Original article

Usefulness of ambulatory ECG in the diagnosis of sleep-related breathing disorders

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Abstract

Background: Sleep-related breathing disorders (SRBD) are the additional factor related to poor prognosis in patients with cardiovascular disorders. The apnoea/hypopnoea index (AHI), describing the number of apnoea and hypopnoea episodes per one hour of sleep, has been used as a marker of severity of the disorder. The disease is present in 4% of men and 2% of women above 40 years of age. However, SRBD are diagnosed in less than 3% of patients with this syndrome due to lack of awareness of the disease among health care practitioners and patients. Polysomnography (PSG) has been used as a golden standard for detecting SRBD, however this test is available only in selected centres. Therefore, a simple, fast and inexpensive test for screening for SRBD is necessary. Respiratory activity influences the amplitude of ECG signal whereas heart rate variability (HRV) depicts the activity of the autonomic nervous system. These associations have been used to develop a new method for detection of SRBD involving analysis of HRV and morphology of ECG signal in ECG monitoring.

Aim: Assessment of accuracy of SRBD detection using estimated AHI (Est.AHI), calculated from Holter ECG recordings.

Methods: In a study group consisting of 74 patients tested for SRBD, simultaneous PSG and 24-hour ECG monitoring were performed. Following PSG, AHI for each patient was calculated. According to the AHI values patients were classified as SRBD patients (AHI >15), non-SRBD patients (AHI <5), whereas 12 individuals had borderline SRBD (5≤ AHI ≤15). Age, prevalence of concomitant disorders and treatment were similar in all groups. In all individuals the Est.AHI value was calculated based on ECG recording. Considering the AHI value as a reference parameter discriminating SDB and non-SRBD patients, the number of false positive and false negative results for detecting SDB with the Est.AHI was calculated. Moreover, the SRBD detection accuracy using the Est.AHI calculation was evaluated by the receiver-operator characteristic (ROC) curves which were used to calculate area under curve (AUC), sensitivity, specificity, as well as positive (PPV) and negative (NPV) predictive values for optimal cut-off value.

Results: According to Est.AHI, 50 (68%) patients were correctly diagnosed. The ROC analysis showed high accuracy of SRBD detection using Est.AHI: AUC – 0.91 with sensitivity – 91.2%, specificity – 87.5%, PPV – 88.6%, and NPV – 88.9%. The cut-off value of Est.AHI set at 17 was optimal for the differentiation between patients with or without SRBD.

Conclusions: The Est.AHI calculated with the Lifescreen Apnea software from Holter ECG is an accurate, specific and sensitive method for the detection and classification of obstructive and mixed SRBD.

Key words: sleep-related breathing disorders, ambulatory ECG monitoring, apnoea

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Introduction

Sleep apnoea is a breathing disorder characterised by pauses in breathing during sleep. In the situation when there are no pauses in breathing but episodes of significant reduction of airflow through the airways (expressed as decreased breathing amplitude by at least 50%) occur, one deals with shallow breathing (hypopnoea).

The apnoea and hypopnoea index (AHI) per one hour sleep is used to determine sleep-related breathing disorders (SRBD). According to AASM (American Academy of Sleep Medicine) obstructive sleep apnoea (OSA) is diagnosed when the AHI value is >5, together with increased daily drowsiness and at least two out of the following four symptoms: chronic snoring, choking

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sensation during sleep, frequent awakening and decreased concentration. Based on the AHI values, AASM identifies three levels of OBS severity: mild (5< AHI <15), moderate (15< AHI <30) and severe (AHI >30) [1].

Depending on the cause, there are three distinct forms of SRBD: OSA, central sleep apnoea (CSA) and mixed form, in which after a CSA episode, there is an obstructive one. Over 85% of patients with SRBD exhibit OSA.

Insufficient and disruptive sleep generates excessive daytime sleepiness. In patients with OSA excessive drowsiness is caused by disruptive sleep patterns. Apart from an undeniable impact on quality of life, OSA is the cause of approximately 20% of all road accidents [2]. There is convincing evidence showing an independent relation between SRBD and the incidence of cardiovascular diseases. The evidence is sound especially in the case of arterial hypertension, and even more convincing as far as ischaemic heart disease, stroke, heart failure, atrial fibrillation and sudden cardiac death are concerned. Obese patients are at high likelihood of having SRBD [3].

There is a high prevalence of SRBD. According to estimates approximately 4% of males and 2% of females over 40 years suffer from SRBD [4]. Undiagnosed cases of patients with moderate to severe SRBD are estimated at 93% of females and 82% of males [2, 4, 5]. In a Polish epidemiological study performed on a representative group of Warsaw inhabitants, SRBD was found in 11% of studied individuals. Based on estimates, the number of patients suffering from SRBD in our country may range from 200 to 400 thousand [6].

Polysomnography (PSG) is considered to be a golden standard in the diagnosis of SRBD [1]. It allows the recording of airflows through the upper respiratory tract, chest and abdomen movements, saturation and heart rate monitoring, as well as recording of encephalogram, electrooculogram and electromyelogram traces for defining sleep stages. Performing PSG requires much time, qualified staff and necessity of the patient's hospitalisation, which makes it costly. One of the reasons for poor SRBD detectability stems from low accessibility of PSG. The search for a simple, fast and cost-effective method of identification of patients with sleep apnoea results naturally from the diagnostic difficulties of SRBD.

The aim of this study was to assess the usefulness of the method of calculating estimated apnoea-hypopnoea index (Est.AHI), gained from ECG tracing analysis, to detect and grade SRBD.

Methods

The software Lifescreen Apnea by Delmar Reynolds makes it possible to calculate Est.AHI using a simple method, based on the analysis of ECG traces recorded while asleep. Lifescreen Apnea has been found applicable in the diagnosis of both obstructive and mixed apnoea.

Sleep-related breathing disorders influence both breathing activity and central nervous system performance. Respiration influences ECG signal amplitude (ECG-derived respiratory, EDR). Breathing control by the autonomic nervous system affects heart rate variability (HRV). These phenomena were used to work out a method of detecting SRBD through recording heart rate variations and morphological forms of ECG signal [7].

This method relies on ECG trace while asleep being divided into 1-minute intervals for which the likelihood of apnoea incidence is determined. Then Est.AHI is calculated (the algorithm assumes that an apnoea episode could happen if the probability is ≥50%). Time of recording should include at least 4 hours of undisturbed sleep.

The Lifescreen Apnea system is designed to monitor adult patients with the aim of detecting SRBD. The ECG data can be gained at any time and place specified by the doctor. Apart from equipment used for standard Holter ECG monitoring in the Lifescreen system, additional instrumentation is not required.

Algorithms and methods applied in ECG analysis and used in Lifescreen Apnea software have been described in detail in the studies by de Chazal et al. [7].

Our study included patients qualified for PSG at the Department of Lung Diseases at the Medical University in Poznań. Qualification for the study was based on the Epworth sleepiness scale (a questionnaire intended to measure the risk of daytime falling asleep in various situations) and 'Poznań' scale (a questionnaire regarding sleeping disorders) [8].

All participants gave an informed consent for participation in the study. DelMar Reynolds company neither sponsored the study in any way nor influenced its design and execution.

Patients with atrial fibrillation and atrial flutter, coronary artery disease, heart failure, diabetes type I, arterial hypertension treated with 2 or more drugs, past stroke, COPD, and those treated due to endocrinological disorders were excluded. In none of the analysed ECGs did supraventricular arrhythmias hinder HRV analysis done by the system.

Finally, the results of 74 patients with the suspicion of SRBD, who had simultaneous polysomnography test and 24-hour ECG monitoring (Pathfinder700 DelMar Reynolds), were used. Data gathered from the PSG test showed SRBD with features of obstructive apnoea or mixed apnoea.

The AHI value from PSG was a decisive factor for patients' assignment to one of the three groups. Standard criteria recommended by AASM were considered [1], and patients were assigned to one of the three groups depending on AHI: Group I with SRBD (AHI >15), Group II without SRBD (AHI <5), and Group III with borderline/uncertain SRBD (5≤ AHI ≤15).

Group I included 34 patients (26 males, 8 females, and median age of 54 years, range 39-66), group II – 28

Table I. Patients characteristics

Parameter	Group I	Group II	Group III	p
Number of patients	34	28	12	
Male gender	26 (76%)	22 (78%)	8 (67%)	NS
Age [years]	54 (39-66)	53 (43-71)	50 (39-75)	NS
BMI [kg/m^2]	29.6 (24.0-37.2)	29.2 (24.3–39.2)	29.1 (25.7-36.5)	NS
Snoring	23 (68%)	19 (68%)	9 (75%)	NS
Daily drowsiness*	2	0	0	NS
Epworth score	10 (6-17)	7 (0-11)	7.5 (2-11)	NS
Arterial hypertension	19 (56%)	12 (43%)	6 (50%)	NS
Type 2 diabetes mellitus	7 (20%)	5 (18%)	2 (17%)	NS
Current treatment				
Beta-blockers	16 (47%)	13 (46%)	4 (33%)	NS
ACE-I	16 (47%)	14 (50%)	7 (58%)	NS
Ca-channel blockers	5 (15%)	4 (14%)	2 (17%)	NS
Statins	26 (76%)	19 (68%)	8 (67%)	NS
Insulin	0	0	0	
Oral hypoglycemic drugs	7 (20%)	5 (18%)	2 (17%)	NS

**Number of patients in the group with Epworth sleepiness score of ≥16*
Abbreviations: BMI – body mass index, ACE-I – angiotensin-converting enzyme inhibitors

patients (22 males, 6 females, median age of 53 years, range 43-71), and group III – 12 subjects (8 males, 4 females, median age of 50 years, range 39-75). There was no difference between the groups with respect to age, comorbidities or treatment (Table I).

With the use of Lifescreen Apnea software, ECG Holter monitoring was analysed and Est.AHI was calculated for each studied subject. Gathered Est.AHI values were analysed paying special attention to the compatibility with AHI from the PSG test, and especially to the compatibility of patients' assignment to SRBD group.

Statistical analysis

Results were tested for normal distribution using W Shapiro-Wilk test. The results are presented as the median and maximum and minimum values (range). Assuming AHI value as a parameter differentiating ill patients from healthy ones, the number of false positive and negative results was calculated while diagnosing SRBD and using Est.AHI. By designating area under curve (AUC) using receiver operating characteristic (ROC) detection quality of SRBD incidence based on Est.AHI to AHI (calculated from PSG) was assessed. Sensitivity, specificity and positive and negative predictive values for optimal cut-off were calculated. A p value <0.05 was considered significant.

Results

The Est.AHI and AHI median values are shown in Table II. An analysis of Est.AHI values was performed paying special attention to the compatibility of a patient's assignment to SRBD group based on AHI. A proper qualification to one of the SRBD groups on the basis of Est.AHI was made in 50 (68%) studied patients.

The value of Est.AHI <5 was found in 9 (12%) subjects. In all those patients AHI was <5 as well. In the remaining patients with AHI <5, Est.AHI was in 9 patients ≥5 and ≤15, whereas in 10 patients it was >15. The Est.AHI value ≥5 and ≤15 was found in 22 (30%) patients. In 10 patients it corresponded with the value range determined on the basis of AHI (≥5 and ≤15). In this study group 9 patients had AHI <5, and 3 of them – >15. Forty-three (58%) patients had AHI >15, characteristic for patients with SRBD, while 31 of them had AHI >15 and 10 subjects – <5 (see Table III).

An assessment of SRBD based on Est.AHI showed a strong tendency to false positive and a small tendency to false negative results. Among patients without breathing disorders (AHI <5) as many as 10 (35%) had

Table II. The Est.AHI and AHI in each study group

Group	Est.AHI		AHI	
	median	range	median	range
I	49	10-71	45	18-74
II	10	1-30	3.5	0-4
III	10	5-22	10	7-13

Abbreviations: AHI – apnoea/ hypopnoea index, Est.AHI – estimated AHI

Table III. The Est.AHI observed in the study population and distribution of respective AHI values

Est.AHI	Number of patients	AHI	Number of patients
<5	9 (12%)	<5	9 (100%)
		≥5 and ≤15	0
		>15	0
≥5 and ≤15	22 (30%)	<5	9 (41%)
		≥5 and ≤15	10 (45%)
		>15	3 (14%)
>15	43 (58%)	<5	10 (23%)
		≥5 and ≤15	2 (5%)
		>15	31 (72%)

Table IV. Evaluation of SRBD diagnosis quality based on Est.AHI vs. AHI

	Area under curve	Sensitivity	Specificity	Cut-off	PPV	NPV	p
A	0.91	91.2%	85.7%	17	88.6%	88.9%	>0.0001
B	0.82	71.7%	89.3%	17	91.7%	65.8%	>0.0001
C	0.89	91.2%	87.5%	17	83.8%	91.9%	>0.0001

A: Analysis excluded group III patients, B: Group III patient included, qualified as SRBD, C: Group III patient included, qualified as non-SRBD Abbreviations: PPV – positive predictive value, NPV – negative predictive value

Table V. Evaluation of SRBD diagnosis quality based on Est.AHI vs. AHI

	Est.AHI >17 and AHI >15	Est.AHI <17 and AHI <15	Percentage of correct SRBD diagnosis
A	31/34	25/28	90%
B	34/46	25/8	80%
C	31/34	35/40	89%

Abbreviations: see Table IV

Est.AHI ≥15, which indicates SRBD of diverse severity, whereas 9 (32%) had a borderline, undistinguishing result (Est.AHI ≥5 and <15). Among patients with SRBD (AHI >15) only 3 (9%) had Est.AHI <15. None of the results showed no episodes of SRBD (AHI <5).

An analysis done using ROC curves for patients from groups I and II showed excellent accuracy in typing patients with SRBD based on Est.AHI (AUC=0.91). For optimisation of results interpretation, a higher cut-off point (Est.AHI >17) was found. Gathered values of cut-off point, sensitivity, specificity and area under curve for this point are presented in Table IV.

Additional analysis of ROC was performed including patients from group III [12 subjects with borderline results Est.AHI (≥5 and <15)] at one time into group II (without SRBD) and at the second time as patients from group I (with SRBD). The Est.AHI values of patients from group III treated as ones without SRBD did not change the quality of detection of SRBD. Treating patients from group III as those with SRBD slightly undermined the diagnostic power of the study, although it remained good (Figure 1).

Using the cut-off point for Est.AHI=17 allowed for correct qualification of 90% of patients in the group with differentiating AHI result (AHI >15 or AHI <5, 62 of the studied patients). By including studied subjects with undistinguishing result (AHI ≥5 and ≤15) into the group of patients with SRBD correct qualification amounted to 80%. Analysing those study patients as ones without SRBD, accuracy of typing reached 90% as well (Table V).

Discussion

Sleep-related breathing disorders are highly widespread, cause negative effects, and increase the risk of occurrence and aggravation of other diseases. Undiagnosed cases with SRBD are estimated to be about 93% in women and 82% in men [2, 4, 5]. Considering the possibility of effective treatment and reduction of SRBD effects, there is a need to improve the effectiveness of the SRBD diagnosis.

Taking standard criteria of SRBD detection [9], the method used in our work made it possible to classify correctly 50 (68%) of the studied subjects. At the same time, the results of ROC analysis showed very good distinguishing properties of Est.AHI for SRBD (AUC=0.91), having high sensitivity and specificity [10].

Our results indicate that in order to get such a correct typing it is necessary to assume Est.AHI value >17 as a diagnostic value for SRBD. Achieved in this way the accuracy of SRBD diagnosis reaches 90%, that is, it approaches the value shown in the original report [7]. The analysis of patients' results with uncertain AHI (group III) did not essentially alter the diagnostic value of the test. On the other hand, the ROC analysis can be applied to determine the accuracy of 'healthy-ill' typing. Therefore in the light of our results, using the method only to detect rather than to classify SRBD seems to be justified.

It has been documented that AHI >15 together with excessive daytime sleepiness and at least two out of four symptoms – chronic snoring, the feeling of choking while asleep, frequent awakening, decreased concentration – should urge the diagnosis of SRBD [9]. The most noticeable effects of sleep apnoea are snoring and daytime sleepiness, which are reported respectively in 70-95% and 30-50% of patients [11]. In our study group snoring and tendency to daytime sleepiness occurred in 82% (61) and 61% (45) of subjects, respectively. With regard to the widespread occurrence of those symptoms in the general population, they are not useful in the diagnosis of SRBD [12]. Diagnostic methods based on clinical course, despite medical history often extended

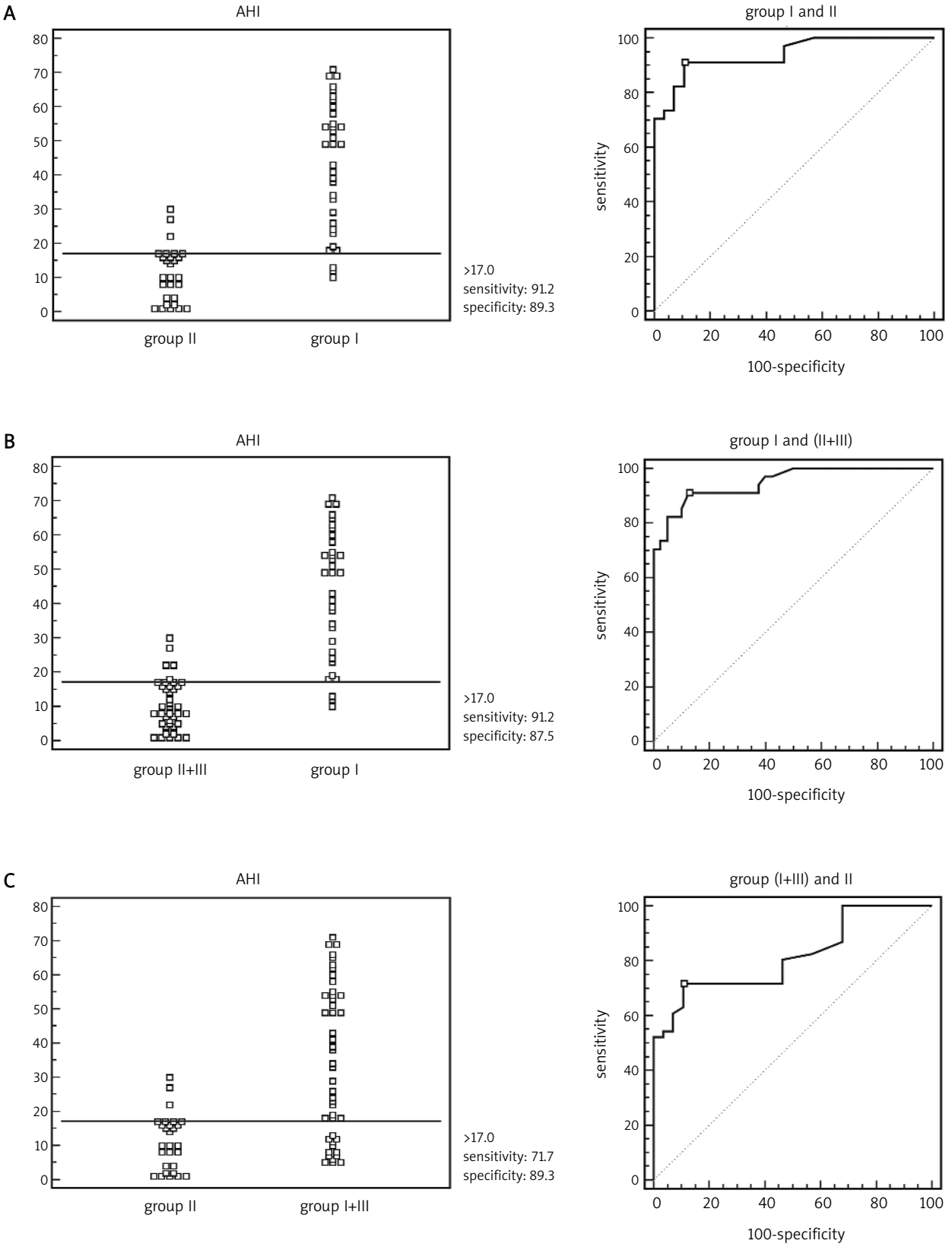

Figure 1. Distribution of Est.AHI and ROC curves for each study group. **A** – Analysis excluded group III patients, **B** – group III patient included, qualified as non-SRBD, **C** – group III patient included, qualified as SRBD

Abbreviations: AHI – apnoea/hypopnoea index, Est.AHI – estimated AHI, SRBD – sleep-related breathing disorders

towards apnoea, fail in over 50% of cases [13]. This happens because none of the SRBD symptoms is sensitive and specific enough [14]. The effectiveness of diagnosis is improved by increasing the number of observed symptoms. Snoring and periods of sleep apnoea confirmed by partners identify patients with SRBD with 78% sensitivity and 67% specificity. The probability of AHI >15 for these patients is 3-4-fold greater than for those who do not present with serious symptoms [15].

Obesity is an important risk factor of SRBD incidence and is reported in about 50% of patients (BMI >30) [16]. Neck circumference, fatty tissue distribution, facial skeleton deformation, hypertrophy of tonsils, CT and MRI images, and cephalometric data characteristics for some patients with SRBD have low predictive value [17].

Diagnostic models predicting the probability of SRBD on the basis of symptom analysis taken from patient's self-monitoring and extended by demographic and anthropometric data have been developed with the aim of improving diagnostic value of clinical data. The greater the frequency of diagnosed sleep apnoea the greater the demand to use such models in screening. Rowley et al. [18] estimated that the number of PSG tests could be reduced by 40% with the use of those methods. It would allow significant costs and time reduction needed for diagnosis. However, having relatively high sensitivity (76-96%), they show low specificity (13-54%) [18].

There is a growing interest in using nocturnal, percutaneous pulsoximetry in diagnosing BRSD. The advantage of this method is reasonable cost, the possibility of the out-patient evaluation, simplicity and easy results interpretation. Sensitivity of pulsoximetry in SRBD diagnostics ranges from 31% to 98% and specificity from 41% to 100%. Such a wide distribution of results may be caused by a great discrepancy of diagnostic criteria, studied population and the equipment used [19-21].

Sleep-related breathing disorders affect both breathing and the autonomic nervous system. Breathing has an impact on ECG amplitude, and at the same time balance of autonomic nervous system can be assessed by HRV [22-24]. Therefore, Tong et al. [25] assessing breathing activity based on R wave changes from 24-hour ECG monitoring explored the likelihood of SRBD episodes. In a study group of 80 subjects they showed a sensitivity of 88.3%, specificity of 35%, with 84.1% positive and 50% negative predictive value of such an approach.

Confirmed influence of SRBD on HRV is reflected in the attempts to use time and frequency domain parameters of HRV in the SRBD diagnosis. The ROC analysis and/or various models of regression analysis in different studies produced quite different results of SRBD detection. They fluctuate to a great extent (78.1% to 92.4% for sensitivity at 70.4% to 94.7% specificity for the frequency domain analysis and respectively 83.0% to 89.7% and 96.5% to 98.1% for the time domain analysis) [26-28].

The system used in our study is an integral part of the commercial system for 24-hour ECG monitoring. The study documented that Est.AHI >17 should prompt the suspicion of SRBD, which is generally underestimated, but significantly influences patient's health and well-being. The holistic approach based on symptoms and clinical examination is to determine patient's need to undergo follow-up and specialist tests to diagnose SRBD. Considering the numeric value of Est.AHI a proof of SRBD seems unjustified.

Atrial fibrillation and atrial flutter limit the methods used in this study and prevent HRV assessment. The other problem that could be faced is frequent and complex arrhythmia, which even when using very good elimination algorithms may disturb HRV and EDR analysis. Besides, the usefulness of this test in patients with cardiovascular comorbidities, diabetes or neurological diseases has not been determined so far. The PSC results may also differ between laboratories where the study is performed as a result of methodological differences [21, 29].

Conclusions

The method of automatic determination of Est.AHI from ECG seems to be a valuable differentiating method in patients with obstructive and mixed type SRBD.

Regardless of indications for the test, integration of the method with standard Holter analysis allows detection of potential risk and at the same time limits the number of undiagnosed SRBD cases.

The Est. AHI value >17 should suggest a SRBD episode. The presence of other symptoms typical for SRBD should determine the decision to refer a patient to a specialist centre.

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Ocena przydatności zapisów EKG w diagnostyce zaburzeń oddychania podczas snu typu obturacyjnego i mieszanego. Nowe zastosowanie monitorowania holterowskiego

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Streszczenie

Wstęp: Zaburzenia oddychania podczas snu (ZOPS) są czynnikiem obciążającym rokowanie w wielu chorobach układu sercowo-naczyniowego. Wykładnikiem ZOPS jest wskaźnik bezdechów i spłyceń oddychania przypadający na godzinę snu, zwany AHI (ang. *apnoe/hypopnoe index*). Na ZOPS cierpi ok. 4% mężczyzn i 2% kobiet w wieku >40 lat. Z powodu niskiej świadomości problemu zarówno wśród chorych, jak i lekarzy zdiagnozowanych jest <3% chorych. Polisomnografia (PSG), „złoty standard" diagnostyki ZOPS, dostępna jest w Polsce tylko w nielicznych ośrodkach. Wynika z tego potrzeba stosowania prostego, taniego i łatwo dostępnego badania przesiewowego. Kontrola oddychania przez autonomiczny układ nerwowy wpływa na zmienność rytmu serca (HRV). Czynność oddechowa wpływa na zmianę amplitudy sygnału EKG. Zjawiska te zostały wykorzystane do opracowania metody wykrywania ZOPS opartej na analizie HRV oraz form morfologicznych sygnału EKG w zapisach holterowskich.

Cel: Ocena jakości wnioskowania o obecności ZOPS na podstawie uzyskanego z analizy 24-godzinnych zapisów EKG przybliżonego wskaźnika AHI (Est.AHI).

Metodyka: U 74 osób z podejrzeniem ZOPS wykonano jednocześnie badanie PSG i 24-godzinne monitorowanie EKG. W grupie występowały wyłącznie ZOPS typu obturacyjnego lub mieszanego. Wartość wskaźnika AHI uzyskanego z PSG decydowała o kwalifikacji badanych do jednej z trzech grup. Do grupy z ZOPS (AHI >15) zakwalifikowano 34 chorych. W grupie bez ZOPS (AHI <5) znalazło się 28 osób, natomiast 12 osób z AHI ≥5 i ≤15 zaliczono do grupy z granicznymi/niepewnymi ZOPS. Przy zastosowaniu oprogramowania Lifescreen Apnea przeanalizowano zapisy holterowskie EKG i wyznaczono wartość wskaźnika Est.AHI dla każdego z badanych. Grupy były porównywalne pod względem wieku, występujących schorzeń i leczenia. Przyjmując wartość AHI jako parametr odróżniający chore osoby od zdrowych, obliczono liczbę wyników fałszywie dodatnich i ujemnych uzyskanych przy rozpoznawaniu ZOPS przy zastosowaniu wskaźnika Est.AHI. Dla oceny jakości wnioskowania o obecności ZOPS na podstawie Est.AHI wobec AHI zastosowano metodę charakterystyki roboczej odbiorcy (ROC). Wyznaczono czułość, swoistość, wartość punktu odcięcia, pole pod krzywą dla tego punktu oraz pozytywną i negatywną wartość predykcyjną.

Wyniki: Na podstawie wskaźnika Est.AHI poprawnie sklasyfikowano ZOPS u 50 (68%) badanych. Analiza ROC wykazała bardzo dobre (AUC=0,91) właściwości różnicujące dla Est.AHI w typowaniu chorych z ZOPS. Metodę cechowała duża czułość (91,2%), swoistość (85,7%) oraz pozytywna i negatywna wartość predykcyjna (88,6% i 88,9%). Przeanalizowano dodatkowo grupę badanych, traktując 12 osób z granicznymi wynikami AHI (5≤ AHI ≥15) raz jako osoby bez ZOPS, drugi raz jako osoby z ZOPS. Nie wpłynęło to zasadniczo na dokładność wnioskowania na podstawie Est.AHI.

Wnioski: Zastosowaną w pracy metodę cechowała duża dokładność typowania chorych z ZOPS typu obturacyjnego i mieszanego.

Słowa kluczowe: diagnostyka, zaburzenia oddychania podczas snu, bezdech senny, EKG, analiza ROC

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