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Original Article

# Obstructive sleep apnea as a predictor of reduced heart rate variability

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ABSTRACT

*Purpose:* This study aimed to analyze the relationship between the occurrence of obstructive sleep apnea (OSA) and heart rate variability (HRV) in a group of patients with clinical suggestion of OSA.
*Methods:* 104 patients with clinical suspicion of OSA were qualified to participate in the study (age: 53.15 ± 13.43 years). All participants took part in a survey and were subjected to laboratory tests, 24-hour ECG Holter monitoring, and polysomnography. The participants were divided into groups depending on the criterion of the presence of OSA.
*Results:* The analysis of time HRV demonstrated lower parameters of SDNN for the entire recording and a 15-minute fragment of daily activity, as well as a lower pNN50 for the entire recording in those patients with diagnosed OSA. A statistically significant difference was observed for the spectral analysis of the LF/HF which was higher in the participants with OSA during the 15-minute fragment of N3 sleep. A negative correlation was observed between AHI and the following parameters: SDSD from the entire Holter recording ($r = -0.21$, $p < 0.05$) and from the 15-minute fragment of daily activity ($r = -0.19$, $p < 0.05$), mRR from the fragment of N3 sleep ($r = -0.19$, $p < 0.05$) and VLF from the entire Holter recording ($r = -0.26$, $p < 0.05$). A statistically significant positive correlation between AHI and LF/HF in 15-minute fragments of N3 sleep was found ($r = 0.26$, $p < 0.05$).
*Conclusions:* The study group of patients with OSA is characterized by reduced HRV. The higher AHI constitutes an independent predictor of reduced HRV, both in the sympathetic and parasympathetic components, and the sympathetic-parasympathetic balance.



## 1. Introduction

Obstructive sleep apnea (OSA) is a set of respiratory disorders occurring during sleep, characterized by the occurrence of upper airway obstruction, leading to recurrent hypoxia, awakenings from sleep, deterioration of sleep quality and pathological daytime sleepiness. The degree of severity of sleep apnea can be assessed using the AHI (Apnea Hypopnea Index) parameter during the polysomnographic examination. AHI's ranging from 5 to 15 events/hour indicate mild apnea, AHI's ranging from 15 to 30 events/hour indicate moderate apnea, and AHI's ≥ 30 events/hour indicate severe apnea [1]. It has been demonstrated that OSA is a risk factor for cardiovascular diseases, including hypertension [2,3], ischemic heart disease [4,5], heart failure [6–8], stroke [9,10] and arrhythmias [11,12]. Additionally, recent studies show that untreated severe apnea increases general and cardiovascular mortality, regardless of other risk factors [13–15]. The pathomechanism of the impact of OSA on the development of cardiovascular diseases is complex involving: sympathetic hyperactivity [16], endothelial dysfunction [17], inflammation and oxidative stress [18], in addition to hypercoagulability [19], insulin resistance [20] and changes in juxta-cardiac pressure [21]. The most reliable evidence obtained in randomized clinical trials was shown for increased activation of the sympathetic system [22]. In

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sleep apnea, dysregulation of the autonomic nervous system occurs. Sleep, which under normal physiological conditions should ensure regeneration of the body through the parasympathetic system, is disturbed by recurrent hypoxia, respiratory acidosis and awakenings which lead to the dominance of the sympathetic system. There are a multitude of methods for assessing autonomic nervous system function. One in particular is the analysis of heart rate variability, considered to be a significant non-invasive indicator of autonomic circulatory function [23].

The measurement of sympathetic nervous system activity can be illustrated using the analysis of heart rate variability, in which an elevated low-frequency LH and LF/HF ratio are observed [24], both of which correlate with increased cardiovascular risk. Numerous studies confirmed the clinically significant correlation between apnea and the occurrence of cardiovascular disease, a correlation which should result in the introduction of routine polysomnography diagnostics in a group of patients with cardiovascular disease. These diagnostics could contribute to the adequate risk stratification and treatment intensity of patients with cardiovascular disease. However, the minimal availability of equipment and the high costs of polysomnography significantly limit diagnostic possibilities. Considering the impact of apnea on heart rate variability, we suggest that 24-hour ECG Holter monitoring, if routinely performed in patients with cardiovascular disease, could be a promising screening tool for sleep apnea. The breath phase affects relative changes in the position of ECG Holter electrodes on the chest in relation to the heart and transthoracic resistance during inspiration and expiration. Therefore, changes in the precise measurement of the heart's electrical axis in different phases of the respiratory cycle may be observed. Changes in the ECG wave amplitude associated with breathing are used in the EDR technique (ECG-derived respiratory) [25,26], which may be used to assess the presence of respiratory events - apneas and shallow breathing. Consistent with previous studies, the EDR technique and HRV analysis may turn out to be a potential, inexpensive and easily accessible diagnostic test for the diagnosis of obstructive sleep apnea [27,28].

The objective of this study was to analyze the relationship between the occurrence and the degree of OSA severity and heart rate variability in a group of patients with clinical suggestion of OSA, and the assessment of AHI compliance estimated in polysomnography and ECG Holter monitoring.

## 2. Material and methods

### 2.1. Study group

Overall, 104 patients qualified for this study. All participants were hospitalized in the Department of Internal Diseases, Occupational Diseases and Hypertension and previously referred to the hospital with a clinical suggestion of the obstructive sleep apnea syndrome. The study group consisted of 60 men and 44 women. The average age of the participants was 53 years, ranging from 20 to 73 years. The majority of subjects were obese (64.4%) and diagnosed with hyperlipidemia (81.7%). Diabetes was present in 23.1% of the participants, arterial hypertension in 83.6%, ischemic heart disease in 9.6%; 3.8% of the participants had a stroke in their past. Active smokers constituted 36.5% of the participants (Table 1).

### 2.2. Study methodology

All participants were subjected to laboratory tests, 24-hour ECG Holter monitoring and full polysomnography (PSG).

Patients were divided into groups for statistical purposes depending on the criteria of the presence and severity of OSA. The first division involved creating a group of patients with apnea (group A) and a group of healthy patients (group B). The second division involved the AHI threshold value [1]; for subgroups A1 and A2 = 15 events/hour (for A1 AHI ≥15 events/hour, for A2 AHI <15 events/hour), and [2] for subgroups A3 and A4 = 30 events/hour (for A3 AHI ≥30 events/hour, for A4 AHI <30 events/hour).

### 2.3. Survey

The survey consisted of questions about demographic and anthropometric data (age, sex, weight, height), cardiovascular risk

**Table 1**
Clinical characteristics of the study group.

| | Whole study group | OSA (group A) | Without OSA (group B) |
|---|---|---|---|
| Number | 104/100.0 | 89/85.6 | 15/14.4 |
| Men | 60/57.7 | 51/57.3 | 9/60.0 |
| Women | 44/42.3 | 38/42.7 | 6/40.0 |
| Age [years] | 53.15 ± 13.43 | 53.74 ± 12.52 | 49.67 ± 18.09 |
| Height [m] | 1.71 ± 0.09 | 1.71 ± 0.10 | 1.71 ± 0.09 |
| Body mass [kg] | 94.38 ± 20.58 | 94.08 ± 20.29 | 96.20 ± 22.94 |
| BMI [kg/m$^2$] | 32.15 ± 6.62 | 32.00 ± 6.47 | 33.05 ± 7.62 |
| Obesity | 67/64.4 | 56/62.9 | 11/73.3 |
| Total cholesterol [mg/dl] | 198.03 ± 44.34 | 196.47 ± 44.68 | 207.27 ± 42.54 |
| LDL cholesterol [mg/dl] | 115.66 ± 37.11 | 114.87 ± 36.93 | 120.07 ± 39.16 |
| HDL cholesterol [mg/dl] | 47.94 ± 11.48 | 47.61 ± 10.36 | 49.93 ± 17.04 |
| Triglicerides [mg/dl] | 186.93 ± 103.26 | 185.58 ± 107.20 | 194.93 ± 78.28 |
| Hyperlipidemia | 85/81.7 | 71/79.8 | 14/93.3 |
| Glucose [mg/dl] | 117.99 ± 41.14 | 119.15 ± 42.57 | 111.13 ± 31.73 |
| Diabetes mellitus | 24/23.1 | 20/22.5 | 4/26.7 |
| Arterial hypertension | 87/83.6 | 76/85.4 | 11/73.3 |
| Coronary artery diseases | 10/9.6 | 10/11.2 | 0/0.0 |
| Stroke | 4/3.8 | 3/3.4 | 1/6.7 |
| **Smoking** | 38/36.5 | **36/40.4** | **2/13.3** |
| **AHI (full PSG) [events/h]** | 26.81 ± 24.56 | **30.91 ± 24.23** | **2.46 ± 1.50** |
| **AHI (PSG 00:00–04:00) [events/h]** | 26.06 ± 23.63 | **30.07 ± 23.25** | **2.27 ± 1.84** |
| **AHI (Holter 00:00–04:00) [events/h]** | 18.60 ± 18.00 | **20.70 ± 18.65** | **7.22 ± 6.76** |
| **Apnea (full PSG) [events/h]** | 12.20 ± 12.82 | **14.11 ± 12.91** | **0.88 ± 0.63** |
| **Hypopnea (full PSG) [events/h]** | 14.60 ± 15.14 | **16.80 ± 15.30** | **1.58 ± 1.11** |
| **ODI (full PSG) [events/h]** | 31.13 ± 25.91 | **35.88 ± 25.02** | **2.92 ± 2.30** |

Statistically significant differences are in bold font ($p < 0.05$).

factors (smoking, hypertension, hyperlipidemia, diabetes) and cardiovascular diseases (ischemic heart disease, stroke).

### 2.4. Laboratory tests

Total cholesterol, LDL and HDL cholesterol, triglycerides and fasting glucose concentrations were determined for all participants.

### 2.5. 24-hour Holter monitoring

All patients were given 24-hour ECG Holter monitoring. Holter recordings were obtained using the 12-channel recorder Lifecard CF, serial number LIFE-045348/2015; the analysis was performed using the Sentinel Spacelabs Healthcare Pathfinder SL system, version 1.7.1.5164, serial number 8395 (Delmar Reynolds, Hertford, Great Britain).

During 24-hour ECG Holter monitoring, patients tried to carry out their normal daily activities; activities performed were registered in diaries, including the time of night sleep. The patients were instructed to follow the established time of daily activity (6:00–22:00) and night rest (22:00–6:00) during continuous ECG recording. To properly prepare the ECG for subsequent analysis, the editing of automatic record was verified visually. The study did not include patients with arrhythmias exceeding >10% of the recording. Results were analyzed by one person who, while doing the analysis, had no access to any patients' clinical data, in particular, no information concerning the occurrence and severity of OSA.

Heart rate variability was assessed in a linear analysis: time parameters (mRR, SDNN, rMSSD, SDSD, pNN50) and frequency parameters (VLF, LF, HF, VHF, LH/HF) – Table 2. The time analysis for the entire recording was done for the defined periods of daily activity and night rest and for the 15-minute fragments of daily activity and N3 stage of sleep. Also, based on a 4-hour fragment of night rest from midnight (00:00) to 4:00 a.m., the program analysis of AHI was calculated.

### 2.6. Polysomnography

Each patient underwent full, unsupervised, type II polysomnography using the NoxA1 device (serial number 992901595) ResMed at the Laboratory of Sleep Medicine. Brain bioelectrical activity (electroencephalogram – EEG), eyeball movements (electrooculography – EOG), muscle tone from the chin and anterior tibial electrodes (electromyography – EMG), air flow from the oronasal thermistor sensor and pressure sensor of the nasal cannula, chest and abdomen movements using induction plethysmography and blood saturation using pulse oximetry were registered. Tests were analyzed by a physician specializing in polysomnography following the guidelines of the American Academy of Sleep Medicine for the Nocturnal system (version 5.1.2.20294) [1]. A manual analysis of the PSG record was made (verifying the record obtained automatically) analyzing episodes lasting 30 seconds.

Apneas were defined as the absence of airflow for ≥10 seconds. Hypopnea was defined as a reduction in the amplitude of breathing by ≥ 30% for ≥10 seconds with ≥3% decline in blood oxygen saturation, or arousal. AHI was determined as the sum of apneas and hypopneas for the entire time range of PSG and additionally for the same 4-hour time interval (00:00–04:00). OSA was diagnosed when AHI ≥5 events/hour. OSA was classified as mild at AHI 5–15 events/hour, moderate at AHI 16–30 events/hour and severe at AHI ≥30 events/hour.

Holter monitoring and polysomnography were carried out in each patient simultaneously. The time of the PSG recorder was synchronized with the time of the Holter ECG recorder.

**Table 2**
Definitions of the assessed parameters of heart rate variability.

| Abbreviation | Definition |
|---|---|
| Time domain analysis | |
| mRR [ms] | Mean RR interval during sinus rhythm |
| SDNN [ms] | Standard deviation of all NN intervals |
| rMSSD [ms] | The square root of the mean of the sum of the squares of differences between adjacent NN intervals |
| SDSD [ms] | Standard deviation of differences between adjacent NN intervals |
| pNN50 [%] | NN50 count divided by the total number of all NN intervals |
| Frequency domain analysis | |
| VLF [$ms^2$] | Power of very low-frequency spectrum |
| LF [$ms^2$] | Power of low-frequency spectrum |
| HF [$ms^2$] | Power of high frequency spectrum |
| VHF [$ms^2$] | Power of very high-frequency spectrum |
| LF/HF | Ratio of powers LF/HF |

### 2.7. Statistical analysis

Using the statistical program STATISTICA 13 (Dell Inc., USA), quantitative variables, arithmetic means and standard deviations of the studied parameters were calculated. The variable distribution was verified using Lilliefors and W-Shapiro-Wilk tests. Due to the lack of normal distribution of the quantitative variables, the Mann–Whitney U test was used for further analyses. The results for qualitative variables were expressed in %. Additional statistical analyses of qualitative variables were done using the chi-square test of the highest credibility. To determine the dependency between the studied variables, analyses of correlation and regression were carried out. Spearman R correlation coefficients were marked. Parameters of the model obtained in the regression analysis were estimated using the least squares method. Results at the level of $p < 0.05$ were considered to be statistically significant.

## 3. Results

The analysis of time heart rate variability demonstrated lower parameters of SDNN for the entire recording and for the 15-minute fragment of daily activity, and a lower pNN50 for the entire recording in those patients with diagnosed obstructive sleep apnea (Table 3). A statistically significant difference was observed for the spectral analysis of the LF/HF which was higher in the participants with OSA during the 15-minute fragment of N3 sleep (Table 4).

Based on the division of the participants into subgroups A1, A2, A3, and A4 (comparing various degrees of apnea severity), it was demonstrated that HRV time parameters are statistically significantly lower in those patients with moderate and severe apnea in comparison to the patients with mild apnea. The differences mentioned above are mostly observed during the 15-minute fragment of daily activity within the following parameters: SDNN, rMSSD, SDSD, pNN50. Similar results were obtained for the division into subgroups A3 (severe apnea) and A4 (mild and moderate apnea), where the participants with severe apnea indicate lower time parameters of heart rate variability, particularly observed during night rest (Table 5).

The spectral analysis of heart rate variability indicated lower HF and LF parameters and higher LF/HF indices in patients with a more severe form of obstructive sleep apnea, indicating the dominance of the sympathetic nervous system in the group of patients with moderate and severe apnea (Table 6).

Table 7 presents the results of the analysis of the correlation between polysomnographic parameters (AHI, apnea, hypopnea, ODI) and heart rate variability parameters. AHI (calculated in full

**Table 3**
Parameters of the time analysis of heart rate variability in the study group.

| | Whole study group | OSA (group A) | Without OSA (group B) |
|---|---|---|---|
| 24 h monitoring (6:00–6:00) | | | |
| mRR [ms] | 884.80 ± 94.26 | 880.03 ± 92.40 | 913.08 ± 103.45 |
| **SDNN [ms]** | 121.38 ± 40.72 | **120.36 ± 42.49** | **127.43 ± 28.44** |
| rMSSD [ms] | 43.18 ± 43.80 | 43.68 ± 46.99 | 40.23 ± 14.92 |
| SDSD [ms] | 32.49 ± 31.97 | 33.18 ± 34.27 | 28.38 ± 10.90 |
| **pNN50 [%]** | 12.04 ± 14.54 | **11.39 ± 15.09** | **15.91 ± 10.28** |
| Daily activity (6:00–22:00) | | | |
| mRR [ms] | 839.88 ± 94.82 | 836.33 ± 95.01 | 860.93 ± 94.10 |
| SDNN [ms] | 106.23 ± 37.90 | 105.75 ± 36.39 | 109.10 ± 47.23 |
| rMSSD [ms] | 37.29 ± 42.39 | 35.66 ± 34.21 | 46.98 ± 75.81 |
| SDSD [ms] | 28.12 ± 30.08 | 27.45 ± 25.91 | 32.11 ± 49.16 |
| pNN50 [%] | 8.91 ± 13.36 | 8.38 ± 11.63 | 12.08 ± 21.23 |
| Night rest (22:00–6:00) | | | |
| mRR [ms] | 955.04 ± 109.78 | 956.03 ± 115.90 | 949.15 ± 64.65 |
| SDNN [ms] | 98.07 ± 37.99 | 98.34 ± 37.37 | 96.46 ± 42.86 |
| rMSSD [ms] | 49.73 ± 47.08 | 49.00 ± 42.54 | 54.03 ± 70.06 |
| SDSD [ms] | 35.76 ± 34.65 | 35.64 ± 33.02 | 36.49 ± 44.49 |
| pNN50 [%] | 16.97 ± 17.87 | 16.87 ± 17.03 | 17.58 ± 22.95 |
| 15 min daily activity period | | | |
| mRR [ms] | 848.17 ± 119.69 | 842.73 ± 122.27 | 880.44 ± 100.53 |
| **SDNN [ms]** | 64.52 ± 41.54 | **61.89 ± 35.78** | **80.15 ± 65.92** |
| rMSSD [ms] | 33.10 ± 42.91 | 30.37 ± 32.79 | 49.29 ± 80.38 |
| SDSD [ms] | 22.68 ± 28.45 | 20.99 ± 22.41 | 32.67 ± 51.68 |
| pNN50 [%] | 8.76 ± 15.89 | 7.87 ± 14.51 | 14.05 ± 22.33 |
| 15 min N3 period | | | |
| mRR [ms] | 960.80 ± 126.48 | 958.31 ± 132.96 | 975.53 ± 79.36 |
| SDNN [ms] | 60.27 ± 44.51 | 60.85 ± 43.75 | 56.82 ± 50.26 |
| rMSSD [ms] | 47.98 ± 50.96 | 47.21 ± 46.04 | 52.51 ± 75.85 |
| SDSD [ms] | 32.42 ± 35.12 | 32.41 ± 32.88 | 32.48 ± 47.77 |
| pNN50 [%] | 17.31 ± 20.39 | 17.12 ± 19.78 | 18.46 ± 24.41 |

Statistically significant differences are in bold font ($p < 0.05$).

**Table 4**
Parameters of the spectral analysis of heart rate variability in the study group.

| | Whole study group | OSA (group A) | Without OSA (group B) |
|---|---|---|---|
| 24 h monitoring (6:00–6:00) | | | |
| VLF [ms$^2$] | 5939.26 ± 33757.52 | 6708.71 ± 36461.20 | 1373.85 ± 1239.71 |
| LF [ms$^2$] | 1859.19 ± 4040.37 | 1894.94 ± 4148.53 | 1647.09 ± 3444.89 |
| HF [ms$^2$] | 1232.94 ± 3308.91 | 1096.71 ± 2616.60 | 2041.25 ± 6057.96 |
| VHF [ms$^2$] | 276.12 ± 1184.70 | 217.47 ± 921.55 | 624.09 ± 2199.12 |
| LF/HF | 2.17 ± 1.63 | 2.22 ± 1.69 | 1.90 ± 1.18 |
| 15 min daily activity period | | | |
| VLF [ms$^2$] | 835.59 ± 1168.16 | 765.66 ± 1039.04 | 1250.52 ± 1742.93 |
| LF [ms$^2$] | 908.16 ± 2264.67 | 785.60 ± 1783.93 | 1635.38 ± 4131.22 |
| HF [ms$^2$] | 772.13 ± 3041.97 | 544.91 ± 1759.54 | 2120.28 ± 6807.63 |
| VHF [ms$^2$] | 215.42 ± 1093.33 | 136.64 ± 639.23 | 682.88 ± 2439.76 |
| LF/HF | 3.01 ± 2.53 | 3.11 ± 2.61 | 2.41 ± 1.96 |
| 15 min N3 period | | | |
| VLF [ms$^2$] | 2109.33 ± 6825.38 | 2297.60 ± 7344.23 | 992.29 ± 1462.73 |
| LF [ms$^2$] | 1292.83 ± 3472.94 | 1345.60 ± 3660.41 | 979.72 ± 2096.28 |
| HF [ms$^2$] | 1336.05 ± 4076.53 | 1211.98 ± 3690.45 | 2072.17 ± 5997.97 |
| VHF [ms$^2$] | 287.71 ± 1460.87 | 229.11 ± 1277.55 | 635.43 ± 2300.13 |
| **LF/HF** | 2.42 ± 4.45 | **2.56 ± 4.89** | **1.55 ± 2.58** |

Statistically significant differences are in bold font ($p < 0.05$).

polysomnography) was negatively correlated with the following HRV parameters: SDSD from the entire Holter recording and from the 15-minute fragment of daily activity, mRR from the fragment of N3 sleep and VLF from the entire Holter recording. A statistically significant positive correlation between AHI and LF/HF in the 15-minute fragment of N3 sleep was obtained (Fig. 1). ODI (calculated in full polysomnography) was negatively correlated with rMSSD in 15-minute daily activity periods and VLF from the 24-hour monitoring. A statistically significant positive correlation between ODI and LF/HF in the 15-minute fragment of N3 sleep was obtained (Fig. 2).

Based on the multivariate regression analysis the presence of independent predictors affecting reduced heart rate variability was observed. In the analysis these variables possibly confounding the results were considered: anthropometric data (age, BMI, gender), basic laboratory tests (total cholesterol, LDL-, HDL-cholesterol, triglycerides, glucose), cardiovascular diseases (arterial hypertension, coronary artery diseases, stroke, diabetes, hyperlipidemia) and the frequency of smoking and respiratory parameters (AHI from full PSG, AHI from PSG 00:00–04:00 time interval, AHI from Holter 00:00–04:00 time interval, ODI from full PSG). A statistically significant independent relationship was demonstrated for AHI and the parasympathetic component (rMSSD), the sympathetic component (VLF) as well as the parameter of the sympathetic-parasympathetic balance (LF/HF). Moreover, with the increase in AHI, lower values of rMSSD and VLF, and a higher LF/HF parameter were observed. Other independent predictors of reduced heart rate variability include high body mass index, increased triglycerides, reduced HDL cholesterol, ischemic heart disease, stroke, hypertension and smoking (Table 8).

In addition, we analyzed the compliance of the AHI calculations from the polysomnography with the AHI estimated on the basis of Holter monitoring. It was demonstrated that the AHI criterion (Holter 00:00–04:00) $\geq$5 events/hour indicates the occurrence of obstructive sleep apnea (defined by AHI $\geq$5 events/hour during full polysomnography) with a sensitivity of 53.3% and a specificity of 24.7%, which results in prediction accuracy of 29.2%. At the same time, the AHI criterion (Holter 00:00–04:00) $\geq$5 events/hour indicates the occurrence of obstructive sleep apnea (defined by AHI $\geq$5 events/hour in the same time interval in polysomnography) with a sensitivity of 60.0% and a specificity of 25.9%, which results in a prediction accuracy of 31.3%.

## 4. Discussion

Sleep apnea is a disease associated with cyclic heart rate variability. During an episode of sleep apnea at first the heart rate slows down, and then violent tachycardia occurs with an elevation of blood pressure during the return of the respiratory rhythm [29]. Recurrent episodes of hypoxia and awakening from physiological sleep lead to autonomic system dysregulation. The dominance of the sympathetic nervous system in sleep apnea leads to the development of cardiovascular diseases. During Holter monitoring of heart rate variability, Aydin et al., observed sympathetic hyperactivity both by the elevated LF/HF ratio and the elevated absolute values of ULF, VLF, LF [30]. Similar results were obtained by Trimer et al., who additionally demonstrated the difference in heart rate variability between REM and N2 sleep stages as well as sympathetic hyperactivity in patients with apnea in a period free from respiratory events, confirming the chronic nature of autonomic dysfunction in such patients [31]. Balachandran et al., demonstrated that autonomic system dysfunction also affects patients with diagnosed asymptomatic sleep apnea who were not burdened with additional cardiovascular diseases [32].

In our study, we demonstrated that patients with the obstructive sleep apnea syndrome are characterized by reduced heart rate variability regarding both time and spectral parameters. Additionally, we observed that such changes occur not only during sleep but also during daily activity. A greater number of statistically significant differences were observed when comparing the group of patients with moderate and severe apnea (subgroup A1) with the control group of healthy patients as well as the patients with mild apnea (subgroup A2). Sleep apnea led to a decrease in the parameters of parasympathetic and sympathetic components, simultaneously shifting the balance of the autonomic nervous system towards the dominance of the

**Table 5**
Parameters of the time analysis of heart rate variability in the subgroups separated on the basis of AHI threshold values.

| | AHI ≥15 events/h (subgroup A1) | AHI <15 events/h (subgroup A2) | AHI ≥30 events/h (subgroup A3) | AHI <30 events/h (subgroup A4) |
|---|---|---|---|---|
| 24 h monitoring (6:00–6:00) | | | | |
| mRR [ms] | 873.27 ± 89.52 | 898.35 ± 99.43 | 862.63 ± 90.66 | 890.79 ± 92.65 |
| SDNN [ms] | 116.13 ± 42.18 | 131.80 ± 42.07 | 121.85 ± 46.81 | 119.43 ± 40.01 |
| rMSSD [ms] | 43.01 ± 52.17 | 45.48 ± 29.46 | 55.05 ± 69.37 | 36.65 ± 22.93 |
| **SDSD [ms]** | 32.83 ± 37.36 | 34.13 ± 24.64 | **27.41 ± 18.92** | **42.51 ± 49.00** |
| **pNN50 [%]** | **9.66 ± 14.93** | **16.07 ± 14.80** | 12.08 ± 18.93 | 10.96 ± 12.31 |
| Daily activity (6:00–22:00) | | | | |
| mRR [ms] | 833.47 ± 94.56 | 844.08 ± 97.81 | 842.48 ± 98.71 | 832.53 ± 93.36 |
| SDNN [ms] | 102.36 ± 33.59 | 114.93 ± 42.51 | 101.36 ± 40.14 | 108.46 ± 33.97 |
| **rMSSD [ms]** | **31.22 ± 18.04** | **47.70 ± 58.00** | 31.47 ± 21.37 | 38.25 ± 40.12 |
| **SDSD [ms]** | **24.36 ± 17.05** | **35.82 ± 40.73** | 24.76 ± 20.88 | 29.12 ± 28.64 |
| **pNN50 [%]** | **6.60 ± 7.31** | **13.20 ± 18.33** | 6.07 ± 7.48 | 9.81 ± 13.45 |
| Night rest (22:00–6:00) | | | | |
| mRR [ms] | 953.10 ± 120.44 | 963.97 ± 104.61 | 943.84 ± 124.16 | 963.56 ± 110.99 |
| **SDNN [ms]** | 95.26 ± 35.26 | 106.68 ± 42.24 | **85.98 ± 25.03** | **105.98 ± 41.68** |
| **rMSSD [ms]** | 45.91 ± 34.96 | 57.37 ± 58.50 | **38.39 ± 25.63** | **55.56 ± 49.32** |
| SDSD [ms] | 33.98 ± 30.59 | 40.12 ± 39.25 | 28.69 ± 24.00 | 39.93 ± 37.09 |
| **pNN50 [%]** | 15.14 ± 15.02 | 21.56 ± 21.24 | **10.84 ± 12.43** | **20.59 ± 18.47** |
| 15 min daily activity period | | | | |
| mRR [ms] | 848.10 ± 120.16 | 828.17 ± 129.32 | 859.46 ± 130.34 | 832.38 ± 117.04 |
| **SDNN [ms]** | **56.70 ± 29.67** | **75.95 ± 46.53** | 56.07 ± 28.45 | 65.49 ± 39.45 |
| **rMSSD [ms]** | **25.66 ± 17.70** | **43.12 ± 54.87** | 24.27 ± 11.20 | 34.14 ± 40.47 |
| **SDSD [ms]** | **17.81 ± 13.00** | **29.63 ± 36.68** | 16.83 ± 7.70 | 23.57 ± 27.66 |
| **pNN50 [%]** | **5.57 ± 10.14** | **14.10 ± 21.54** | **5.02 ± 8.41** | **9.63 ± 14.08** |
| 15 min N3 period | | | | |
| mRR [ms] | 954.10 ± 138.01 | 969.71 ± 120.20 | 937.26 ± 147.80 | 971.33 ± 122.50 |
| **SDNN [ms]** | 56.89 ± 41.13 | 71.57 ± 49.54 | **50.58 ± 25.76** | **67.20 ± 41.06** |
| **rMSSD [ms]** | 42.91 ± 31.95 | 58.87 ± 71.24 | **35.30 ± 24.71** | **54.58 ± 44.19** |
| SDSD [ms] | 29.73 ± 26.02 | 39.65 ± 46.66 | 25.46 ± 21.23 | 36.70 ± 37.91 |
| **pNN50 [%]** | 15.39 ± 18.57 | 21.79 ± 22.51 | **10.19 ± 15.36** | **21.40 ± 21.09** |

Statistically significant differences are in bold font ($p < 0.05$).

**Table 6**
Parameters of the spectral analysis of heart rate variability in the subgroups separated on the basis of AHI threshold values.

| | AHI ≥15 events/h (subgroup A1) | AHI <15 events/h (subgroup A2) | AHI ≥30 events/h (subgroup A3) | AHI <30 events/h (subgroup A4) |
|---|---|---|---|---|
| 24 h monitoring (6:00–6:00) | | | | |
| VLF [ms$^2$] | 8675.59 ± 42576.62 | 1381.73 ± 1305.46 | 13314.74 ± 58326.68 | 2624.98 ± 6557.19 |
| LF [ms$^2$] | 1931.91 ± 4554.49 | 1794.82 ± 2848.35 | 1886.26 ± 5215.54 | 1900.31 ± 3379.78 |
| HF [ms$^2$] | 832.11 ± 1144.52 | 1813.33 ± 4670.87 | 712.39 ± 1108.32 | 1334.29 ± 3202.54 |
| VHF [ms$^2$] | 133.39 ± 278.85 | 445.20 ± 1720.12 | 160.35 ± 367.73 | 252.78 ± 1139.30 |
| LF/HF | 2.34 ± 1.86 | 1.91 ± 1.12 | 2.44 ± 2.08 | 2.08 ± 1.40 |
| 15 min daily activity period | | | | |
| VLF [ms$^2$] | 717.00 ± 1050.80 | 897.44 ± 1016.54 | 811.43 ± 1324.53 | 827.71 ± 737.36 |
| **LF [ms$^2$]** | 625.23 ± 1671.19 | 1219.91 ± 2033.51 | **373.24 ± 386.61** | **1040.51 ± 2218.46** |
| **HF [ms$^2$]** | **279.18 ± 620.90** | **1264.61 ± 3167.44** | 193.83 ± 241.67 | 761.95 ± 2209.98 |
| **VHF [ms$^2$]** | **51.17 ± 64.02** | **368.11 ± 1214.67** | 38.00 ± 41.21 | 197.62 ± 809.28 |
| **LF/HF** | **3.91 ± 3.37** | **2.82 ± 2.22** | 2.99 ± 2.65 | 3.19 ± 2.60 |
| 15 min N3 period | | | | |
| VLF [ms$^2$] | 2728.53 ± 8540.17 | 1130.48 ± 1214.86 | 1689.88 ± 5409.49 | 3673.28 ± 8345.02 |
| LF [ms$^2$] | 1240.21 ± 3456.30 | 1631.03 ± 4231.65 | 890.37 ± 2469.36 | 1627.02 ± 4230.51 |
| HF [ms$^2$] | 861.11 ± 1494.91 | 2162.26 ± 6678.35 | 447.41 ± 753.32 | 1684.03 ± 4610.01 |
| **VHF [ms$^2$]** | **93.35 ± 177.17** | **596.78 ± 2442.17** | 71.90 ± 176.38 | 326.29 ± 1617.28 |
| **LF/HF** | 2.76 ± 7.95 | 2.04 ± 2.28 | **4.08 ± 8.81** | **1.63 ± 1.87** |

Statistically significant differences are in bold font ($p < 0.05$).

sympathetic nervous system (HF reflects the activity of the parasympathetic system, while LF is a component of the influence of both sympathetic and parasympathetic systems [33]). Despite the reduction of both LF and HF frequency analysis parameters, an increase in the LF/HF ratio was observed, which was caused by a significantly larger decrease in the HF parameters in comparison to LF. Our results confirm reduced parasympathetic activity in patients with OSA, which is consistent with currently available medical knowledge [32,34].

A higher AHI is an independent predictor of decreased heart rate variability. At the moment, a golden diagnostic standard in the assessment of the AHI parameter in sleep apnea is polysomnography. This test is expensive and still not widely accessible due to the need to the requirement of using highly specialized equipment, monitoring the patient in a familiar room and the employment of additional medical staff qualified to interpret polysomnography. There are new alternative diagnostic methods for calculating the AHI index, which are based on HRV analysis and the EDR technique. Sun et al., demonstrated approximately 81% sensitivity and 47% specificity of OSA diagnostics based on the analysis of time and frequency parameters of heart rate variability [35]. Tong et al., using the EDR

**Table 7**
Results of the correlation analysis in the study group.

| | | AHI (full PSG) [events/h] | AHI (PSG 00:00–04:00) [events/h] | AHI (Holter 00:00–04:00) [events/h] | apnea (full PSG) [events/h] | hypopnea (full PSG) [events/h] | ODI (full PSG) [events/h] |
|---|---|---|---|---|---|---|---|
| 24 h monitoring (6:00–6:00) | mRR [ms] | ns | ns | ns | ns | ns | ns |
| | SDNN [ms] | ns | ns | −0.23 | ns | ns | ns |
| | rMSSD [ms] | ns | −0.19 | −0.30 | ns | ns | ns |
| | SDSD [ms] | −0.21 | −0.24 | −0.33 | ns | −0.21 | ns |
| | pNN50 [%] | ns | ns | ns | ns | ns | ns |
| Daily activity (6:00–22:00) | mRR [ms] | ns | −0.20 | ns | ns | −0.19 | ns |
| | SDNN [ms] | ns | ns | ns | ns | ns | ns |
| | rMSSD [ms] | ns | ns | ns | ns | ns | ns |
| | SDSD [ms] | ns | ns | ns | ns | ns | ns |
| | pNN50 [%] | ns | ns | ns | ns | ns | ns |
| Night rest (22:00–6:00) | mRR [ms] | ns | −0.19 | ns | ns | ns | ns |
| | SDNN [ms] | ns | −0.20 | ns | ns | ns | ns |
| | rMSSD [ms] | ns | ns | ns | ns | ns | ns |
| | SDSD [ms] | ns | ns | ns | ns | ns | ns |
| | pNN50 [%] | ns | −0.21 | ns | −0.22 | −0.19 | ns |
| 15 min daily activity period | mRR [ms] | ns | ns | ns | ns | ns | ns |
| | SDNN [ms] | ns | ns | ns | ns | ns | ns |
| | rMSSD [ms] | ns | ns | ns | ns | ns | −0.22 |
| | SDSD [ms] | −0.19 | ns | ns | ns | ns | ns |
| | pNN50 [%] | ns | ns | ns | ns | ns | ns |
| 15 min N3 period | mRR [ms] | −0.19 | −0.25 | ns | −0.19 | −0.20 | ns |
| | SDNN [ms] | ns | ns | ns | ns | ns | ns |
| | rMSSD [ms] | ns | ns | ns | ns | ns | ns |
| | SDSD [ms] | ns | ns | ns | ns | ns | ns |
| | pNN50 [%] | ns | −0.21 | ns | −0.19 | ns | ns |
| 24 h monitoring (6:00–6:00) | VLF [ms$^2$] | −0.26 | −0.25 | ns | ns | −0.41 | −0.25 |
| | LF [ms$^2$] | ns | ns | ns | ns | −0.25 | ns |
| | HF [ms$^2$] | ns | ns | ns | ns | ns | ns |
| | VHF [ms$^2$] | ns | ns | ns | ns | ns | ns |
| | LF/HF | ns | 0.21 | 0.25 | 0.21 | ns | ns |
| 15 min daily activity period | VLF [ms$^2$] | ns | ns | ns | ns | ns | ns |
| | LF [ms$^2$] | ns | ns | ns | ns | ns | ns |
| | HF [ms$^2$] | ns | ns | ns | ns | ns | ns |
| | VHF [ms$^2$] | ns | ns | ns | ns | ns | ns |
| | LF/HF | ns | ns | ns | ns | ns | ns |
| 15 min N3 period | VLF [ms$^2$] | ns | ns | ns | ns | ns | ns |
| | LF [ms$^2$] | ns | ns | ns | ns | ns | ns |
| | HF [ms$^2$] | ns | ns | ns | ns | ns | ns |
| | VHF [ms$^2$] | ns | ns | ns | ns | ns | ns |
| | LF/HF | 0.26 | 0.26 | ns | 0.21 | 0.27 | 0.25 |

ns – non statistically significant.

method, demonstrated a statistically significant relationship between the AHI obtained from EDR and from PSG, with a high correlation coefficient (0,879) [27]. In another study based on the EDR technique, compliance in estimating the presence of apnea was found, but only assuming a diagnostic criterion of AHI >17 events/hour [36].

Our results indicated a moderate prediction accuracy of an AHI measurement based on an EDR Holter analysis, compared to classic

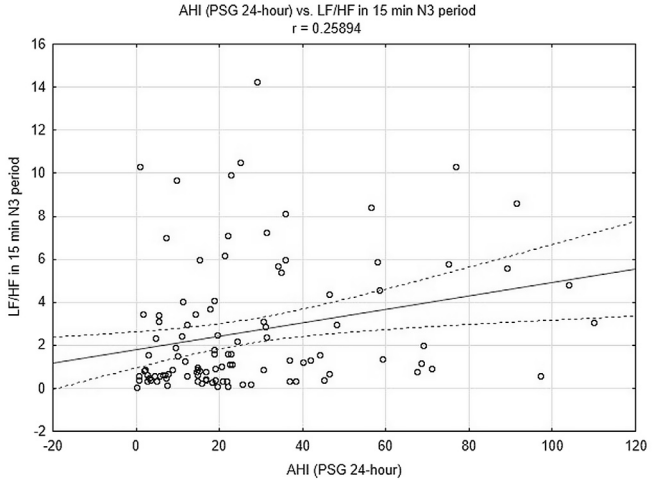


**Fig. 1.** Statistically significant correlation between AHI (calculated in full polysomnography) and LF/HF in 15 min N3 period (r = 0.26; p < 0.05).

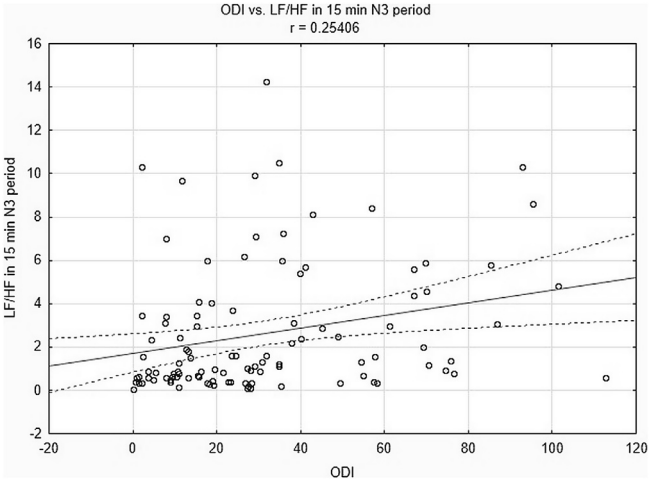


**Fig. 2.** Statistically significant correlation between ODI (calculated in full polysomnography) and LF/HF in 15 min N3 period (r = 0.25; p < 0.05).

**Table 8A**
Results of the regression analysis determining independent predictors of reduced heart rate variability in the study group. Model of relationship determining independent predictors of lower rMSSD (parasympathetic component parameter) values.

| Model for: rMSSD in 24h monitoring (6:00–6:00) | | | | | | |
|---|---|---|---|---|---|---|
| | Intercept | AHI[a] [events/h] | BMI [kg/m$^2$] | HDL cholesterol [mg/dl] | Coronary artery diseases | Stroke |
| Regression coefficient | 53.77 | −0.81 | −0.82 | 0.53 | −23.87 | −22.38 |
| SEM of Rc | 24.64 | 0.25 | 0.39 | 0.19 | 10.80 | 12.21 |
| p value | <0.05 | <0.01 | <0.05 | <0.01 | <0.05 | <0.05 |

[a] Holter 00:00–04:00.

**Table 8B**
Results of the regression analysis determining independent predictors of reduced heart rate variability in the study group. Model of relationships determining independent predictors of lower VLF (sympathetic component parameter) values.

| Model for: VLF in 24h monitoring (6:00–6:00) | | | | | |
|---|---|---|---|---|---|
| | Intercept | AHI[a] [events/h] | BMI [kg/m$^2$] | Triglicerides [mg/dl] | Arterial hypertension |
| Regression coefficient | 719.27 | −60.63 | −53.18 | −14.04 | −265.67 |
| SEM of Rc | 264.44 | 18.04 | 31.59 | 3.02 | 95.91 |
| p value | <0.05 | <0.001 | <0.05 | <0.001 | <0.01 |

[a] Full PSG.

**Table 8C**
Results of the regression analysis determining independent predictors of reduced heart rate variability in the study group. Model of dependencies determining independent predictors of higher LF/HF (sympathetic-parasympathetic balance parameter) values.

| Model for: LF/HF in 15 min N3 period | | | | | | |
|---|---|---|---|---|---|---|
| | Intercept | AHI[a] [events/h] | Triglicerides [mg/dl] | Arterial hypertension | Coronary artery diseases | Smoking |
| Regression coefficient | 1.97 | 0.14 | 0.02 | 4.37 | 2.60 | 1.42 |
| SEM of Rc | 0.62 | 0.03 | 0.01 | 1.64 | 1.27 | 0.09 |
| p value | <0.05 | <0.01 | <0.05 | <0.001 | <0.01 | <0.001 |

[a] PSG 00:00–04:00.

polysomnography. Previous studies brought rather promising results, showing that the analysis of heart rate variability could be a predictor of sleep apnea, reaching sensitivities and specificities of approx. 70–90% [27,37–40]. However, it should be underlined that such studies were limited to small groups of patients and they were based primarily on qualitative, and not quantitative analyses. Additionally, the criteria of excluding cardiovascular diseases and diabetes from these studies reduced the representativeness of the study groups in relation to the general population.

Unquestionable advantages of our study include [1] a similar profile of patients in terms of sex, age and obesity and in the control group [2]; blinded HRV analysis [3]; independence of the polysomnography results [4]; one-stage PSG and ECG Holter monitoring [5]; designation of additional laboratory screening tests; as well as [6] a 24-hour HRV assessment, including periods of wakefulness, thanks to which the chronic and not episodic nature of autonomic nervous system disorders was demonstrated.

The main limitations of this research include [1] a smaller group without OSA compared to the OSA group [2]; heterogeneity of the study group (people with cardiovascular disease - CAD, hypertension, stroke, diabetes) [3]; lack of the EDR analysis in Holter ECG [4]; synchronization of Holter ECG recorder and PSG recorder by adjusting the clocks; and [5] a subjective time interval (00-00-04:00) when comparing AHI from PSG and AHI from Holter ECG.

## 5. Conclusions

Our conclusions are as follows:

(1) The study group of patients with OSA is characterized by reduced heart rate variability.
(2) In the study group of patients, the higher AHI constitutes an independent predictor of reduced heart rate variability regarding both sympathetic and parasympathetic components and the sympathetic-parasympathetic balance.
(3) AHI measurement made during the Holter analysis has a moderate OSA prediction accuracy in comparison to gold-standard test based on polysomnography.

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## Conflicts of interest

The authors report no conflicts of interest.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2018.09.014.

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