CLINICAL AND BIOLOGICAL IMPACT OF CPAP THERAPY IN PATIENTS WITH OBSTRUCTIVE SLEEP APNEA AND CARDIO-METABOLIC COMORBIDITIES

Ioana Mădălina Zota[1#], Maria Magdalena Leon Constantin[1#], Cristian Stătescu[1#], Radu Andy Sascău[1#], Mihai Roca[1#*], Radu Sebastian Gavril[1#], Teodor Flaviu Vasilcu[1#], Daniela Boișteanu[2#], Cojocaru Elena[3#*], Alexandra Maștaleru[1#], Ovidiu Mitu[1#], Florin Mitu[1#]

[1]Department of Medical Specialties (I), Faculty of Medicine, "Grigore T. Popa" University of Medicine and Pharmacy, 16 University Street, Iasi 700115, Romania - [2]Department of Medical Specialties (III), Faculty of Medicine, "Grigore T. Popa" University of Medicine and Pharmacy16 University Street, Iasi 700115, Romania - [3]Department of Morphofunctional Sciences (I), Faculty of Medicine, "Grigore T. Popa" University of Medicine and Pharmacy, 16 University Street, Iasi 700115, Romania

[#]*All authors contributed equally to this work*

ABSTRACT

Objective: *This study aims to highlight the benefit of CPAP therapy in patients with cardio-metabolic comorbidities (hypertension, diabetes, obesity) assessed in a cardiovascular rehabilitation clinic.*

Methods*: We performed a prospective study that included 33 patients newly-diagnosed with moderate up to severe OSA, who were evaluated before and after 2 months of CPAP therapy.*

Results*: Male sex, abdominal obesity, hypertension, impaired glucose and lipid metabolism were main features in our OSA group. OSA severity was correlated to heart rate, inflammation markers and total cholesterol. After 2 months, CPAP induced significant improvement in weight, abdominal circumference, resting heart rate, total cholesterol and glycated hemoglobin. CPAP was also associated with improved results in the Euro Quality of Life and Epworth questionnaires.*

Conclusion*: Noninvasive ventilation is associated with improved weight status, total cholesterol, HbA1c levels and quality of life, but OSA therapy is limited by poor device tolerance and suboptimal CPAP use.*

Keywords: *Obstructive sleep apnea, hypertension, metabolic syndrome, CPAP.*

DOI: 10.19193/0393-6384_2020_3_309

Received *November 30, 2019;* ***Accepted*** *January 20, 2020*

Introduction

Obstructive sleep apnea (OSA) represents a common comorbidity in cardiovascular patients, with potential impact on cardiovascular morbidity and mortality. Obstructive sleep apnea (OSA) is a form of sleep disordered breathing, in which nocturnal collapse of upper respiratory airways causes repetitive apneic and hypoxic episodes. The subsequent activation of the sympathetic nervous system and the renin-angiotensin-aldosterone axis, along with smoldering systemic inflammation, explain the high incidence of cardiovascular complications associated with OSA[(1)].

OSA prevalence increases with age and is reported to range between 4-24% and 2-16% in men and women, respectively. Sleep apnea is strongly associated with insulin resistance, systemic inflammation, hypertension (with a non-dipping profile) and obesity, explaining the emerging correlation between OSA and metabolic syndrome[(2)].

Although polysomnography remains the gold standard diagnostic test for sleep disordered breathing, cardiorespiratory polygraphy remains an accepted alternative for OSA diagnosis(3). CPAP is the standard therapy for moderate up to severe OSA and it seems to partially reverse the increased cardiovascular risk associated with OSA[(4,5)], as well as to

improve blood pressure level[4], arterial stiffness[6], lipid and glucose metabolism[2].

However, CPAP effectiveness is limited in patients with low daytime sleepiness[7], which can be assessed via the Epworth, Berlin or STOP questionnaires[8]. Bariatric and oto-rhino-laryngological surgical interventions can also be applied in selected patients. The efficacy of other OSA treatment options, such as mandibular devices or oropharyngeal exercises is inferior to that of CPAP[9].

Methods

We performed a prospective study that included patients with moderate-severe OSA, prior to the initiation of CPAP therapy, admitted in our cardiovascular rehabilitation clinic between October 2017 and June 2018. OSA diagnosis was made by ambulatory or in-hospital six-channel cardio-respiratory polygraphy, using either a Philips Respironics Alice Night One or a DeVilbiss Porti 7 device. The recordings were manually scored by a trained physician, according to the American Academy of Sleep Medicine (AASM) standards. Patients with an apnea-hypopnea index (AHI) of 15 - 30 and > 30 were considered to have moderate and severe OSA, respectively. A Philips Respironics DreamStation Auto CPAP or a Resmed Airsense 10 Autoset were used for CPAP effective pressure autotitration in the sleep laboratory.

All patients signed a written informed consent prior to their inclusion in the study. The research was conducted in accordance with the ethical standards presented on Declaration of Helsinki and the protocol was approved by the Ethics Committee of "Grigore T. Popa" University of Medicine and Pharmacy, Iasi, Romania. All subjects underwent clinical examination (weight, body mass index (BMI), abdominal circumference (AC), blood pressure (BP), heart rate (HR)), routine blood tests and completed the Epworth[8] and Euro Quality of Life (EQ-5D-5L)[10] questionnaires, before and after 2 months of CPAP therapy. Diabetes and impaired fasting glucose diagnosis were established according to the American Diabetes Association criteria. Hypertension was defined as office blood pressure ≥ 140/90 mmHg or hypertensive patients currently on blood pressure lowering treatment. Dyslipidemia was defined as total cholesterol ≥ 200 mg/dl, serum triglycerides ≥ 150 mg/dl or patients currently on lipid lowering treatment.

Statistical analysis was performed in SPSS v 20.0, using chi-square and student's t test for comparisons between groups. A potential relationship between variables was evaluated using Pearson correlation coefficient. Descriptive data was expressed as means ± SD (standard deviation) or percentages, as appropriate. A p value < 0.05 was considered statistically significant.

Results

Our study included 33 patients (24 males and 9 females), with a medium apnea-hypopnea-index of 41 events/h (See Tables 1, 2). 63,63% of patients were diagnosed with diabetes or impaired fasting glucose. Hypertension and dyslipidemia were present in 96,96% and 87,87% of cases, respectively. Although average nocturnal oxygen saturation (O2Sa) was similar in the 2 subgroups, patients with severe OSA presented a significantly lower minimum nocturnal O2Sa and required a higher CPAP pressure regimen.

	Moderate-severe OSA	Moderate OSA	Severe OSA
N	33	13	20
Age	57,57 ± 8,93	57,38 ± 8,46	57,7 ± 9,43
M	24 (72,72%)	9 (69,23%)	15 (75%)
F	9 (27,27%)	4 (30,76%)	5 (25%)
Type 2 diabetes	14 (42,42%)	7 (53,84%)	7 (35%)
Impaired fasting glucose	7 (21,21%)	2 (15,38%)	5 (25%)
HT	32 (96,96%)	12 (92,3%)	20 (100%)
Hypercholesterolemia	24 (72,72%)	9 (69,2%)	15 (75%)
Hypertrygliceridemia	5 (15,15%)	2 (15,38%)	3 (15%)

Table 1: Study group analysis - associated comorbidities. *OSA - obstructive sleep apnea; N - number; M - males; F - females; HT - hypertension.*

	Moderate-severe OSA	Moderate OSA	Severe OSA	P value
AHI (events/h)	41,16 ± 18,47	23,55 ± 2,81	52,59 ± 14,22	0,00
Average nocturnal O2Sa (%)	91,4 ± 3,59	92 ± 3,18	91,05 ± 3,78	0,45
Minimum nocturnal O2Sa (%)	73,15 ± 11,55	79,54 ± 7,32	68,45 ± 11,8	0,02
Recommended CPAP pressure (cmH20)	11,39 ± 2,64	9,8 ± 2,34	12,28 ± 2,41	0,014
Epworth score	7,12 ± 5,68	7,69 ± 5,57	6,74 ± 5,88	0,64

Table 2: Study group analysis – associated comorbidities. *OSA - obstructive sleep apnea; AHI - apnea hypopnea index; DI - desaturation index; O2Sa - oxygen saturation; CPAP - continuous positive airway therapy.*

Abdominal obesity was highly prevalent in our study group, but we found no significant differences regarding BMI and AC between the two subgroups (See Table 3). However, patients with severe OSA presented a poorer lipid profile and higher ESR (erythrocyte sedimentation rate).

	Moderate-severe OSA	Moderate OSA	Severe OSA	P value
Weight (kg)	104,68 ± 18,02	104,19 ± 20,7	105 ± 16,61	0,90
BMI (kg/m²)	35,33 ± 5,26	35,15 ± 6,4	35,44 ± 4,54	0,88
AC (cm)	116,2 ± 11,32	117,04 ± 12,69	115,68 ± 10,7	0,75
SBP (mmHg)	141,3 ± 19,67	141,69 ± 21,79	141,05 ± 18,74	0,92
DBP (mmHg)	86,18 ± 12,12	85,46 ± 13,92	86,65 ± 11,15	0,78
HR (bpm)	71,78 ± 10,29	66,69 ± 7,36	75,1 ± 10,72	0,01
Glycemia (mg%)	116,8 ± 24,55	115,23 ± 32,16	117,83 ± 18,96	0,77
ESR (mm/h)	17,57 ± 18,44	9 ± 4,43	23,15 ± 21,85	0,01
CRP (mg%)	0,93 ± 1,24	0,56 ± 0,39	1,19 ± 1,54	0,15
Uric acid (mg%)	5,08 ± 1,36	4,86 ± 1,29	5,23 ± 1,41	0,44
Total cholesterol (mg%)	177,51 ± 40,66	159,08 ± 45,4	189,49 ± 33,16	0,03
LDL (mg%)	94,22 ± 33,36	79,72 ± 32,85	103,65 ± 30,9	0,04
TG (mg%)	165,87 ± 94,24	156,63 ± 76,67	171,87 ± 105,59	0,65
HbA1c (%)	6,74 ± 1,28	7,05 ± 1,67	6,53 ± 0,96	0,33
Perceived health status (%)	64,43 ± 19,81	60,15 ± 19,89	67,36 ± 19,74	0,32

Table 3: Anthropometric and biological parameters.
OSA - obstructive sleep apnea; BMI – body mass index; AC -abdominal circumference; SBP - systolic blood pressure. DBP - diastolic blood pressure. HR - heart rate ESR - Erythrocyte sedimentation rate; CRP - C reactive protein; TC - total cholesterol; TG - triglycerides; HbA1c - glycated hemoglobin.

We did not find statistically significant correlations between apnea severity and BMI (p=0,53), age (p=0,07), AC (p=0,65) or blood pressure values. However, AHI was correlated to resting heart rate (R=0,41; p=0,01), inflammation markers (ESR: R=0,43, p=0,01; CRP: R=0,40, p=0,02) and total cholesterol (R=0,37, p=0,03).

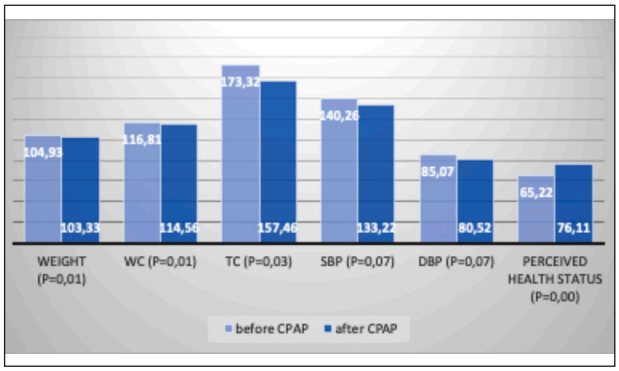

Fig. 1: Changes in weight, waist circumference, total cholesterol, systolic and diastolic blood pressure and perceived health status after 2 months of CPAP.

Four patients (12,12%) did not tolerate CPAP or APAP therapy and returned the device in less than 14 days. 2 patients (6,06) were not present for the second clinical evaluation. Average CPAP use in our study group was 4,1 h/night.

Resting HR, ESR and CRP were not significantly different after 2 months of CPAP therapy (p=0,14, 0,47 and 0,96, respectively). Average SBP and DBP values were lower after treatment, with borderline statistical significance (Δ=-7,04 mmHg, p=0,07 and Δ=-4,55 mmHg, p=0,07, respectively). CPAP therapy was associated with a significant improvement in weight status, total cholesterol, glycated hemoglobin, daytime sleepiness and perceived health status (according to the EQ-5D-5L visual analog scale) (Figure 1-2).

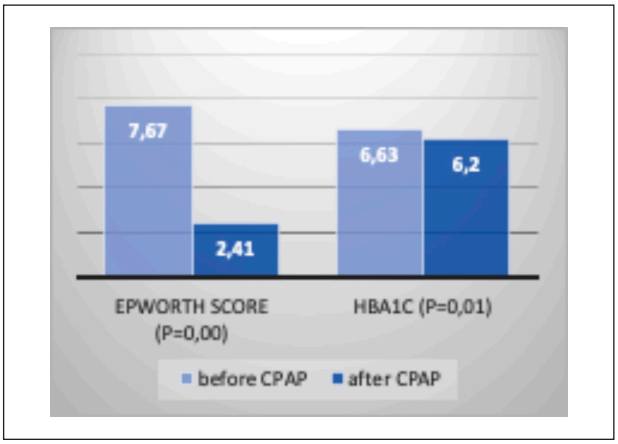

Fig. 2: Changes in Epworth score results and HbA1c after 2 months of CPAP.

Discussion

As shown by previous population-based studies, OSA is twice more common in males than in females[11], similar to our results (male: female ratio 2,53). Obesity was highly prevalent in our group, but severe and moderate OSA patients had a similar average BMI and AC, proving that abdominal obesity is not the only trigger for OSA[2].

A previous metaanalysis showed that CPAP is effective in reducing TC (-6,23 mg/dl, p<0,001) and TG (-12,6 mg/dl, p<0,001), but not LDL cholesterol (-1,01 mg/dl, p=0,62)[12]. The strong link between OSA and an atherogenic lipid profile is partly explained by the high prevalence of abdominal obesity which aggravates the systemic proinflammatory status. Although the overall lipid profile was poorer in subjects with severe OSA, we only found a statistically significant correlation between AHI and total cholesterol levels, which also exhibited a significant decrease after 8 weeks of CPAP therapy (-16 mg/dl, p=0,03). The relation between AHI and LDL has borderline statistical significance (R=0,336 and p=0,06) and should be further analyzed in larger study groups.

Studies have shown that metabolic syndrome (MS) and obstructive sleep apnea coexist in up to 60% of cases[2]. We found an extremely high prevalence of hypertension, impaired glucose and lipid metabolism in our study group, emphasizing the importance of OSA screening in patients with MS.

In the last years, CPAP use was consistently associated with effective weight loss. Our analysis also illustrates a significant weight loss and abdominal circumference reduction. However, a recent metaanalysis showed that noninvasive ventilation induces only a mild weight loss[13] and Tachikawa et al. reported even a reduced basal metabolic rate by 75 kilocalories after CPAP therapy[14].

The role of systemic inflammation in OSA pathogenesis is supported by previous reports regarding elevated inflammatory markers and their correlation with apnea severity[15]. Our study confirms the presence of a significant correlation between AHI, ESR and CRP, but fails to show a significant impact of CPAP in reversing systemic inflammation.

Recent research emphasizes that obstructive sleep apnea is associated with an impaired glucose metabolism and that a high BMI induces a higher risk of insulin resistance in OSA patients[16]. To our knowledge, our analysis is the first report showing higher HbA1c values in the moderate OSA subgroup. Although not statistically significant (p=0,33), this surprising result is due to the small population included in this research, and also to a higher prevalence of diabetes in our moderate versus severe OSA subgroups (53,84% versus 35%, respectively). Although other studies report divergent results concerning the effect of CPAP on HbA1c in diabetics[17-19], we found that HbA1c levels improve after 8 weeks of CPAP (-0,43% p=0,01).

CPAP therapy was previously associated with a reduction in systolic and diastolic BP values by 2,6 and 2 mmHg, respectively[4] Although we obtained a greater reduction of resting BP, our results did not reach statistical significance (p=0,07). Further studies on a larger number of patients are needed in order to support our findings.

Our analysis shows that Epworth score does not correlate with AHI and does not reflect OSA severity. Although our patients did not present significant daytime sleepiness, CPAP therapy improved Epworth score results (p=0,000), similar to other literature reports[20].

OSA is associated with impaired quality of life, as documented by the use of several questionnaires such as Short Form 36, Functional Limitations Profile and EQ-5D-5L. As reported by Jenkinson et al[21], it seems that the latter does not appropriately reflect the impact of OSA on current health status, as we found that patients with severe apnea obtained a higher score in the EQ-5D-5L visual analogue scale. This result could be influenced by other comorbidities not taken into consideration in this analysis. However, we did find a significant improvement in perceived health status according to the EQ-5D-5L visual analog scale after 8 weeks of CPAP therapy. Our findings are consistent with those reported by Schmidlin et al.[10].

The most important limitation in our study is the suboptimal average use of CPAP. Other negative factors include the small number of patients, the presence of cardiovascular and metabolic comorbidities and also the different treatment regimens applied in each case. Furthermore, the low Epworth score in our study group (despite a relatively high average AHI), reflects a less symptomatic form of apnea, which is known to have a poor response to CPAP therapy. During the first clinical evaluation all patients received medical advice concerning the importance of lifestyle changes (diet and exercise). This could explain the marked improvements in weight status, lipid and glucose metabolism which partly exceed other literature reports. However, we were not able to objectively evaluate individual patient adherence to lifestyle changes.

Conclusion

In conclusion, our study shows that abdominal obesity and male sex are strong predictors of OSA. Impaired glucose metabolism, dyslipidemia and hypertension are common comorbidities in patients with obstructive sleep apnea. Although OSA severity is correlated with resting HR, as well as routine inflammation markers (ESR, CRP), CPAP does not significantly improve these parameters. Noninvasive ventilation is associated with improved weight status, total cholesterol, HbA1c levels and quality of life, but OSA therapy is limited by poor device tolerance and suboptimal CPAP use.

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Corresponding Author:
Elena Cojocaru
Department of Morphofunctional Sciences (I), "Grigore T. Popa" University of Medicine and Pharmacy Iași, 16 University Street, Iasi 700115, Romania
E-mail: ellacojocaru@yahoo.com
Mihai Roca
Department of Medical Specialties (I), "Grigore T. Popa" University of Medicine and Pharmacy Iași, 16 University Street, Iasi 700115, Romania
E-mail: roca2m@gmail.com
(Romania)