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DOCTORAL THESIS

OBSTRUCTIVE SLEEP APNEA IN HIGH CARDIO-VASCULAR RISK PATIENTS: FROM SCREENING TO TREATMENT

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Key words: obstructive sleep apnea, cardiovascular risk, screening, resistant hypertension, heart failure with mid-range ejection fraction, body-mass index, continuous positive airway pressure

INTRODUCTION

The high frequency of obstructive sleep apnea (OSA) in cardiovascular (CV) diseases has suggested the possibility of pursuing OSA as a new and modifiable CV risk factor while taking into consideration sleep health as vital to the CV condition. As OSA still remains underdiagnosed in CV patients, gaps in evidence exist on the effects CPAP has on various CV outcomes.

The primary objective of this thesis is to emphasize the close relationship between OSA and CV diseases with three different studies with completely different subject groups that are at an increased CV risk due to myocardial ischemia, heart failure (HF) and resistant hypertension (RHTN). Each study tries to provide novel insights in the pathology of OSA, from screening tools to CPAP treatment while attempting to tackle controversial topics.

The thesis is structured in two parts: the general theoretic part and the special part that consists of three different studies. The first study has as main objective screening for OSA in a group of Romanian patients with recent myocardial ischemia using a series of sleep questionnaires and comparing the use of a single sleep questionnaire to a combined method in order to better identify subjects at high-risk for OSA. The second study's main objective is to assess the particularities of OSA patients with HF with focus on the new class with mid-range ejection fraction (HFmrEF) in a study that combines cardiology and pulmonology expertise and takes place between 2014 and 2018. The last study collects data starting from 2001 until 2015 and analyses a group of RHTN patients with OSA from "Victor Babes" Infectious Disease and Pulmonology Hospital, Timisoara. It investigates the impact of CPAP therapy on obesity parameters, specifically BMI and CV comorbidities.

Hopefullz this thesis can raise awareness not only to the high prevalence OSA has in CV patients but also to the importance of CPAP therapy in lowering the CV risk, while encouraging future studies to be conducted and strengthen the grounds for effective treatment. While CPAP is and will continue to be the primary treatment for sleep apnea, compliance remains a big issue in Romania. It is only

by voicing the concerns of untreated sleep apnea, especially in cardiac patients that the issue of adequate treatment is raised, thus facilitating the access to future therapies.

GENERAL PART

The general theoretical part presents the current data from literature and takes a close look at the correlation between OSA and CV diseases, highlighting obesity and the metabolic syndrome as common ground between the two. The final chapter of the theoretical part takes into consideration the impact CPAP therapy has on CV comorbidities and obesity and discusses the economic aspects in regards to CPAP compliance and impact on Romanian CPAP users.

Even though OSA has been shown to be highly prevalent in nearly all major CV diseases, screening in high CV risk groups has been uncertain. In the long run it is vital that the cardiology community actively starts to detect OSA patients and be convinced that early treatment is essential. More randomized trials that clearly show the effect OSA treatment has on hard cardiac end-points are needed. This continues to be a challenge as few studies exist that randomizes OSA patients without treatment, especially those with severe OSA.

SPECIAL PART

1. INTRODUCTION/MATERIAL AND METHODS

1.1 SCREENING FOR OBSTRUCTIVE SLEEP APNEA IN HIGH CARDIOVASCULAR RISK PATIENTS WITH NORMAL AND IMPAIRED RENAL FUNCTION

Based on the hypothesis that a large number of sleep apnea patients with high CV risk go undetected, mainly due to lack of symptoms, and current screening methods for detecting OSA in such patients is inadequate, we hypothesize that a combination of sleep questionnaires may be better suited in screening CV patients than the use of a single questionnaire. The purpose of this study is to assess a screening tool that combines three questionnaires in detecting OSA in patients with high CV risk.

This is a cross sectional descriptive, single centered study performed at the Institute for Cardiovascular Disease Timisoara, Romania between January 2016 and December 2017. We included patients that were diagnosed either myocardial infarction (MI) or instable angina (MI) and that underwent percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) within the last two years. We excluded patients that had an active or unstable cardiovascular disease, sleep disorders and those receiving CPAP treatment. The patient study group was divided into two groups based on the estimated glomerular filtration rate (eGFR) with the cut-off value of 60 ml/min/1.73 m2: low and normal eGFR group.

The primary objectives were the following:

- Screening for OSA in a high CV risk group of Romanian patients with recent myocardial ischemia using a series of sleep questionnaires;
- Comparing the use of a single sleep questionnaire to a combined method in order to better identify subjects at high-risk for OSA;

As secondary objectives, we sought to evaluate whether renal function impairment as described by eGFR plays a role in heightening the OSA risk.

Clinical and paraclinical evaluation was made including medical history analysis for comorbidities. The sleep questionnaires used were the Berlin Questionnaire (BQ), the STOP-BANG score (SBs), the SASscore (SASs) and the Epworth sleepiness scale (ESS) for quantification of daytime sleepiness. Additional questions were asked regarding reported apneas and snoring.

1.2 OBSTRUCTIVE SLEEP APNEA IN PATIENTS WITH HEART FAILURE: COMPARISON BETWEEN LEFT VENTRICLE EJECTION FRACTION CLASSES

The epidemiology and particularities of OSA in patients with HF as classified by the latest ESC Guidelines from 2016 have not been addressed properly, especially in regards to the new class of HFmrEF. Based on the hypothesis that OSA in patients with HFmrEF may present itself different to those with preserved or reduced EF, we set out to investigate the particularities and associated comorbidities of OSA patients in this new classification of HF.

We consecutively enrolled patients diagnosed with both HF and OSA from “Victor Babes” Infectious Disease and Pulmonology Hospital Timisoara and the Institute of Cardiovascular Disease Timisoara, Romania between 2014 and 2018.

Inclusion criteria were: age over 40 years old, echocardiographic diagnosis of HF, diagnosis of OSA on polygraphy/polysomnography (PSG), ability to complete a sleep questionnaire. We excluded patients with other forms of sleep apnea, those with acute MI, recent acute HF episodes, any form of malignancy, end-stage renal insufficiency and pregnancy. Detailed clinical and paraclinical evaluation was done for each patient including echocardiography and at-home polygraphy.

The primary objective of the study was to assess the particularities of OSA patients with HF with a focus on the new class HFmrEF and compare it to HF patients with reduced EF (HFrEF) and preserved EF (HFpEF).

1.3 LONG-TERM EFFECTS OF CPAP THERAPY ON OBESITY AND CARDIOVASCULAR COMORBIDITIES IN HIGH-RISK CARDIOVASCULAR PATIENTS

The purpose of this study is to evaluate whether long-term CPAP therapy can lead to weight loss in a high CV risk group of patients with RHTN. Based on the hypothesis that there are several mechanisms that potentially can be involved in weight loss (leptin resistance, plasma ghrelin changes and increased daytime vigilance), we hypothesize that long-term CPAP therapy in high-risk CV patients associating RHTN may have a positive effect on obesity thus reducing their cardiovascular risk.

The present study is an observational, case-control, single centered study performed at “Victor Babes” Infectious Disease and Pulmonology Hospital, Timisoara, Romania. 1329 patient records were evaluated between 2001 and 2011 referred with clinical suspicion of sleep apnea. After exclusion criteria we selected 33 patients for a follow-up visit that included clinical and paraclinical evaluation with BP measurements, new polysomnography and a review of medical records. Patients were divided based on CPAP compliance into two groups: CPAP and non-CPAP group.

The objectives of the study were the following:

- impact of long-term CPAP therapy on obesity parameters in high cardiovascular risk patients presenting RHTN and OSA
- evaluation of CPAP therapy efficiency in influencing systolic and diastolic BP in patients with RHTN and OSA;
- determining whether CPAP therapy in high CV risk patients with OSA has any impact on present comorbidities.

2. RESULTS

2.1. SCREENING FOR OBSTRUCTIVE SLEEP APNEA IN HIGH CARDIOVASCULAR RISK PATIENTS WITH NORMAL AND IMPAIRED RENAL FUNCTION

A total of 299 patients (225, 75.3% male) diagnosed with myocardial infarction (48.8%, 146 patients) and instable angina (51.2%, 153 patients) were included in the study. The mean age was 61.21 ± 9.4 years with the majority being overweight (mean BMI of 29.9 kg/m^2). The patient lot was divided into two groups: normal eGFR group (n=161, 46.15% and low eGFR group (n=138 patients, 53.85%).

69.9%, 72.3% and 44.5% of all the patients scored as high risk when screening with SBs, BQ and SASs respectively. When comparing the two groups, we found that patients with impaired renal function were significantly older (58.57 ± 9.1 vs. 64.29 ± 8.9, p<0.001) more overweight (p=0.002) and with increased female prevalence (19.3% vs. 31.2%, p = 0.01), hypertension (85% vs. 96%, p=0.01) and reported apneas (12% vs. 25%, p=0.002).

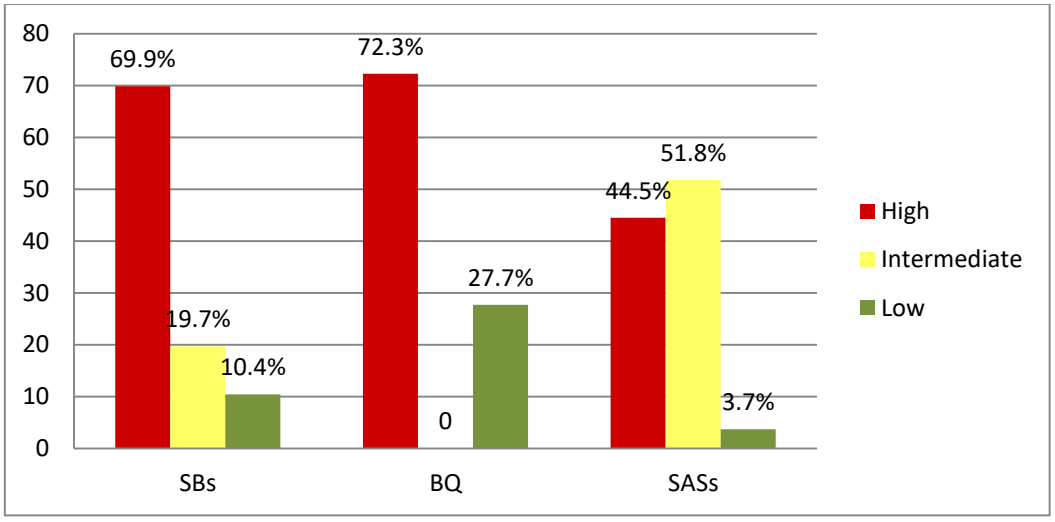

Figure 1. Classification of OSA risk as per each individual sleep questionnaire.

Table 1. Descriptive statistics of statistically significant parameters in high-risk OSA patients as assessed by the combined method

Variable	BQ + SBs + SASs (Low Risk) n = 205	BQ + SBs + SASs (High Risk) n = 94	P value
Age, years	60.46 ± 9.8	62.82 ± 8.29	**0.04**
BMI, kg/m2	29.07 ± 4.38	31.73 ± 6.63	**<0.001**
Neck circumference, cm	37.77 ± 5.06	39.36 ± 4.07	**0.007**
Albumin/creatinine ratio, mg/g	14.99 ± 36.67	36.31 ± 111.71	**0.02**
Snoring, n (%)	112 (55)	84 (89)	**<0.001**
Reported apneas, n (%)	27 (13)	27 (29)	**0.001**
ESS	3.31 ± 3.22	7.94 ± 3.62	**<0.001**

The combined method (BQ+SBs+SASs) classified 94 patients out of 299 (31.4%) with high risk for OSA while maintaining a significant difference in most known OSA predictors (table 1) and yielding the highest ESS as compared to single questionnaire. Impaired renal function as per eGFR did not increase OSA risk although significant differences were noted for albumin/creatinine ratio (p=0.02).

2.2. OBSTRUCTIVE SLEEP APNEA IN PATIENTS WITH HEART FAILURE: COMPARISON BETWEEN LEFT VENTRICLE EJECTION FRACTION CLASSES

We included a number of 143 OSA patients (99 male, 69.2%) with a mean age of 61.97 ± 9.67 years old, obese (BMI 36.49 ± 6.80 kg/m^2) and with increased ESS (13.41 ± 4.72). The patients were divided in three groups based on LVEF as followed: HFpEF (n=93, 65%), HFmrEF (n=33, 23.1%) and HFrEF (n=17, 11.9%).

Table 2. Comparison between EF classes for echocardiographic, paraclinical and polygraphic data. Data is represented as mean (IQR). P-values in bold are statistically significant

Variable	HFrEF group (n = 17)	HFmrEF group (n = 33)	HFpEF group (n = 93)	p value
LV end–diastolic volume (ml)	185 (140–220)	118 (94–155)	130 (110–147.5)	**0.002**
LV end–systolic volume (ml)	123.5 (90–154)	64.9 (53–84.5)	60 (48.5–65.5)	**<0.001**
LA diameter (cm)	4.7 (4.6–5)	4.95 (4.5–5.3)	4.3 (3.9–4.64)	**<0.001**
Tricuspid insufficiency, no. %	13 (76.5)	28 (84.8)	55 (59.1)	**0.018**
Aortic insufficiency, no. %	6 (35.3)	14 (42.4)	19 (20.4)	**0.038**

eGFR (mL/min/1.73 m2),	61.8 (58.9–78)	48.8 (38.7–61)	65.7 (51.3–82.3)	**<0.001**
AHI (events/h)	42 (24–53)	38 (24–48.5)	44 (27–62)	0.163
Desaturation index	24 (14.5–51)	30.5 (13.4–46.4)	39.5 (19–53)	0.185
Longest duration SpO2 <88% (sec),	50 (21–115)	61 (27–110.5)	83 (30–139)	0.331
Seric glucose (mg/dL)	122.5 (104–130.5)	126 (107–180.5)	108.5 (94–127)	**0.008**

No significant differences were noted for OSA severity as evaluated by AHI and DI. Regarding comorbidities, the HFmrEF group had significantly more cases of type 2 diabetes (72.7%, 24 patients, p=0.006) and chronic kidney disease (57.6%, 19 patients, p<0.001). The HFrEF group had more patients with chronic obstructive pulmonary disease (COPD) (52.9%, 9 patients, p=0.009) and CAD (82.4%, 14 patients, p=0.026).

2.3. LONG-TERM EFFECTS OF CPAP THERAPY ON OBESITY AND CARDIOVASCULAR COMORBIDITIES IN HIGH-RISK CARDIOVASCULAR PATIENTS

A total of 33 OSA patients (18 male, 54.5%) with RHTN, age 54.67 ± 7.46 were included in the study. They were divided based on CPAP compliance as followed: CPAP group (n=12, 36.4%) and non-CPAP group (n=21, 63.3%). The groups were homogenous at baseline apart from OSA severity (AHI Non-CPAP 47.1±17.9 vs. CPAP 65.8±23.3, p=0.015) and smoking status (p=0.041).

Patients from the CPAP group lost in BMI an average of 1.4±3.5 kg/m^2, while in the non-CPAP group there was an average weight gain of 1.6 ± 2.5 kg/m^2. There was a significant decrease in BMI in the CPAP group with a large effect size (p=0.006, η2 = 0.218).

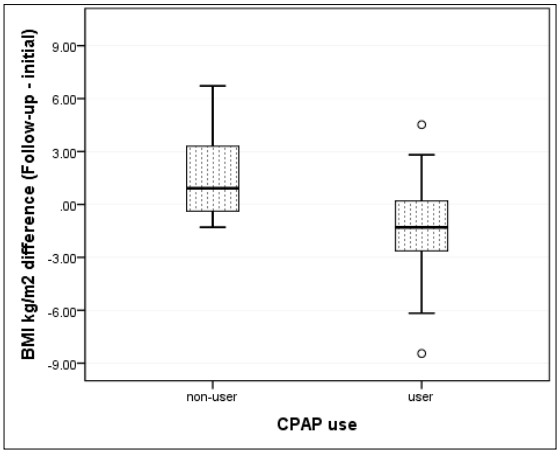

Figure 2. Mean BMI changes between initial and follow-up evaluation

We found no statistically significant differences in regards to any comorbidity but we found that the arrhythmia prevalence at baseline evaluation was numerically higher for the CPAP group compared to non-CPAP group (p=0.274). That prevalence changes significantly at follow-up evaluation (Table 3.)

Table 3. Heart rate and CV comorbidities changes between initial and follow-up evaluation

	Baseline		**Follow-Up**	
	CPAP-Group (*n* = 12)	**Non-CPAP Group (*n* = 21)**	**CPAP-Group (*n* = 12)**	**Non-CPAP Group (*n* = 21)**
Average HR, beats/min mean (SD)	69.2 (13.5)	70.7 (13.0)	58.6 (9.5)	67.8 (7.8)
Arrhythmias (no./%)	6 (50.0)	6 (28.6)	3 (25)	9 (42.9)
HF (no./%)	4 (33.3)	8 (38.1)	4 (33.3)	11 (52.4)
Stroke (no./%)	2 (16.7)	0 (0)	2 (16.7)	1 (4.8)
CAD (no./%)	8 (66.7)	13 (61.9)	8 (66.7)	18 (85.7)

3. CONCLUSIONS

3.1. Screening for Obstructive Sleep Apnea in high cardiovascular risk patients with normal and impaired renal function

I. High risk of OSA as detected by sleep questionnaires was highly prevalent among adult Romanians with recent myocardial ischemia;
II. A combination of SBs, BQ and SASsc was best at detecting patients at high risk for OSA while maintaining the relevance of known OSA predictors;
III. As single use sleep questionnaire, we found that the novel SASs was a more appropriate screening tool in detecting high risk for OSA than SBs or the BQ;
IV. We recommend regular screening for OSA during the hospitalization and as routine before discharge in patients with myocardial ischemia and high CV risk;
V. The prevalence of reported apneas in patients with high CV risk and low eGFR was significantly higher than those with normal renal function;
VI. Impaired renal function did not heighten the risk of OSA in myocardial ischemic patients as per sleep questionnaires;

3.2 Obstructive Sleep Apnea in patients with heart failure: comparison between left ventricle ejection fraction classes

I. Patients with OSA and HF with mid-ranged EF (HFmrEF) presented a significantly higher prevalence of chronic kidney disease and diabetes in comparison to those with preserved and reduced EF.

II. OSA patients with HFmrEF were significantly older in comparison to those with preserved and reduced EF, while the whole study group was obese, predominantly male and with increased neck circumference.

III. Compared to HFrEF and HFpEF, OSA patients with HFmrEF did not present with a severe sleep apnea as primarily defined by AHI and DI.

IV. Regarding echocardiographic parameters, patients from the HFmrEF group had significantly higher LA diameter, aortic and tricuspid insufficiency as compared to the HFrEF group.

3.3 Long-term effects of CPAP therapy on obesity and cardiovascular comorbidities in patients with obstructive sleep apnea and resistant hypertension

I. Long-term CPAP therapy in OSA patients with resistant hypertension was associated with a significant decrease in body-mass index and improved anthropometric parameters like abdominal and neck circumference;

II. We noticed an improvement in mean heart rate and a decrease in arrhythmias prevalence in patients compliant with CPAP therapy for a follow-up period of approximately four years;

III. No significant changes were observed in systolic or diastolic blood pressure in patients treated with CPAP, although 75% of patients from the CPAP group managed to achieve BP control.

IV. Non-compliance to CPAP therapy due to cost is a real issue in Romania that needs to be resolved and long-term solutions implemented.