the ventricular repolarization.[26] Seyis *et al*. and Rossi *et al*. reported a significant reduction in the frequency of nocturnal ventricular extrasystoles.[25,27] One study reported improvement in the severity of ventricular

extrasystoles, and patients got in a lower level of the Lown classification, after CPAP treatment.[18]

Simantirakis stressed that moderate/severe apnea is associated with frequent episodes of bradycardia, sinus pauses, or sinus arrest, especially during sleep.[28] Abe *et al*., in their study done on a large Japanese population, demonstrated that CPAP therapy significantly reduced the occurrences of sinus pause ($P = 0.004$).[17] In our study, the results are similar: sinus pauses had significantly higher median values compared to those recorded after treatment with CPAP ($P < 0.001$). CPAP therapy is effective in reducing the frequency of bradycardia episodes and has long-term effects.[28] This reduces parasympathetic activity during the night, thus reducing the incidence of arrhythmias.[24] CPAP treatment, by restoring normal breathing, eliminates both the adverse effects of hypoxia and of autonomic changes during obstructive events and therefore prevents the occurrence of OSA-induced bradyarrhythmia.[26] Episodes of asystole lasting up to 10 s were reported in a study conducted by Maeno *et al*.[29] Patients with sleep apnea often present bradyarrhythmia, but they might disappear following treatment with CPAP.[30] Sinus pauses and atrioventricular blocks can be reduced by CPAP, thus avoiding the implantation of a pacemaker.[31] The best example in our case is that of a 34-year-old patient with morbid obesity, severe sleep apnea, and frequent pauses in nocturnal cardiac activity – the longest of 6.8 s, whose cardiac pauses became no longer than 2 s 3 months after CPAP therapy and who needed no cardiac stimulation.

The high prevalence of sleep apnea (59%) in patients with pacemakers should also be noted.[32] Asymptomatic patients with bradyarrhythmia requiring pacemaker implantation should be investigated for the presence of sleep apnea as it can cause bradyarrhythmia.[4]

Reviewed evidence from the observational and nonrandomized studies has shown significant positive effects of CPAP treatment in patients with cardiac arrhythmias, from baseline to follow-up. These effects have determined the following: reduction in heart rate mean and in the frequency and progression of AF episodes; reduction in nocturnal bradyarrhythmia (sinus bradycardia, second-degree and third-degree AV blocks, and sinus pauses); and reduction in the frequency of nocturnal ventricular extrasystoles.[26]

Six months after initiating CPAP treatment, patients were contacted by phone to note their compliance with the treatment. Only 42% of patients were still receiving CPAP, of these, mostly young patients. Soltaninejad *et al*. have shown that like in our study, younger patients had better compliance to treatment; also, BMI, education, and smoking are important factors in adherence to CPAP in patients with OSA.[33]

Some of the limitations of the study could be the small number of patients enrolled in this data set and the fact that polysomnography was not available.

Our study analyzed the correlation between sleep apnea and cardiac arrhythmias using home respiratory polygraphy recording simultaneous with Holter ECG monitoring, which demonstrated the efficacy of CPAP therapy in the treatment of cardiac arrhythmias. No interventions were made on the medication followed by patients. The study was conducted for 3 months, while most of the other studies were conducted for a shorter period, usually under 1 month. In the literature, favorable results occurred after 6 months of treatment with CPAP, whereas in our case, they were obtained after 3 months.

CONCLUSION

The results obtained in this study indicate that the prevalence of cardiac arrhythmias has been reduced following CPAP therapy and highlights the fact that cardiac arrhythmias were correlated with the severity of sleep apnea.

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Conflicts of interest

There are no conflicts of interest.

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