Screening in patients with coronary heart disease for severity of night episodes of obstructive sleep apnea and its impact on heart rate variability

Badanie przesiewowe pacjentów z chorobą wieńcową w kierunku obturacyjnego bezdechu sennego i ocena jego wpływu na zmienność rytmu zatokowego

Tomasz Rechciński¹, Aneta Kosiorek¹, Urszula Cieślik-Guerra¹, Jarosław D. Kasprzak¹, Barbara Uznanska-Loch¹, Janusz Wróblewski², Małgorzata Kurpesa¹

¹Department of Cardiology, Medical University of Lodz, Lodz, Poland
²Institute of English, University of Lodz, Lodz, Poland

Abstract

Introduction. Obstructive sleep apnea (OSA) is one of the most common sleep disorders, which affects 4% of men and 2% of women in the world population. The disorder can be diagnosed in men and women of all ages; however, its incidence increases with age. Patients with OSA experience increased levels of sympathetic nervous system activity, which is evidenced by the increased catecholamines secretion. They are at an increased risk of developing complications of coronary heart disease (CHD).

The aim of the study was to evaluate the influence of results of screening for OSA on the activity of the sympathetic and parasympathetic nervous systems within the scope of selected heart rate variability (HRV) parameters (time-domain and frequency-domain analyses of the HRV) in patients with CHD.

Material and methods. Holter recordings of 146 patients aged 43–78 (106 of whom were men) were analysed retrospectively. The patients were divided into four groups on the basis of the estimated apnea–hypopnea index (eAHI), assessed by means of 24-hour recordings of electrocardiogram with Lifescreen Apnea software: < 5 (control group), from 5 to < 15 (mild), from 15 to < 30 (moderate) and ≥ 30 episodes (severe). For each patient, a profile of power spectrum alterations was developed for low frequency (LF) and high frequency (HF) in 60-minute periods between 10 p.m. and 6 a.m. and standard deviation of RR intervals (SDNN) and root mean square of successive differences (rMSSD) values were calculated. The power spectrum in the consecutive one-hour periods was averaged in both groups. In view of the right-skewed distribution of data, the average power spectra were converted into natural logarithms. In order to assess the significance of variations, the natural logarithms of the average values were compared using the univariate analysis of variance (ANOVA).

Results. In the examined groups, there were statistically significant differences in the HF band of power spectrum between the control group and the group of patients with mild OSA (p < 0.01), those with severe OSA (p < 0.01) and also between the group with mild and moderate OSA (p < 0.01). In the LF band of power spectrum, the only difference was seen between the group of patients with mild OSA and those with moderate OSA (p < 0.01). In the time-domain analysis of HRV (SDNN, rMSSD), no statistically significant differences between the groups were observed.

Conclusions. High frequency band of power spectrum [HF] in frequency-domain HRV analysis could be a more effective parameter to distinguish patients with mild OSA (from 5 to < 15) and severe OSA (≥ 30) in patients suffering from CHD, than the power spectrum for LF or SDNN and rMSSD.

Key words: obstructive sleep apnea, autonomic dysfunction, heart rate variability

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Introduction

Obstructive sleep apnea (OSA) is one of the most common sleep disorders present in about 4% of men and 2% of women [1, 2]. Recent study by Pappard et al. [3] indicates that prevalence of sleep-disordered breathing tend to increase over the last two decades. OSA is the result of an excessive drop in the tension of the muscles of the soft palate, tongue and the back wall of the throat. Depending on the severity of this drop, the patient develops impairment (hypopnea) or a temporary blockage of the airflow (apnea) in the upper respiratory tract [4, 5]. The disease can be diagnosed regardless of age and sex, and its incidence increases with age [6]. Heart rate variability (HRV) is the cyclically repeated occurrence of differences in the time interval between two successive heartbeats in the electrocardiogram (ECG). Heart rate variability is influenced by the interaction between the sympathetic and parasympathetic components of the autonomic nervous system, which undergo changes in certain morbid conditions. The measurements of time-domain and frequency-domain analyses of HRV are valuable and non-invasive methods of assessing the function of the autonomic regulation of the heart rate [7, 8].

During sleep, a person with OSA experiences rapid changes in the frequency of the sinus rhythm, with periods of deceleration of the rhythm (bradycardia) and parasympathetic predominance, which alternate with periods of rapidly increasing acceleration of the rhythm as a result of the stronger activity of the adrenergic system. Although the pathophysiological mechanism of OSA is not fully understood, it is assumed that repeated drops in oxygen saturation of arterial blood, an increased activity of the renin–angiotensin–aldosterone system, and an increased secretion of catecholamines are risk factors for arterial hypertension [9], metabolic syndrome [10], and cardiac arrhythmias [11, 12]. There were already some attempts performed to find a relationship between severity of OSA and changes in HRV — nevertheless their limited value is caused by a small sample size [13, 14]. Since Holter ECG monitoring is recorded in every patient during cardiac rehabilitation programme, we decided to use our database in purpose to verify this relationship in a larger sample [15].

The aim of the study was to evaluate retrospectively the relationship between values of calculated index of OSA and the activity of the sympathetic and parasympathetic nervous systems as regards selected HRV parameters in patients with a coronary artery disease, with special reference to selected most frequently used time-domain parameters (the standard deviation of all RR intervals [SDNN]; the root mean square of the successive differences between adjacent RRs [rMSSD]) and frequency-domain parameters (low frequency [LF] power spectrum [0.04 - 0.15 Hz]; high frequency [HF] power spectrum [0.15 - 0.4 Hz]). The assumption of this study was that the level of OSA severity in patients with a diagnosed coronary artery disease, can be associated with the differences in degree of activity of the sympathetic nervous system interacting with the activity of the parasympathetic system. The abovementioned calculated index of OSA — so called estimated apneahypopnea index (eAHI) is obtained from 24-hour ECG Holter recordings and is used by cardiologists to refer cardiac patients with its highest values to perform polysomnography.

Material and methods

The study group

The Holter ECG recordings of 146 patients (106 men) aged 43 – 78 with a coronary artery disease confirmed by means of coronary catheterisation were analysed retrospectively. The Holter recordings of patients qualified for the study were chosen from the archive of data of those who were hospitalised in the Department of Cardiology because of an acute coronary syndrome (ST-elevation myocardial infarction, non ST-elevation myocardial infarction or unstable angina), and who were later — in the second stage of cardiac rehabilitation — patients of the Department of Cardiac Rehabilitation in the same hospital. The patients began cardiac rehabilitation programme within 30 days after being discharged from hospital. The inclusion criterion was sinus rhythm in the baseline ECG on the first day of the rehabilitation. We did not include patients with a history of paroxysmal atrial fibrillation, with an implanted device for electrotherapy, or with premature ventricular contractions present in the resting ECG, since these conditions might make impossible to analyse the Holter recordings for the purpose of this study. Patients with wearable cardioverter-defibrillator due to recent (less than 40 days after the event) myocardial infarction and subsequent low ejection fraction of left ventricle (≤ 35%) were excluded from this study. We excluded patients with anaemia, with thyroid dysfunction, and with clinical or laboratory features of inflammation, as having conditions with reversible impact on heart rate. Also patients with known diagnosis of sleep apnea, neuromuscular or skeletal disease affecting breathing were excluded. The protocol of presented study was approved by the Local Ethics Commission. As retrospective study, performed using archived data, in this case signing informed consent by patients was not necessary.

All the patients underwent a 24-hour ECG Holter monitoring (Pathfinder 700, DelMar Reynolds, Hertford, UK) performed within last week of 24-day cardiac rehabilitation programme for out-patients. The patients were assigned to four groups on the basis of the estimated apnea–hypopnea index (eAHI — the predicted number of apnea or hypopnea episodes) calculated on the basis of
the 24-hour ECG Holter recordings evaluated by means of the Lifescreen Apnea software: < 5 episodes — the control group, from 5 to < 15 — mild sleep apnea, from 15 to < 30 — moderate sleep apnea and ≥ 30 episodes — severe sleep apnea (Figure 1). The clinical characteristics of patients is presented in Table 1.

Material and methods

Twenty-four-hour ECG monitoring was performed using a three-channel recorder Lifecard CF. It was followed by a further analysis with the Pathfinder 700 software and evaluation of the estimated AHI with Lifescreen Apnea (Spacelabs Healthcare, Issaquah WA, USA). As it was mentioned, an apneic event triggers the autonomic nervous system activation, which results in a specific sinus heart rhythm modulation. Lifescreen Apnea is a screening tool, which calculates the probability of apneic events on the basis of changes in the beat-to-beat intervals and the ECG-derived respiration signal. A detailed description of the method was given by de Chazal et al. [16]. Thanks to the inclusion of the ECG-derived respiration signal into the diagnostic algorithm, it is possible to evaluate chest movements indirectly. This method can be used to detect obstructive and mixed apnea. The probability of sleep apnea is calculated for consecutive one-minute intervals and then for longer intervals. When the probability is greater than 50%, the program assumes, that an event occurred. Similarly to the polysomnographic AHI, in this method the estimated AHI (eAHI) is calculated for the whole sleep period, and eAHI < 5 is regarded as normal, eAHI ≥ 5 but < 15 is considered as borderline, and eAHI ≥ 15 as sleep disordered breathing. The minimum required sleep length was six hours, and the hours of sleep were self-reported by the patients. The usefulness of this method was verified by comparison with polysomnography [17]. The HRV was assessed according to the guidelines of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [18]. Time-domain analysis was performed from whole 24-Holter recordings and included SDNN and rMSSD. The frequency-domain analysis was performed with Fast Fourier Transform method and power spectrum of low- as well high-frequency were assessed. The power spectrum for both frequencies was expressed in ms². Each hour of Holter recording was divided into 5-minute intervals. In order to measure the analysed parameters of spectral analysis of HRV from each hour, a 5-minute period from first four intervals with lowest percentage of exclusions was chosen. The following were eliminated from the analysis: the RR intervals which lasted > 2 s and < 300 ms and > 120% and < 80% of the last RR interval. The minimal percentage of the evolutions of rhythm qualified for the assessment of HRV was > 90%.

For each patient, the profile of power spectrum changes in the LF and HF bands in 60-minute intervals between 10.00 p.m. and 6.00 a.m. was determined. LF/HF ratio was calculated for every individual and averaged in investigated subgroups.

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Figure 1. Study flow chart; STEMI — ST-elevation myocardial infarction; NSTEMI — non-ST-elevation myocardial infarction; ECG — electrocardiogram; eAHI — estimated apnea–hypopnea index; SDNN — standard deviation of all RR intervals, rMSSD — root mean square of the successive differences between adjacent RRs; LF — low frequency; HF — high frequency
Statistical methods

The results of the power spectrum measurements were averaged for successive 1-hour intervals in the four groups. Because of the rightward-skewed distribution of the mean values of the power spectrum, they were converted to natural logarithms. In order to assess the significance of the differences, the natural logarithms of the mean values were compared, using one-way analysis of variance (ANOVA). In order to compare the groups of patients with respect to the severity of OSA in terms of risk factors of atherosclerosis, or the percentage of people taking beta-adrenolytics — a chi-square test was used. Results with p < 0.05 were considered to be statistically significant.

Results

Calculation of eAHI revealed, that 23 (15.7%) patients had high probability of severe sleep apnea (eAHI ≥ 30), 52 patients (35.6%) — moderate (eAHI from 15 to < 30), 49 (33.6%) — mild (eAHI — from 5 to < 15) and 22 (15.1%) could be included into control group, as their eAHI was below 5.

Patients after a myocardial infarction constituted 85.6% of the investigated group, arterial hypertension was diagnosed in 78.7%; type 2 diabetes mellitus — in 26%; obesity (BMI > 30 kg/m²) — in 25.3%. In comparison with the control group, patients from the groups with mild and moderate OSA had obesity (BMI > 30 kg/m²) significantly more frequently (p < 0.05), and a higher percentage of a myocardial infarction. The percentage of men was the highest in the group with moderate OSA and was significantly different from the percentage of men in the control group. There were no significant differences in any OSA category in comparison with the control group as regards type 2 diabetes mellitus, arterial hypertension or taking beta-adrenolytics. When patients with eAHI < 15 (controls and mild OSA) were compared with those having eAHI ≥ 15, no significant differences were found in prevalence of male gender, BMI > 30, diabetes mellitus, history of myocardial infarction, arterial hypertension or treatment with beta-adrenolytics (Table 1).

The results of time-domain and frequency-domain analyses of HRV in patients with three categories of OSA (mild, moderate, and severe) and in the control group are presented in Table 2. Spectral power analysis showed that there were statistically significant differences in the HF band between the control group and the patients with mild OSA (p < 0.01) and severe OSA (p < 0.01). Spectral power analysis in the LF band did not show any statistically significant differences. Time-domain analysis of HRV (SDNN, rMSSD) did not show any statistically significant differences between the groups. Despite numerical trend showing increasing LF/HF ratio in dependence from eAHI value, only difference between LF/HF ratio in patients with severe OSA and controls reached statistical significance. Also when patients with eAHI < 15 (controls and mild OSA) were compared with those having eAHI ≥ 15 neither differences in SDNN, nor in rMSSD, LF, HF band or LF/HF values reached statistical significance (Table 2).

Discussion

First most important finding of our study was very high prevalence of OSA in patients treated due to acute coronary
syndromes, with absence of self-reported sleepiness or presence of risk factors for sleep-disordered breathing. This observation is concordant with results of previous studies by Ben Ahmed [19] and Mehre [20].

Second most important result of this study is the finding, that severity of sleep apnea in patients with coronary artery disease can be correlated with power spectrum changes in the HF band, and that from the two methods of HRV analysis, only the frequency-domain analysis is helpful in identifying patients with breathing disturbances of the OSA type in this group.

The significant role of HRV analysis in the identification of patients with OSA, but without concomitant diseases was shown recently also by Gammoudi et al. [21]. Using polysomnography and 24-hour ECG Holter monitoring, the authors showed, on the basis of a relatively small group of patients, the strongest correlation between the severity of OSA (AHI from 5 to < 30 vs. ≥ 30) and the mean value of the RR interval. In contrast to those results, in a study of 36 patients, Aydin et al. observed an increase in the power spectrum in the LF band, VLF band (very low frequency), and the ULF band (ultralow frequency) and a decrease in the power spectrum in the HF band in patients with OSA (both mild — AHI < 20 and severe — AHI > 20) in comparison with the control group [22]. That group demonstrated also a significantly lower rMSSD, which appeared in a comparison of the group with severe OSA and the control group, with emphasis on no cardiac history and no other diseases (arterial hypertension, heart failure, etc.) in the study group. Similar results and conclusions for patients with no previously diagnosed cardiovascular diseases, and who did not take any medication, were obtained by Narkiewicz et al. [23]. Additionally, Park et al. demonstrated elegantly in 59 males with apnea–hypopnea index > 17 and free from other diseases, that frequency domain indices tend to reveal the differences between patients with moderate and severe OSA better than time domain indices [24].

It must be emphasised, however, that an analysis of the activity of the autonomic system must take into account not only concomitant diseases (which have a big influence on the autonomic activity), especially arterial hypertension, heart failure [25] and diabetes mellitus [26], the type of medication taken by the patient, but even their gender and age [27]. In comparison with the patients discussed by the above-mentioned researchers, our patients did not have a previously diagnosed OSA, nor were they free from atherosclerosis risk factors and from medication which affected the heart rate and sleep apnea, namely beta-adrenolytics (Table 2). Our patients with mild and moderate OSA showed significant differences in comparison with the controls with regard to the frequency of a history of a myocardial infarction and obesity. Palma et al. in a group of 30 patients with OSA with moderate and severe OSA and mean BMI > 31 kg/m² demonstrated that both acute and long-term continuous positive airway pressure reduces the sympathovagal imbalance by decrease LF modulation and increase HF modulation [28]. It is worth quoting here the results of a pilot study, which demonstrated that bariatric surgery had better effects on the improvement of HRV parameters in people with obesity and OSA than the use of continuous positive airway pressure treatment in this group of patients [29]. In our study, the frequency of type 2 diabetes mellitus did not differ significantly between the groups (p < 0.05) nor did that of arterial hypertension and the percentage of patients who took beta-adrenolytics. The repeated drops in arterial blood saturation and the increased activity of the renin–angiotensin–aldosterone system and the increased activity of the sympathetic system could be the potential

<table>
<thead>
<tr>
<th>HRV parameter</th>
<th>Mild OSA</th>
<th>Moderate</th>
<th>Severe OSA</th>
<th>Control</th>
<th>Mild OSA vs. control</th>
<th>Moderate OSA vs. control</th>
<th>Severe OSA vs. control</th>
<th>eAHI &lt; 15</th>
<th>eAHI ≥ 15</th>
<th>eAHI &lt; 15 vs. ≥ 15</th>
</tr>
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<tbody>
<tr>
<td>SDNN [ms]</td>
<td>127.29</td>
<td>± 32.77</td>
<td>£ 28.50</td>
<td>£ 32.82</td>
<td>± 33.90</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>127.23</td>
<td>124.57</td>
</tr>
<tr>
<td>rMSSD [ms]</td>
<td>24.35</td>
<td>± 9.51</td>
<td>£ 10.55</td>
<td>£ 9.31</td>
<td>± 11.06</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>24.41</td>
<td>25.91</td>
</tr>
<tr>
<td>LF [ms²]</td>
<td>588.74</td>
<td>± 590.97</td>
<td>£ 899.20</td>
<td>£ 976.58</td>
<td>± 494.19</td>
<td>ns</td>
<td>ns</td>
<td>517.37</td>
<td>£ 560.95</td>
<td>£ 922.93</td>
</tr>
<tr>
<td>HF [ms²]</td>
<td>259.49</td>
<td>± 320.53</td>
<td>£ 347.30</td>
<td>£ 366.07</td>
<td>± 343.65</td>
<td>&lt; 0.01</td>
<td>ns</td>
<td>&lt; 0.01</td>
<td>261.82</td>
<td>294.21</td>
</tr>
<tr>
<td>LF/HF</td>
<td>1.15</td>
<td>± 0.68</td>
<td>£ 0.74</td>
<td>£ 1.88</td>
<td></td>
<td>ns</td>
<td>ns</td>
<td>&lt; 0.05</td>
<td>1.51</td>
<td>1.87</td>
</tr>
</tbody>
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HRV – heart rate variability; ns – not significant; SDNN – standard deviation of all RR intervals; rMSSD – root mean square of the successive differences between adjacent RRs; LF – low frequency; HF – high frequency

Table 2. Comparison of HRV parameter in patients with obstructive sleep apnea (OSA) and controls, as well as those with estimated apnea–hypopnea index (eAHI) < 15 (control and mild OSA) and ≥ 15 (moderate and severe OSA)
pathophysiological mechanism of the development of arterial hypertension, which appeared in most of our patients (Table 2) [30]. It is worth noting, that almost all our patients took beta-adrenolytics (100% of patients with severe OSA). It is a controversial issue whether this group of medicines should be used for the treatment of arterial hypertension and coronary artery disease in patients with OSA. Taking into account the mechanism of OSA, we must note, however, that the final phase of apnea is associated with recurrent bradycardia, and beta-adrenolytics have the potential to exacerbate this dangerous effect because of its negative chronotropic effect [31]. It has been shown, that around 52% of patients with heart failure who take beta-adrenolytics on a regular basis have OSA (AHI > 15) [32]. Additionally, recent study by Wolf et al. in hypertensive patients with OSA revealed that beta-adrenolytics attenuate apnea-induced heart rate acceleration [33].

Another disputable issue is the usefulness and accuracy of the Holter diagnostics of sleep apnea. A reference polysomnographic examination is a costly procedure, time-consuming and less available, and therefore cannot be used as a screening test. Recent publication confirms the reliability of a simpler diagnosis of obstructive respiratory disorders on the basis of 24-hour Holter monitoring by means of the Lifescreen Apnea software using eAHI in various groups of patients for screening purposes. This method is especially reliable with eAHI > 18 [17]. The identical method was used in our study. One study confirms the repeatability of the results from two consecutive nights on the basis of 48-hour ECG Holter monitoring [34]. Electrocardiographic techniques are also proposed to be used for monitoring of OSA [35]. An example of how cardiologists use Holter monitoring to assess the influence of sleeping pills on the possible aggravation of sleep apnea can be the publication describing the lack of significant changes in the eAHI in patients taking melatonin [36]. Nevertheless, it has to be emphasised, that Palma et al. recently reported that also sleep-related alveolar hypoventilation presents similar abnormalities in autonomic tone as observed in OSA [37]. This observation supports the importance of nocturnal hypoxia in inducing night-time abnormalities in frequency-domain indices, since the same author reported that patients with OSA, but without hypoxia, exhibit lower LF oscillations when compared with patients with OSA and hypoxia [38].

Conclusions

Our up-to-date largest study focused on relationship between HRV and OSA, suggests that when 24-hour ECG Holter monitoring can be used as screening for OSA, high frequency power spectrum in frequency-domain heart rate variability analysis can offer better parameters for the discrimination of coronary disease patients with mild OSA (from 5 to < 15) and with severe OSA (≥ 30) as compared to power spectrum in the LF band or time domain indices, such as SDNN and rMSSD.

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Financing

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Conflict of interest(s)

None.

Streszczenie

Obturacyjny bezdech senny (OSA) jest jednym z najczęstszych zaburzeń snu, obecnym u około 4% mężczyzn i 2% kobiet. Choroba może być rozpoznawana niezależnie od wieku i płci; jej częstość wzrasta z wiekiem. U chorych z OSA w trakcie snu dochodzi do wzmożonej aktywności układu współczulnego i zwiększonego wówczas wydzielania amin katecholowych. Pacjentów z OSA cechuje zwiększone ryzyko choroby wieńcowej (CHD).

Celem badania była ocena wpływu OSA na aktywność układów para- i sympatycznego w zakresie wybranych parametrów zmienności rytmu serca (HRV) – analizy czasowej i częstotliwościowej u chorych na CHD oraz przydatności tych parametrów w ustaleniu prawdopodobieństwa występowania bezdechów w czasie snu.
Material i metody. Obserwacji retrospektywnej poddano 146 pacjentów w wieku 43–78 lat (106 mężczyzn) z CHD. Chorych przydzielono do 4 grup na podstawie szacowanego wskaźnika bezdechów–spłyconych oddechów (eAHI) uzyskanego na podstawie 24-godzinnego zapisu elektrokrótkowęskiego metodą Holtera za pomocą oprogramowania Lifescreen: wynik poniżej 5 (grupa kontrolna), od 5 do mniej niż 15 (łagodny OSA); od 15 do mniej niż 30 (umiarkowany OSA) oraz ponad 30 (ciężki OSA). Dla każdego pacjenta opracowano profil zmian mocy widma dla niskiej częstotliwości (LF) i mocy widma dla wysokiej częstotliwości (HF) w 60-minutowych przedziałach czasu od godziny 22:00 do 06:00, a także obliczono wartości odczytu stanu kontraktu przesuniętego w zakresie R (SDNN) i pierwiastek średnicy sumy kwadratów różnic mięśni między sąsiadującymi odstępami NN (rMSSD) w poszczególnych grupach. Moc widma w kolejnych przedziałach godzinowych usredniono w obu grupach. Ze względu na prawoskórożne rozkład wartości średniej mocy widma przejrzano na logarytmy naturalne. W celu oceny istotności różnic porównano logarytmy naturalne ich szwark w kolejnych przedziałach godzinowych uśredniono w obu grupach. Wnioski. Podsumowując, moc widma w zakresie LF analizy częstotliwościowej HRV może być lepszym parametrem do wyodrębnienia grupy chorych z OSA łagodnym (od 5 do < 15) i ciężkim (≥ 30) u pacjentów z CHD niż moc widma w zakresie LF lub SDNN i rMSSD.

Słowa kluczowe: obturacyjny bezdech senny, dysfunkcja układu autonomicznego, zmienność rytmu serca

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