

SEVERE NOCTURNAL CARDIAC ARRHYTHMIAS CAUSED BY SLEEP APNEA-INDUCED HYPOXEMIA IN MALES

E. Szaboova¹, Z. Tomori², P. Szabo³, S. Gresova², V. Donic²

¹Clinic of Internal Medicine, Faculty of Medicine and ²Department of Physiology and Sleep Laboratory, Faculty of Medicine, Safarik University; ³Faculty of Aeronautics, Technical University, Kosice, Slovakia

Abstract

Nocturnal cardiac arrhythmias (NCA) were analyzed in patients with sleep apnea/hypopnea syndrome (SAHS) and controls. Occurrence and severity of NCA were compared in 33 SAHS patients and 16 control subjects, matched for cardiovascular risk factors. Continuous overnight polysomnography provided ECG, respiratory and sleep parameters for a comparative analysis. Various types and severity of NCA were detected already in moderate SAHS (apnea/hypopnea index = $26 \pm 15.6/h$), reflecting the respiratory and atherosclerotic changes. Moderately severe arrhythmias, represented with benign and 2 complex types were caused by hypoxemia characterized by AHI, minimal SaO₂, and lower values after desaturation. Three-time higher prevalence of complex arrhythmias in SAHS patients was not significantly different by usual statistical comparison, likely due to a low number of controls and a joint occurrence of various types and complex severity of arrhythmias in some patients. Therefore, a complex assessment of different types and varying severity of arrhythmias would require a scale specifically constructed for their evaluation.

Key words: cardiac arrhythmias sleep apnea, hypoxemia, polysomnography, carotid ultrasonography

INTRODUCTION

Several epidemiological studies have indicated a connection between the sleep apnea/hypopnea syndrome (SAHS) and cardiovascular (CV) diseases, resulting in increased morbidity and mortality. Nocturnal cardiac arrhythmias (NCA) are frequent and represent a potential risk in cases of severe sleep apnea, particularly during long obstructive apneic events. There is increased risk for the development of various malignant arrhythmias, when sleep apnea is associated with pre-existing structural cardiac changes [1]. There are conflicting data concerning the prevalence and severity of NCA in patients with SAHS. While some authors have detected an increase in both brady- and tachyarrhythmias, others have found their low incidence in patients without severe cardiac or pulmonary diseases. No clear epidemiological evidence for a causal relation between SAHS and arrhythmias has been found when confounders were considered [2]. Nevertheless, most experts agree that cardiac arrhythmias occur more frequently in patients with SAHS and that their incidence increases with the degree of arterial oxygen desaturation and the number of apnoeic episodes [3]. General mechanisms and cardio-respiratory as well as neuro-physiological and sleep parameters contributing to development of arrhythmias are illustrated in Fig 1.

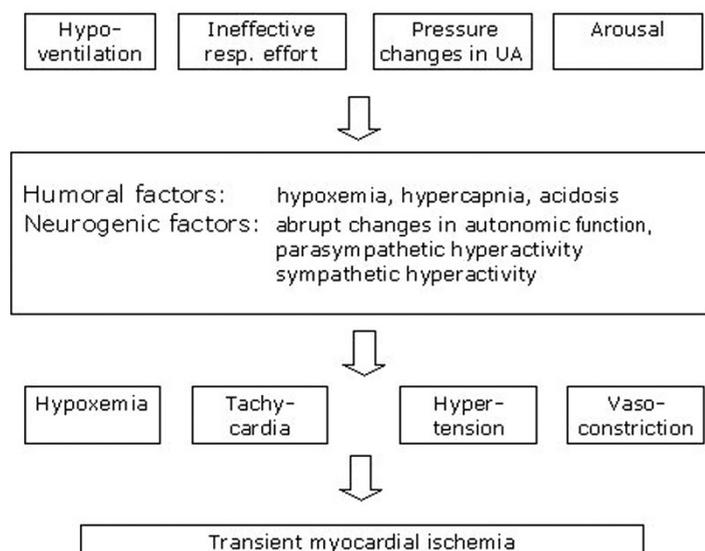


Fig. 1. General mechanisms and cardio-respiratory and neuro-physiological effects of sleep disordered breathing.

The aim of the present study was to assess and compare the occurrence and severity of NCA in subjects with and without moderate SAHS, matched for traditional risk factors for atherosclerosis (AS) and CV pathology. There are many studies analyzing separately the occurrence and severity of cardiac arrhythmias in patients with sleep apnea, but there is no method for a complex assessment and a quantitative comparison of different types and severity of arrhythmias in patients with SAHS.

MATERIAL AND METHODS

The study was performed in accordance with the Declaration of Helsinki for Human Research. The protocol obtained approval of the Ethics Committee of Medical Faculty Safarik University in Kosice, Slovakia and informed consent was obtained from all the subjects enrolled into the study.

ANTHROPOMETRIC, LABORATORY, AND CLINICO-PHYSIOLOGICAL CHARACTERISTICS OF SUBJECTS

Adult males were investigated in this study, because of the lower prevalence of SAHS in middle-aged females. Thirty-three males with moderate SAHS and 16 subjects without SAHS, matched for specific CV comorbidity (apparently healthy adults and patients with arterial hypertension - AH or coronary artery diseases - CAD) were studied. Overnight polysomnography including simultaneous electrocardiogram (ECG) was performed in the sleep laboratory of P.J. Safarik University in Kosice, Slovakia. The subjects underwent careful laboratory and clinical examination, including analysis of fasting venous blood samples, after their informed consent in cardiologic outpatient department of the 4th Clinic of Internal Medicine the day after polysomnographic recording. The medical history, physical examination and clinical documentation of subjects were evaluated. Current and past dietetic and pharmacological treatments were also recorded. Exclusion criteria included insufficiency of vital organs, severe bronchial asthma, complicated hematological disorders, endocrinopathy, diabetes mellitus (DM) type 1 or 2 with specific chronic complications or treated with insulin, malignant diseases, marked neurological abnormalities, current use of antiarrhythmic drugs, and non-compliance. None of the patients were alcoholic, nor were treated with nasal continuous positive airway pressure (nCPAP).

Traditional risk factors for AS (age, positive family history of premature CV diseases, hyperlipoproteinaemia - HLP, DM, AH, smoking habit, and obesity, were defined according to international guidelines [4]. Height, weight, waist-to-hip ratio (WHR), and body mass index (BMI= kg/m²) were measured following a standardized protocol [5]. CAD was based on the presence of clinical symptoms, positive exercise ECG, thallium scan, and/or the finding of significant (>50%) stenosis on coronarography [6].

Intimo-media thickness (IMT) of common carotid arteries as a marker of early AS has strong association with major CV risk factors. For its high specificity and negative predictive value, determination of IMT pro-

vides a useful screening test in population with low prevalence of CAD at a cut-off point ≥ 0.85 mm for the prediction of severe CAD in symptomatic patients. A real-time triplex, high-resolution B-mode ultrasonography (AU4 Idea, Esaote Biomedica, 7.5 MHz probe) was used. The IMT was measured from magnified (5x) images at the maximum thickness of the far arterial wall during the end-diastole. A plaque was defined as a localized lesion of the artery (echogenic structure encroaching into the vessel lumen) with IMT thickness >1.2 mm. The largest value (IMT_{max}) out of 4 measurements as well as the occurrence of IMT ≥ 0.85 mm were used to detect the earliest signs of AS. Finally, all extra-cranial vessels were screened for presence of stenotic lesions (advanced AS). More details are described in a previous paper [7].

SLEEP STUDIES

Overnight polysomnographic recording was performed in a sleep laboratory with Alice 3 device (Respironics, Pittsburgh, PA) using a standard methodology. More than 20 parameters were continuously recorded in parallel. Indices calculated per hour of sleep were as follows: apnea-hypopnea index (AHI), indicating the number of apnoeic and hypopnoeic episodes, arousal index (ArI) expressing the number of arousals lasting 3-15 s. Other parameters were: minimal and average nocturnal oxygen saturation (MinSaO₂, AvgSaO₂), mean oxygen saturation after desaturations by $>3\%$ (DeSaO₂), and the time in minutes spent with SaO₂ below 90%. Micro-arousals and macro-arousals lasting <3 s and >15 s, respectively, were also identified [8]. The recorded parameters were stored on optical disc and automatically analyzed by software and corrected by experts after visual analysis to eliminate occasional artifacts. Respiratory events were defined from polysomnographic records as a decrease in airflow to amplitude $<20\%$ (apnea) or $<70\%$ (hypopnea) of the baseline lasting >10 s and associated with oxygen desaturation by $>3\%$. Apneic episodes were identified if airflow was absent for >10 s and the presence of >10 apneas or hypopneas/hour of sleep is characteristic for SAHS syndrome [8]. Healthy persons present apnea-hypopnea episodes occasionally ($<5/h$). More details are given in a previous publication [7].

ECG ANALYSIS

ECG records from a complete overnight polysomnogram monitored continuously before and during sleep were analyzed by a cardiologist in a blinded fashion to the clinical data and classification of SAHS. We assessed the occurrence, type, and frequency of arrhythmias in each subject and compared the results obtained in SAHS patients with the values of healthy controls and patients without SAHS, matched for various CV risk factors and diseases. Each arrhythmia was determined in relation to the apnea, sleep stage, oxyhemoglobin saturation, as well as minimum and maximum heart rate and R-R interval (during a ≈ 30 s period before and after the onset of arrhythmia). Apnea-related arrhythmia was defined, when the arrhythmia occurred at the onset, during, or till 10 s after termina-

tion of apnea. Non-apnea-related arrhythmias have been evaluated separately. The results of a complex estimation of 3 different types and various degrees of severity of NCA have been described elsewhere [9].

STATISTICAL METHODS

The results were expressed as means \pm SD and analyzed by usual statistical methods from a package STATISTICA 1999. The significance of the mean differences in characteristics between the SAHS and non-SAHS subjects was determined by using the nonparametric Mann Whitney U test for continuous parameters. Chi-squared test was used for an assessment of proportions. If the number of a variable was less than 5, the Fisher exact test was used. The difference was considered as significant at $P < 0.05$.

RESULTS

Our patients with moderate SAHS did not differ from subjects without SAHS in various CV risk factors, diseases, and their therapy (Table 1). The mean values of polysomnographic parameters demonstrated a much higher AHI ($P < 0.0001$) by definition in SAHS patients, compared with practically normal nocturnal breathing in the control group, including subjects with some CV pathology (Table 2). SAHS patients had more severe nocturnal hypoxemia with lower MinSaO_2 ($P < 0.0005$), and DeSaO_2 ($P < 0.05$), and a tendency to

Table 1. Baseline, anthropometric, laboratory, and clinical characteristics of subjects.

	SAH (+) n = 33	SAHS (-) n = 16	P
Age (yr)	52 \pm 8	48 \pm 11	NS
BMI (kg/m ²)	28.9 \pm 4.4	29.7 \pm 4.4	NS
Waist circumference (cm)	102 \pm 10	100 \pm 12	NS
Total cholesterol (mmol/l)	5.5 \pm 1.01	5.1 \pm 0.8	NS
TriAcylGlyc (mmol/l)	2.6 \pm 3.9	1.9 \pm 0.9	NS
HDL-chole (mmol/l)	1.2 \pm 0.3	1.2 \pm 0.3	NS
LDL-chole (mmol/l)	3.7 \pm 1.2	3.1 \pm 0.7	NS
Glycemia (mmol/l)	5.6 \pm 0.8	5.6 \pm 1.2	NS
Age risk (≥ 45 years) (n/%)	28/85	9/56	NS
Positive family history (n/%)	7/21	2/13	NS
AH (n/%)	21/64	7/44	NS
DM (n/%)	2/6	3/19	NS
HLP (n/%)	18/55	9/56	NS
Obesity (BMI) (n/%)	9/27	6/38	NS
Central obesity (Waist) (n/%)	14/42	7/44	NS
Smoking (n/%)	19/58	10/63	NS
ACE inhibitors (n/%)	11/33	5/31	NS
Beta-blockers (n/%)	11/33	9/56	NS
Ca-channel blockers (n/%)	10/30	4/25	NS

BMI – body mass index, RF-AS - risk factors for atherosclerosis, AH – arterial hypertension, DM – diabetes mellitus, HLP – hyperlipoproteinemia, use of antihypertensive drugs in subjects with and without SAHS, matched for risk factors.

longer time spent with $\text{SaO}_2 < 90\%$ ($P = 0.14$) and to lower values of AvgSaO_2 ($P = 0.505$).

Such intermittent hypoxemic episodes caused by apnea-hypopnea events resulted in more severe NCA already in moderate SAHS patients (AHI 26 \pm 15.6/h) than in non-SAHS subjects. With regard to the character of arrhythmias, benign types predominated and no malignant arrhythmias were found in our subjects. The most severe types of arrhythmias had complex forms as follows: 1) supraventricular (SV) tachyarrhythmia: a short run of SV tachycardia in one of the 8 patients in a subgroup with SAHS and CAD; 2) ventricular tachyarrhythmia: bigeminy in 2 of the 14 patients with SAHS and AH, 3 of the 8 in a subgroup with SAHS and CAD, and only in one person from the non-SAHS group, who had CAD. The occurrence of complex arrhythmias was 6 of the 33 (18.2%) in SAHS patients *vs.* 1 of the 16 (6.25%) in non-SAHS group ($P > 0.05$). A nearly 3 times higher prevalence of complex forms of arrhythmias was detected in our SAHS patients, compared with non-SAHS subjects.

Table 2. Carotid ultrasonographic data and cardiovascular diseases as well as respiratory and sleep parameters in subjects with and without SAHS.

	SAHS (+)	SAHS (-)	P
IMT_{max} (mm)	0.91 \pm 0.21	0.77 \pm 0.18	<0.05
$\text{IMT} > 0.85\text{mm}$ (n/%)	18/54.5	4/25	<0.05
Sten 1 (n/%)	10/30	4/25	NS
Sten 2 (n/%)	2/6	0/0	NS
CAD (n/%)	8/24	5/31	NS
Previous MI (n/%)	5/15	3/19	NS
AHI (n/h)	26.0 \pm 15.6	4.1 \pm 2.6	<0.001
Arousal index (n/h)	22.2 \pm 13.7	14.9 \pm 13.3	NS
MinSaO_2 (%)	76.7 \pm 10.5	87.0 \pm 6.5	<0.001
AvgO_2 (%)	90.5 \pm 4.8	91.8 \pm 2.4	NS
DeSaO_2 (%)	85.7 \pm 4.9	88.4 \pm 4.8	<0.05
Total sleep time (h)	5.4 \pm 1.98	5.7 \pm 2.0	NS
$\text{SaO}_2 < 90\%$ (%)	18.8 \pm 19.5	14.9 \pm 13.7	NS

IMT – intima-media thickness, Sten – stenosis 1 = up to 40%, Sten – stenosis 2 = 40-60%, CAD – coronary artery disease, MI – myocardial infarction, SaO_2 – arterial oxygen saturation.

DISCUSSION

PREVIOUS DATA ON ARRHYTHMOGENESIS IN SAHS

The present study provides insights into the complicated relationships between SAHS and development of various NCA, which are common [10], but generally benign [11]. Bradycardic forms, such as sinus bradycardia, sinus pauses up to 2 s in duration, and second degree atrio-ventricular block (AVB) type 1 are commonly observed during normal sleep, and are deemed benign [12]. However, patients with SAHS had more nocturnal and diurnal ST-segment depression as well as sinus bradycardia, sinus tachycardia, premature supra-ventricular complexes (PSVC), supra-ventricular

tachycardia, and couplets than the snoring and control groups [11].

Most experts agree that arrhythmias occur more frequently in patients who have sleep apnea and that the incidence increases with the number of apneic episodes and the degree of arterial oxygen desaturation [13]. In 88% of patients referred for pacemaker therapy with asymptomatic bradyarrhythmias occurring during sleep, apnea episodes were documented by overnight polysomnography [14]. Mild SAHS was detected in 26% and moderate to severe SAHS in 34% of patients with ventricular arrhythmias, but without heart failure [15].

Most severe arrhythmias, such as persistent SV tachycardia, atrial fibrillation (AF) or flutter, and paroxysmal ventricular tachycardia seem more likely to occur in the setting of pre-existing structural heart disease [10]. Sleep disordered breathing was found in approximately half of patients with AF, which prevalence is substantially greater than the occurrence of SAHS in patients with established CV disease but without past or current AF [16].

Some studies have demonstrated objective benefits from CPAP therapy on cardiac rhythm disturbances, especially bradyarrhythmic forms [14, 17-20]. Even serious and potentially fatal arrhythmias occurring during sleep in patients with SAHS were attenuated by effective treatment [18, 20]. Electrophysiological studies detected no sustained or structural conduction system abnormalities in most of patients with significant bradycardia caused by SAHS, but impaired initiation of impulses by the sinus node [18]. When treated with CPAP, these patients have an excellent prognosis with regard to five year risk of syncope or cardiac arrest, strongly supporting a causal relationship between SAHS and at least this form of cardiovascular morbidity [18]. We documented more frequent, more severe, and longer duration of hypoxia in our SAHS patients with more severe arrhythmias.

Most of cardiac rhythm disturbances in patients with SAHS showed a significant correlation with nocturnal minimum SaO_2 , sleep fragmentation, and urinary catecholamine excretion. Moreover ST-segment depressions were related to sleep fragmentation and

the sympathetic tone [11]. Accordingly, cardiac arrhythmias were related to the level of sleep-disordered breathing and oxygen desaturation in a morbidly obese population [21], in patients with severe SAHS (AHI >30), prolonged periods of arterial oxyhaemoglobin desaturation, and in patients with low diurnal awake PaO_2 [22], and particularly during REM sleep [19]. An analysis of factors involved in the pathogenesis of heart blocks in patients with sleep apnea indicated that almost 90% of these episodes occur during REM sleep and during an oxygen desaturation of at least 4% [17].

ANALYSIS OF OUR RESULTS

Our study documented a low prevalence of complex forms of arrhythmia in moderate sleep apneics (AHI <30/h) with normal left ventricular (LV) function. The prevalence of rhythm disturbances in SAHS patients was found not significantly different from that in non-apneic snorers or in the general population [2]. Such discrepant results can be explained in terms of selection bias. Moreover, the different CV co-morbidity of study population and the methodology used for detection of SAHS, as well as discrepancy in the assessment of the severity of both SAHS and arrhythmias further enhance the difficulty to compare various studies [2]. However, a significant difference between the groups with and without SAHS, matched for various risk factors, could not be proved by a separate analysis of 3 different types and various severities of NCA induced by intermittent hypoxemia using simple statistical comparison. This can be explained by a low prevalence, a moderate severity of arrhythmias, a small number of subjects, various structural and functional CV changes, but mainly by a joint occurrence of various types and severity of arrhythmias in some subjects. Therefore, a complex estimation of varying severity of NCA using a special 7-grade scale was tested and various structural and functional CV changes have been analyzed in a parallel publication [9]. Fig. 2 illustrates the great importance of REM sleep and the accompanying apneic episodes and hypoxemia for the induction of NCA in one of our patients.

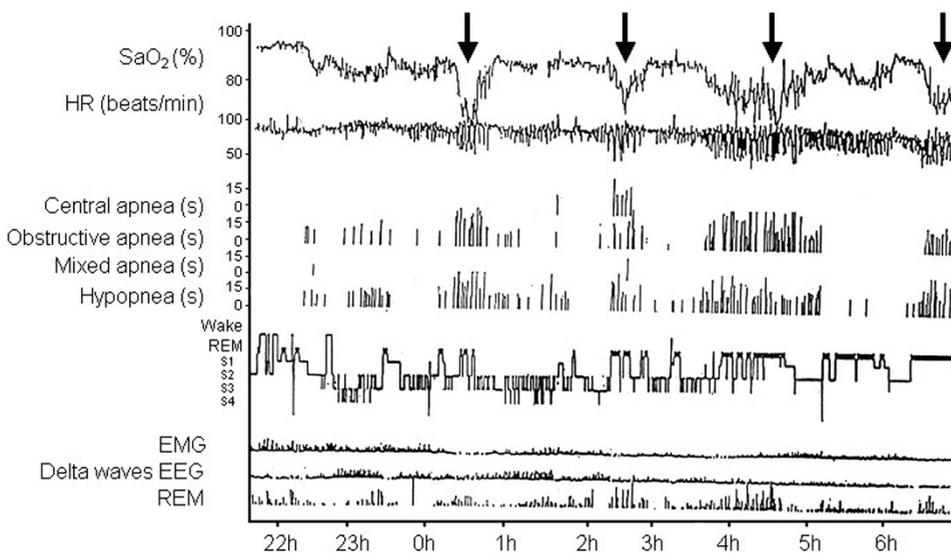


Fig. 2. Recorded: oxygen saturation (SaO_2), HR – heart rate, types of apnea, sleep stages: Wake – wakefulness, REM – rapid eye movement sleep, S1-S4 – stages of non-REM sleep, EMG – limb electromyogram.

SUMMARY

Moderate SAHS in our patients proved to generate severe NCA by modifying the heart function and/or even the structure, which was a result of an action of potent triggering mechanisms. However, more material collected from strictly selected subjects in a prospective study with the evaluation of a large number of confounding factors is needed for a complex analysis of the causal relationship between SAHS and the severity of NCA. Such a complex analysis requires the use of a method with a multi-grade scale for a quantitative assessment of various types and different degrees of the severity of NCA.

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Address for correspondence:

Zoltan Tomori
 Department of Physiology
 Faculty of Medicine
 UPJS, Tr. SNP 1
 04066 Kosice
 Slovakia
 Phone/fax: +421 642 37 63
 E-mail: zoltan.tomori@gmail.com