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ORIGINAL STUDY

Heart rate changes in relation to sleep stages in patients with obstructive sleep apnea syndrome

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ABSTRACT

BACKGORUND. Obstructive sleep apnea syndrome (OSAS) is a major health problem. The complications of this condition decrease the quality of life. Patients with OSAS present an increased risk of cardiovascular diseases: arterial hypertension, heart failure, myocardial ischemia, myocardial infarction, stroke.

MATERIAL AND METHODS. The patients included in the study were divided into 4 groups, depending on the value of the apnea-hypopnea index (AHI): Control Group A with AHI<5; Group B – mild apnea, 5<AHI<15; Group C – moderate apnea, 16<AHI<30; Group D – severe apnea, AHI >30. AHI and heart rate at different sleep stages were correlated.

RESULTS. 133 patients were analyzed. The average age was 47 years±15 years, and the gender distribution shows women 21.1% and men 78.9%. The average value of oxygen saturation was 90.45±4.99%. The average value of heart rate during sleep was 104±67.7 beats/minute. The heart rate was variable depending on the sleep stage, with p = 0.0089 regardless of the sleep stage.

CONCLUSION. It can be argued that sleep apnea is a factor that interferes with the adaptive mechanisms of heart rate during sleep. Polysomnographic evaluation of sleep stages and clinical examination of patients with OSAS allow the initiation of treatments to prevent the occurrence of cardiovascular diseases.

KEYWORDS: obstructive sleep apnea, oxygen saturation, hypertension, heart frequency, sleep stage.

INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is a major health problem that modern medicine is faced with. The complications arising from this condition can be observed in the short term, but also in the long term through the decrease in the quality of life. The prevalence of OSA is 40% to 80% in patients with arterial hypertension, coronary disease, pulmonary hypertension, atrial fibrillation and stroke. It represents a cardiovascular risk factor[1].

Nocturnal micro-awakenings, preceded by the decrease or interruption of the respiratory flow, are generators of the state of daytime sleepiness. Cardiovascular diseases, metabolic syndrome, diabetes mellitus represent an important part of the effects of OSAS. Normal sleep-wake cycles are characterized by variations in blood pressure, heart rate and heart rhythm. Sleep apnea disrupts the interaction between sleep and cardiac activity. There is an association between sleep apnea syndrome and heart diseases[2]. Obstructive sleep apnea occurs in most patients with cardiac disorders and influences cardiac function[3]. OSAS causes the alteration of sleep architecture and a change in cardiovascular and respiratory parameters. This pathology is associated with an increased risk of cardiovascular diseases. In patients with obstructive sleep apnea, as a result of sleep fragmentation, sympathetic stimulation occurs with hypoxia, hypercapnia and increased left ventricular cardiac afterload with hypertension[1]. As a result, obstructive sleep apnea syndrome is associated with hypertension, heart failure, myocardial ischemia, myocardial infarction, stroke and other vascular complications[2].

In OSAS, there is a reduction in heart rate variability between rapid eye movement (REM) and non-rapid eye movement (non-REM, NREM) sleep. Heart rate decreases when transitioning to NREM sleep, both from the REM stage and from wakefulness[4]. This decrease is

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associated with an increase in cardiac vagal modulation. At the same time, when making the transition from NREM sleep to REM sleep, the fluctuations of the autonomic cardiac activity are attenuated in patients with severe apnea. Sleep apnea induces sudden increases in cardiac sympathetic and parasympathetic activities[6,7]. The duration of sleep also varies according to the degree of hypoxia. Thus, although the total period of sleep remains unchanged (3-7 hours ± 0.5), changes may occur in the proportions of sleep that the patients benefited from, namely 83% of sleep in the superficial NREM N1 and N2 sleep stages, with a decrease recorded in slow-wave sleep, and REM sleep, the proportions being 13% and 4%, respectively. During the night, there is an adaptation to hypoxia, the values recorded before sleep in the group of hypoxic patients suggesting a decrease in SaO_2 and in $PaCO_2$ and an increase in pH to 7.46 compared to the patient in normoxia. During both non-REM and REM hypoxic sleep, SaO_2 decreased and PaO_2 increased compared to hypoxic periods during wakefulness[4,5].

Heart rate shows changes in the nervous system affected by apnea and hypopnea events in patients with obstructive sleep apnea syndrome[6]. To evaluate the activity of the nervous system, the heart rate study plays an important role and is frequently used, correlating these parameters with the values of the apnea-hypopnea index (AHI)[8]. The evaluation of the heart rate variability can be assessed by non-invasive methods[9]. The therapy carried out using positive pressure produces changes in the electrocardiographic recordings. These changes can be evaluated by using a Holter for a period of 24 hours, also analyzing possible changes during sleep[10].

There is also an association between sleep apnea syndrome and diabetes mellitus, respectively heart rate in these patients[11]. The association of apnea-hypopnea index values with nocturnal hypoxemia and sleep fragmentation together with changes in heart rate are elements found in patients with obstructive sleep apnea syndrome[12]. It can be stated that sleep breathing disorders, being a frequent condition, are associated with an increased risk of cardiac disorders, heart rhythm disorders and stroke[13]. The use of electrocardiography to identify obstructive sleep apnea syndrome can analyze heart rate variability[14]. Electrocardiographic recordings are used as modern screening methods for the diagnosis of moderate and severe obstructive sleep apnea syndrome[15]. The risk of cardiovascular diseases is known, explained by the association of hypoxia and periods of micro-awakening (arousals) during sleep. Heart rate variability is mediated by sinus arrhythmia, as well as by baroreflex and thermoregulatory fluctuations[16].

Obstructive sleep apnea syndrome, being a condition characterized by repetitive episodes of cessation of breathing during sleep, followed by hypoxemia and sleep interruption, produces at the same time symptoms such as daytime sleepiness, cognitive dysfunctions, the development of cardiovascular and metabolic diseases, with secondary impact on the quality of life. It is known that obstructive sleep apnea syndrome is also determined by changes in the craniofacial massif, such as micrognathia and retrognathia, followed by heart rhythm disorders and neurological disorders. The diagnosis by respiratory polygraphy and polysomnography can correlate the sleep breathing disorders with sleep stages, evaluating superficial and deep sleep periods in patients with OSAS. This is important in establishing effective treatments with the aim of reducing symptoms and improving the quality of life[17].

The present study wants to demonstrate how cardiac activity, respectively heart rate, changes in different stages of sleep in patients with different degrees of the apnea-hypopnea index, an important element in the classification of obstructive sleep apnea syndrome.

MATERIAL AND METHODS

We performed an observational, comparative and descriptive study, using the documents obtained in the framework of the research project entitled "Evaluation of patients with sleep breathing pathology and the implications on the quality of life", ongoing project at the University of Medicine, Pharmacy, Sciences and Technology in Targu Mures.

The inclusion criteria in the study consisted of the patient's consent, as well as the presence of sleep breathing disorders, associated with the values of the apnea-hypopnea index evaluated by polysomnographic recording. The exclusion criteria consisted of the lack of a complete polysomnographic record. Patients were recorded during a period of 6 hours, during physiological sleep. The polysomnographic (PSG) recording was analyzed using NREM sleep stages 1, 2, 3, 4 and REM stage.

The study was carried out in compliance with the Declaration of Helsinki, by concluding an agreement with the institution involved and signing the professional ethics policy and respecting the confidentiality of personal data.

From the studied group of 133 patients, 71 patients were evaluated, in which all stages of sleep and wakefulness were found in the polysomnographic recording. They were divided into 4 groups: Group A – 20 patients – was represented by the group of patients used as a control group, with apnea-hypopnea index (AHI) between 0-5; Group B – 8 patients – was represented by the group of patients with mild apnea, with AHI between 5-15; Group C – 7 patients – was represented by the group of patients with moderate apnea, AHI being between 16-30; Group D – 36 patients – was formed by the group of patients with severe apnea, the AHI index having a value >30.

The patient data obtained through the polysomnographic analysis were compared with the clinical results. The results obtained by evaluating the 4 analyzed groups were compared. Descriptive statistics were performed for each group, according to sleep stages, for each degree of

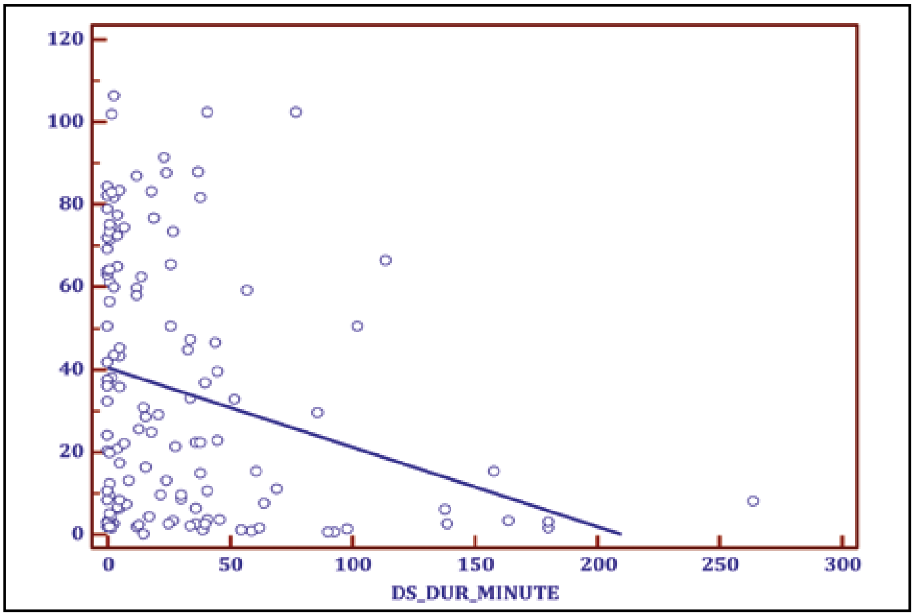

Figure 1. Comparison of the apnea-hypopnea index (AHI) with the duration of deep sleep.

apnea severity. A MANCOVA multiple comparison test was performed, with the heart rate as the dependent variable, the independent covariates being the study groups classified according to apnea severity. The heart rate averages of each sleep stage, from each apnea severity group, were therefore compared with each other.

In all patients who went through all stages of sleep on PSG, the individual variability of heart rate values in different stages of sleep was evaluated with the help of the Bland-Altman method, which establishes a degree of agreement. The Graph Pad 3.1 program was used for statistical data analysis.

RESULTS

The patients included in the study, N=133, had the following gender distribution: 21.1% female and 78.9% male respectively. The average age of the patients was 56±15 years. The average value of the time spent by the 133 patients in a certain sleep stage shows the following distribution: 4.91% REM stage, 0.1% NREM stage 1, 46.20% NREM stage 2, 16.065% NREM stage 3, 1.70% NREM stage 4, 30.93% wakefulness. The average heart rate during the recording period was 104 ±67.7 beats/minute.

From the total of 133 patients included in the study, after applying the exclusion criteria, 71 patients remained, and then a correlation was made between the severity of the apnea syndrome assessed by the value of the AHI index and the heart rate in different stages of sleep, by tracking the way heart rate varies in different stages of sleep.

After a first analysis, comparing the values of the apnea-hypopnea index (AHI) and the duration of deep sleep, one can observe the significant inverse proportionality with p=0.0004, i.e. an increase in the apnea-hypopnea index equivalent to a moderate or severe obstructive apnea syndrome, present in group C and D, is associated with a significant reduction in the period spent in deep sleep (Figure 1).

Analyzing the average apnea period in REM and NREM stages, following descriptive statistics, an average apnea duration of 13.1 seconds is observed in the REM stage, respectively of 28.25 seconds in the NREM stage. The differences recorded between these two variables are statisti-

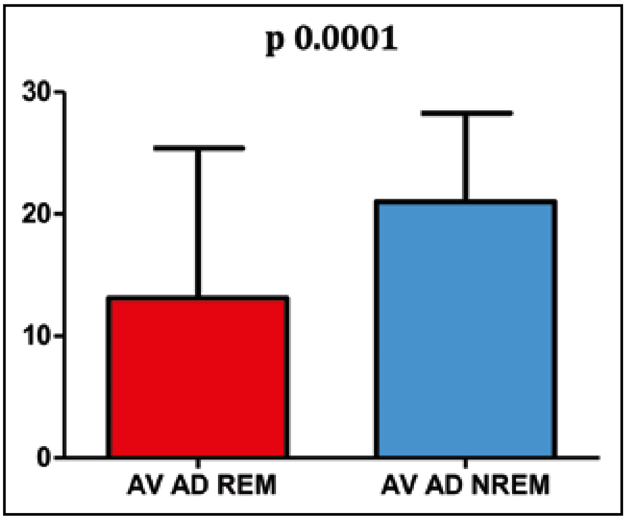

Figure 2. Comparison between the values of apnea periods in the NREM and REM sleep stages.

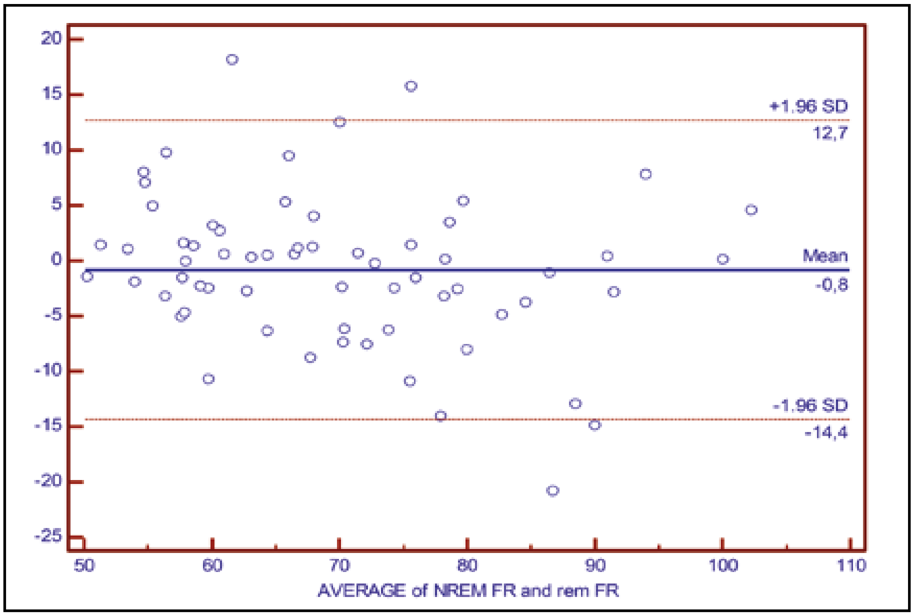

Figure 3. Comparison of heart rate changes in REM and NREM sleep. Distribution of individual variabilities of heart rate averages depending on NREM and REM.

cally significant, with a value of p<0.0001 (Figure 2).

Taking into account the individual variable of heart rate in NREM and REM sleep stages, applying the Bland-Altman method that establishes a threshold of agreement between -14.3559 and 12.7015, it is observed that most of the values fell within the range of agreement, except for 4 patients who present variable values in the NREM and REM stage. It is about heart rate variations in different sleep stages present in the patients, less so in the 4 patients who showed variables in NREM and REM sleep stages. Performing the T-student test, a statistically insignificant p=0.34 value is obtained for the entire group of 71 investigated patients (Figure 3).

Applying the same Bland-Altman analysis method, with an agreement threshold between -15.0764 and 8.48155, taking into account heart rate variability between NREM sleep and wakefulness, it can be seen that the values fall within the range of agreement, except for 5 patients. The T-student test shows a value of p<0.0001, the results being statistically significant (Figure 4).

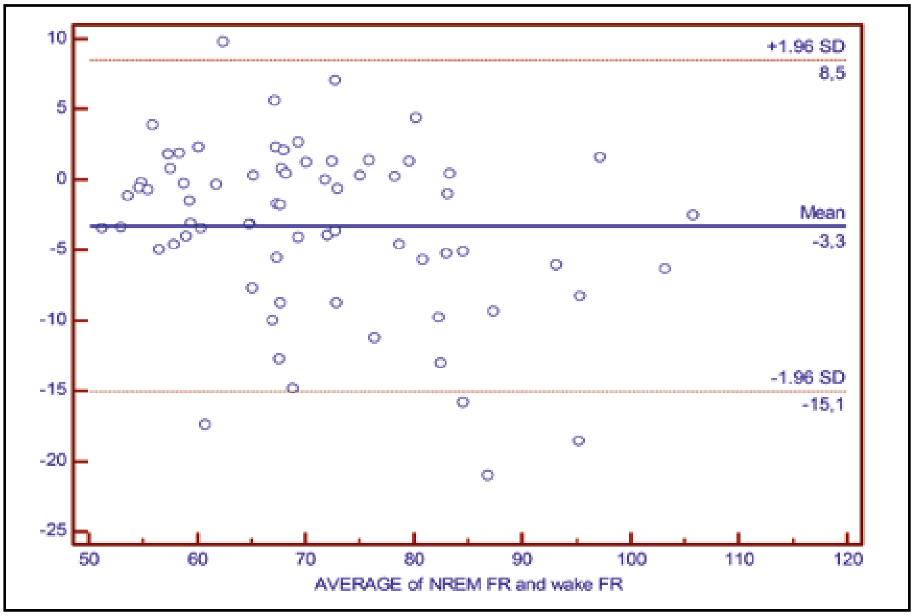

Figure 4. Distribution of individual variabilities of heart rate averages depending on NREM and wakefulness.

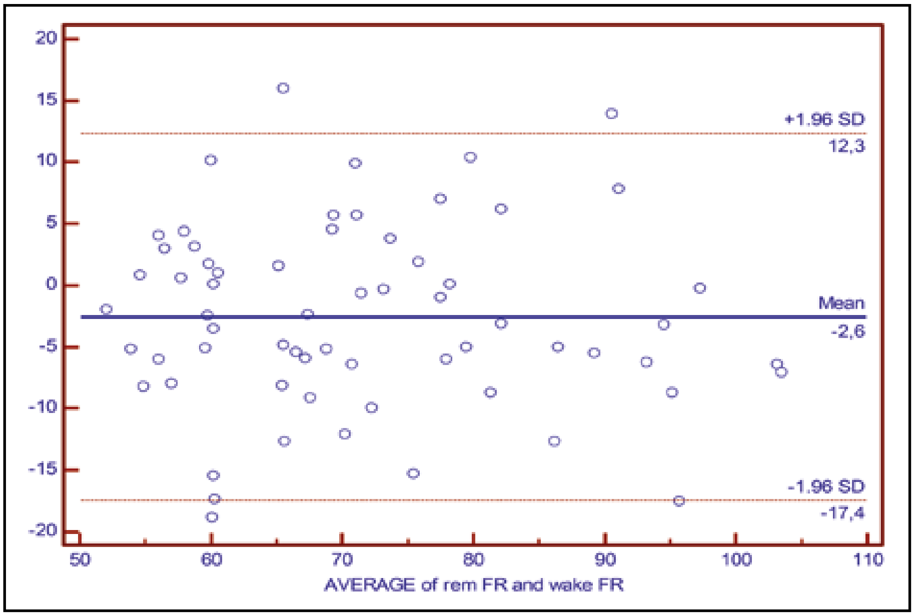

Figure 5. Distribution of individual variabilities of heart rate averages depending on REM and wakefulness.

The same Bland-Altman method was then applied to the individual variability of heart rate in REM and wakefulness stages, in this case the acceptance threshold being between -17.4407 and 12.3179. The comparative relationship between the heart rate in the REM and wakefulness stages of sleep shows that most of the values fell within the range of agreement, the use of the T-student test revealing a value of p=0.0089 (Figure 5).

DISCUSSIONS

Along with oxygen saturation, heart rate is an essential parameter, being monitored throughout any investigation performed for sleep breathing disorders. Descriptive statistics reveal the fact that, although there are differences between the healthy / sick status of the patients, the respiratory pathology analyzed in the present case is not sufficient to produce a statistically significant difference in the average evening heart rate of the patients, who have a normal heart rate most of the night. Only by considering the standard deviation can it be argued that there are periods of transition to interpretable frequencies, but these are only observed in patients with AHI>30.

Possible forms of error in the measurement of sleep by polysomnography (PSG) involve data loss, artifacts, both inter- and intra-event recognition errors, and measurement errors. Since the polysomnogram is considered the reference standard, the reliability and technical accuracy of PSG is largely accepted without doubt or question. However, the polysomnogram, even when accurately measured, recorded and analyzed, may establish an erroneous classification of patients according to the parameters recorded, based on variability from night to night or according to different types of probes used, which may produce an under- or overestimation of events as well as due to a vague clinical definition of the respective disorder. Estimates regarding polysomnography sensitivity in detection of AHI>5 in patients with OSA ranges from 77% to 88%.

Sleep apnea is a common disease associated with daytime sleepiness, fatigue as well as significantly increased morbidity and mortality due to cardiovascular accidents. Male sex, advanced age, obesity, anatomical abnormalities (including small pharyngeal diameter due to excessive adipose tissue in the neck), heredity and instability of respiratory control during sleep have been reported as risk factors for the occurrence of sleep apnea. Visceral obesity is associated with insulin resistance and metabolic syndrome (dyslipidemia, coagulation disorders, arterial hypertension and type II diabetes, associated with cardiovascular sequelae, mostly ischemic cardiopathy).

Regarding the heart rate, no statistically significant difference is observed between the means of the groups with minimal, mild, moderate or severe apnea-hypopnea index.

Due to individual variability in heart rate, regardless of the patients' healthy or sick status, the problem of observing the variations of these parameters was raised, taking into account both individual variations and those that may occur during the change of sleep stages. For this reason, the Bland-Altman method was used, which establishes a so-called "threshold of agreement" or an individual limit between which these personal variations can exist. If there were patients whose limits did not fall within these limits, being either below or above the threshold, these outliers were excluded. The comparative NREM-REM heart rate relationship shows a statistically insignificant difference between the means of the NREM sleep stage, lower than the means of the REM stage values. The comparative relationship between NREM-WAKE heart rate shows a statistically significant difference between the means of the NREM sleep stage, lower than the means of the values in the WAKE stage. The comparative relationship between REM-WAKE heart rate shows a statistically significant difference in the means of the REM sleep stage, lower than the average values in the wakefulness stage.

CONCLUSIONS

In terms of heart rate, no statistically significant difference is observed between the means of the groups with minimal, mild, moderate, or severe apnea-hypopnea index. In light of these findings, it can be stated that sleep apnea is a factor that interferes with the adaptive mechanisms of heart rate during sleep, the transition from one sleep stage to another being variably associated with changes in heart rate.

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Contribution of authors: All the authors have equally contributed to this work.

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