Folia Cardiologica 2016
tom 11, nr 6, strony 504–510
DOI: 10.5603/FC.2016.0107

ISSN 2353–7752

Holter assessment of sleep-disordered breathing in pulmonary arterial hypertension and in pulmonary hypertension due to left ventricular dysfunction

Ocena zaburzeń oddychania w czasie snu z wykorzystaniem rejestracji holterowskiej u pacjentów z tętniczym nadciśnieniem płucnym oraz nadciśnieniem płucnym wtórnym do dysfunkcji lewej komory serca

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Abstract

Introduction. Sleep-disordered breathing (SDB) affects approximately 2–12% of the general population and the prevalence among patients with heart failure due to left ventricular dysfunction (LV–HF) is even higher. SDB is an important determinant of worse clinical outcomes in such patients. In contrast, the prevalence of SDB in pulmonary arterial hypertension (PAH) and its implications remain unclear. The purpose of this study was to compare relations between estimated apnea-hypopnoea index (eAHI) and clinical parameters in patients with LV–HF and PAH, with particular attention to the consequences of SDB.

Material and methods. Eighty-one patients were screened for SDB using commercial Holter electrographic monitoring software that allowed evaluation of eAHI. The study population consisted of 39 LV–HF patients and 42 PAH patients.

Results. While similar N-terminal pro B-type natriuretic peptide (NT-proBNP) levels were noted in both groups, LV–HF patients were characterized by higher age (63 vs. 50 years, respectively, $p < 0.001$), higher proportion of males (87% vs. 40%, $p < 0.0001$), and higher eAHI (24 vs. 14, $p < 0.001$) and body mass index (BMI) (28 vs. 25 kg/m^2, $p < 0.001$) values compared to the PAH group. The prevalence of SDB, defined as eAHI > 15, was 64% in the LV–HF group and 36% in the PAH group. Parameters of time domain heart rate variability (HRV) analysis were lower in PAH vs. LV–HF. Patients with LV–HF had more ventricular arrhythmias than patients with PAH. In the LV–HF group, eAHI correlated positively with NT-proBNP level, and negatively with left ventricular ejection fraction and the mean heart rate. The median eAHI was 18.7, and patients with eAHI above the median had more supraventricular arrhythmias. In the PAH group, a negative correlation between eAHI and age was found. In the subgroup with eAHI < 15, rMSSD values were higher and idiopathic PAH predominated. The median eAHI was 8.4, and patients with eAHI above the median were younger and had higher BMI values.

Conclusions. Sleep-disordered breathing was more frequent and eAHI was higher in patients with LV–HF compared to those with PAH, although it was present in more than one third of patients in the latter group. Higher eAHI values indicated more severe hemodynamic dysfunction in patients with LV–HF. In the PAH group, higher eAHI was associated with clinical presentation at a younger age. Patients with PAH seem to have worse HRV parameters compared to patients with left ventricular dysfunction.

Key words: sleep-disordered breathing, sleep apnea, pulmonary arterial hypertension, heart failure

Folia Cardiologica 2016; 11, 6: 504–510

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Introduction

Sleep-disordered breathing (SDB) is a severe, potentially life-threatening clinical syndrome characterized by occurrence of sleep apnea episodes leading to sympathetic system activation, which results in multiple awakenings and sleep defragmentation. The estimated prevalence of sleep apnea in the general population, depending on the source, ranges from 2% in women and 4% in men [1] to 5.7% in women and 12.4% in men [2]. According to the current guidelines, the major diagnostic test to investigate SDB, which allows the definite diagnosis, is polysomnography (PSG). As this method is not widely available, screening methods are currently used, based on, among others, sleep polygraphic techniques which are widely available and may be used on an outpatient basis. One of the quantitative parameters used to evaluate the severity of SDB is the apnea/hypopnea index (AHI) [3, 4], defined as the number of apnea and hypopnea episodes per an hour of sleep. AHI values > 15 or > 5 with concomitant clinical symptoms of sleep apnea syndrome are considered abnormal and indicate significant sleep apnea. Clinical studies [5, 6] confirmed an association between sleep apnea and hypertension, myocardial infarction incidence, strokes, and development of heart failure.

Due to limited data, the association between sleep apnea and pulmonary hypertension and its significance are still unclear. A role of several parameters in the evaluation of disease severity, stability of its course, and prognosis has been recently documented [7]. However, studies on the usefulness of new parameters are still underway. Of note, pulmonary arterial hypertension (PAH) is a severe disease characterized by constantly elevated pulmonary vascular resistance, ultimately leading to right ventricular failure and death [8]. Major causes of mortality are progressing right ventricular failure, sudden cardiac death (including arrhythmic death), and respiratory failure [9]. Disease progression is observed despite availability of drugs used specifically for its treatment [10].

As already mentioned, the prevalence of SDB in the population of patients with PAH and right ventricular failure and clinical implications of this phenomenon remain poorly understood. It seems that the prevalence of sleep apnea among patients with confirmed PAH may be higher compared to the general population. In the study by Dumitrascu et al., AHI values > 10 were found in more than 25% of patients with established PAH in the World Health Organization (WHO) functional class II or III [11]. For a comparison, SDB is present in a large proportion (40–70%) of patients with heart failure due to left ventricular systolic dysfunction (left ventricular heart failure, LV–HF) [12] and is known to be an important factor determining worse outcomes in these patients [13–15].

Taking into account all the above issues, we designed a study to determine the prevalence of SDB in patients with PAH of various aetiology and patients with LV–HF with secondary pulmonary hypertension, with particular attention to the consequences of SDB.

Material and methods

The study included 81 patients hospitalized in a single centre experienced in hospital treatment and further outpatient care for adult patients with PAH. The patients were included in the study regardless of the presence or absence of sleep apnea syndrome symptoms (e.g., snoring, excessive daytime sleepiness, witnessed apnea episodes). All patients gave their written informed consent for study participation. The study was performed in accordance with the Helsinki Declaration. The study protocol was approved by a local bioethics committee (RNN/194/15/KE). The study population was divided into two groups:

- 42 patients with confirmed PAH (the mean pulmonary artery pressure [MPAP] > 25 mm Hg during right heart catheterization). They received specific therapy according to the pulmonary hypertension therapy program. According to the European Society of Cardiology (ESC) clinical classification of pulmonary hypertension, the included patients were in the group 1 (including 19 patients with idiopathic PAH, 7 patients with PAH due to congenital heart disease and 6 patients with connective tissue disease);
- 39 patients with documented systolic heart failure due to coronary artery disease. The inclusion criteria were: left ventricular ejection fraction (LVEF) ≤ 50%, systolic pulmonary artery pressure (SPAP) > 30 mm Hg, New York Heart Association (NYHA) functional class II–III, and optimal drug therapy.

The exclusion criteria were as follows: moderate or severe left heart valvular dysfunction, atrial fibrillation/flutter, NYHA class IV, acute myocardial infarction, a previous diagnosis of sleep apnea by PSG, and lack of patient consent for participation in the study.

In all patients, in addition to history taking and physical examination including anthropometric parameters, 24-hour Holter electrocardiographic (ECG) monitoring using commercially available software to estimate AHI, standard transthoracic echocardiography, and laboratory tests were performed.

Twenty-four hour ECG monitoring was performed using a 3-channel digital recorder (Del Mar Reynolds Medical Lifecard CF) and analysed using the Pathfinder 700 and Lifescreen Apnea (Spacelabs Healthcare, Issaquah WA, USA) software. As mentioned above, sleep apnea activates autonomic nervous system which results in a specific modulation of sinus rhythm. The Lifescreen Apnea software

Table 1. Group characteristics and comparison

Parameter	Patients with left ventricular systolic dysfunction (n = 39)	Patients with pulmonary arterial hypertension (n = 42)	P value
Age [years], mean ± SD	63 ± 9	50 ± 17	< 0.001
Male gender [n (%)]	34 (87%)	17 (40%)	< 0.0001
BMI [kg/m^2], mean ± SD	28 ± 4	25 ± 5	< 0.001
NYHA/WHO functional class:			
• II [n (%)]	17 (44%)	21 (50%)	NS
• III [n (%)]	22 (56%)	21 (50%)	NS
NT-proBNP [pg/mL], mean ± SD	1855 ± 2516	1521 ± 1929	NS
Etiology: n (%)	Coronary artery disease: 39 (100%)	Idiopathic: 19 (45%)	
		CHD: 17 (40%)	–
		CTD: 6 (15%)	

SD — standard deviation; BMI — body mass index; NYHA — New York Heart Association; WHO — World Health Organization; NS — nonsignificant; NT-proBNP — N-terminal pro-B-type natriuretic peptide; CHD — congenital heart disease; CTD — connective tissue disease

calculates the likelihood of apnea/hypopnea events based on changes of R-R intervals in the ECG and the respiratory signal obtained from the ECG analysis. The methods were described in detail in the study by De Chazal et al. [16]. The likelihood of apnea/hypopnea events is calculated for subsequent 1-minute periods and then for longer periods. If the likelihood is > 50%, the algorithm considers the event to occur and the overall result is reported as the estimated AHI (eAHI) for the whole sleep period. Estimated AHI values ≤ 5 are normal, eAHI > 15 indicates significant SDB, and intermediate values are considered borderline. The minimum required sleep length was 6 hours. The time of falling asleep and awakening was noted by the patient in a diary received for the period of Holter monitoring. In addition to eAHI calculation, a typical analysis of cardiac rhythm was performed, with evaluation of the mean, maximum, and minimum heart rate (mean HR, max HR, min HR), the number of ventricular extrasystoles (ExV) and supraventricular extrasystoles (ExSV), and the occurrence of arrhythmic events including non-sustained ventricular tachycardia (nsVT) and supraventricular tachycardia (SVT). Heart rate variability (HRV) analysis was also performed according to the guidelines [17], with calculation of three parameters: the standard deviation of all sinus rhythm R-R intervals (SDNN), the square root of the mean of the squares of the successive differences between adjacent R-R intervals (rMSSD), and the triangular index, calculated as the total number of R-R intervals divided by the number of R-R intervals with the most frequently seen duration.

Transthoracic echocardiography was performed using the Vivid E9 system with the M5S-D 2D 1.5–4.5 MHz probe. Standard measurements were performed in typical two-dimensional echocardiographic views. Tricuspid annular plane systolic excursion (TAPSE) in M-mode was measured to evaluate right ventricular function, and TAPSE values < 16 mm were considered significantly reduced [18]. Calculation of SPAP was based on the measurement of peak tricuspid regurgitation pressure gradient and the estimated mean right atrial pressure. The modified Simpson method was used to calculate LVEF.

Statistical analysis

Normal distribution of the variables was evaluated using the Shapiro-Wilk test. Two-group comparisons were performed using the Student *t* test for independent variables for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables. Correlations were evaluated using the nonparametric Spearman's rank correlation coefficient. $p < 0.05$ was considered significant. Calculations were performed using the STATISTICA v10.0 statistical package and the Microsoft Excel spreadsheet.

Results

Population characteristics and group comparison

Baseline patient characteristics and comparison of the two study groups are shown in Tables 1 and 2. We found significant differences in regard to age and the body mass index (BMI), with lower values in the PAH group. The two groups also differed by gender distribution, with a higher proportion of women in the PAH group. Elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels were found in both group but did not differ significantly. The results of 24-hour Holter ECG monitoring and echocardiographic studies are shown in Table 2.

Patients with PAH were characterized by good left ventricular systolic function and very high SPAP values compared to the LV–HF group. Patients with LV–HF were characterized by higher rates of ventricular arrhythmia (ExV and nsVT), while PAH patients had more SVT. We found significantly lower HRV parameters in the PAH group. The prevalence of SDB is shown in Figures 1 and 2.

Table 2. Electrocardiographic and echocardiographic group characteristics (data shown are mean values ± standard deviation [SD] unless indicated otherwise)

Parameter	Patients with left ventricular systolic dysfunction (n = 39)	Patients with pulmonary arterial hypertension (n = 42)	P value
Mean HR [1/min]	69 ± 9	70 ± 8	NS
Maximum HR [1/min]	104 ± 14	121 ± 91	NS
Minimum HR [1/min]	53 ± 7	57 ± 15	0.01
ExV [n]	2144 ± 5572	292 ± 559	< 0.0001
nsVT episodes [n]	0.9 ± 1.7	0.2 ± 0.6	0.01
Occurrence of nsVT [%]	20	9	
ExSV [n]	210 ± 625	294 ± 1369	NS
SVT episodes [n]	1.7 ± 4.8	3.3 ± 10	< 0.05
eAHI [1/hour of sleep]	24 ± 14	14 ± 15	< 0.001
SDNN [ms]	118 ± 41	100 ± 37	0.03
rMSSD [ms]	31 ±22	22 ± 11	0.03
TI	33 ± 12	26 ± 10	0.01
LVEF [%]	33 ± 8	56 ± 3	< 0.000001
SPAP [mm Hg]	40 ± 10	93 ± 27	< 0.000001
TAPSE [mm]	19.8 ± 5	18.8 ± 4	NS

HR — heart rate; NS — nonsignificant; ExV — ventricular extrasystole; nsVT — nonsustained ventricular tachycardia; ExSV — supraventricular extrasystole; SVT — supraventricular tachycardia; eAHI — estimated apnea–hypopnea index; SDNN — standard deviation of all sinus rhythm R-R intervals; rMSSD — square root of the mean of the squares of the successive differences between adjacent R-R intervals; IT — triangular index (total number of R-R intervals divided by the number of R-R intervals with the most frequently seen duration); LVEF — left ventricular ejection fraction; SPAP — systolic pulmonary artery pressure; TAPSE — tricuspid annular plane systolic excursion

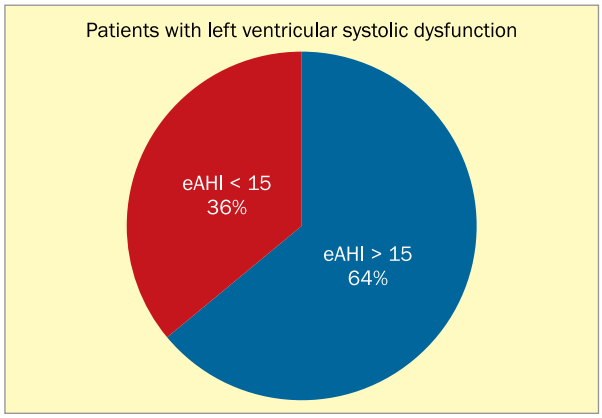

Figure 1. Prevalence of sleep-disordered breathing in patients with left ventricular systolic dysfunction and secondary pulmonary hypertension; eAHI — estimated apnea–hypopnea index

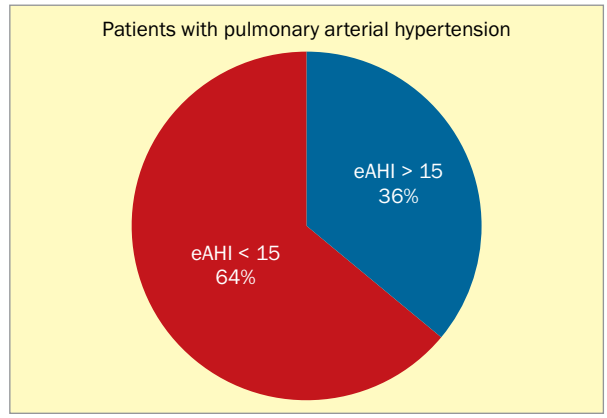

Figure 2. Prevalence of sleep-disordered breathing in patients with pulmonary arterial hypertension; eAHI — estimated apnea–hypopnea index

Clinical importance of sleep-disordered breathing as evaluated based on eAHI values

In patients with LV–HF, we found a significant positive correlation between eAHI and NT-proBNP levels (Spearman R = 0.45, p = 0.005) and a negative correlation between eAHI and LVEF (Spearman R = –0.39, p = 0.01). Thus, patients with LV–HF and more severe sleep apnea (eAHI > 15) had significantly lower LVEF (p = 0.002) and higher NT-proBNP levels (p = 0.01). In Holter ECG monitoring, eAHI was inversely related to the mean HR (Spearman R = –0.38, p = 0.02). In addition, a trend for more ExSV with higher eAHI values was noted in the LV–HF group, which achieved statistical significance for eAHI above the median (18.7, p = 0.03).

In the PAH group, eAHI values were inversely related to age (Spearman R = –0.38, p = 0.01). Patients with eAHI > 15 had significantly lower rMSSD values (p = 0.03) and showed a trend for lower SDNN values (p = 0.07). Abnormal

and higher eAHI values were more frequent in patients with PAH aetiology other than idiopathic pulmonary hypertension ($p = 0.03$). PAH patients with eAHI values above the median (i.e., > 8.4) were characterized by lower age ($p = 0.008$) and higher BMI values ($p = 0.04$).

Discussion

Our study dealt with a rare disease which PAH is, but we were able to include 42 patients with confirmed PAH, the number similar or higher than in other publications. We reported findings for a wide profile of clinical parameters, including the occurrence of SDB. It is a novel approach to the problem of PAH, particularly in the context of actively searching sleep apnea among patients with PAH, as only few studies on this issue were reported previously. A strength of our study is a focus on the importance of eAHI in relation to the parameters conventionally evaluated during the clinical management.

Of note, patients included in the study had a similar functional status (NYHA/WHO classification, similar mean NT-proBNP levels) but significant differences were found between the two groups. Regarding arrhythmic events, ventricular arrhythmia clearly predominated in the LV–HF group, while supraventricular arrhythmia was more severe in patients with PAH. While malignant ventricular arrhythmia is a major cause of sudden cardiac death in heart failure (resulting in prophylactic implantation of cardioverter-defibrillators), it seems that sudden cardiac deaths in the PAH population (amounting to about 28% of all deaths) are rather caused by non-arrhythmic mechanisms [19]. On the other hand, SVT is believed to have a major effect on cardiac function, leading to worse outcomes in patients with PAH. Although patients with atrial flutter/fibrillation were excluded from our study, short SVT episodes were clearly more prevalent in the PAH group compared to the LV–HF group.

We confirmed a very high prevalence of SDB in patients with left ventricular systolic dysfunction. In these patients, higher eAHI values indicated a much worse hemodynamic function (lower LVEF and higher NT-proBNP values) and a higher rate of supraventricular arrhythmia. Relations between natriuretic peptide levels, LVEF and SDB in heart failure were documented in the literature [20, 21]. Our findings are also consistent with previous reports of SDB promoting supraventricular arrhythmia, including both premature supraventricular beats and atrial fibrillation [22]. A high rate of SDB seen in patients with established Group 1 pulmonary hypertension (36%) is a novel observation which may contribute to better understanding of this pathology. Recently, Minic et al. [23] used PSG and showed that the rate of SDB in PAH may be even higher. They also found that the rate and severity of SDB increased with patient age, similarly to the trend observed in the general population. An unexpected finding of our study is the observation of an association between younger age and SDB in PAH patients. Perhaps it is an effect of a high proportion (40%) of younger patients with congenital heart disease in our study group. The association between age and SDB is thus not so clearly defined in patients with PAH and may depend on the group characteristics. In fact, SDB were more related to congenital heart disease and connective tissue disease than to idiopathic PAH. Higher BMI values are an important factor increasing the severity of sleep apnea in PAH, similarly to other observations and studies in the general population [24].

Multiple studies showed that low HRV parameters are significantly associated with worse outcomes, particularly in patients with previous myocardial infarction or congestive heart failure. Autonomic nervous system function disturbances have been recently reported by Polish authors [25]. Of note, the latter study included only 25 patients with group 1 pulmonary hypertension who were compared to healthy subjects. In our study, HRV parameters were found to be much worse even comparted to patients with heart failure, which is an even more worrisome finding. In addition, HRV parameters were even worse in patients with high eAHI values. Whether this may have an effect on long-term outcomes, for example by promoting malignant arrhythmia and sudden cardiac deaths, is clearly an issue which deserves further studies. It is known that increased sympathetic nervous system activity and impaired HRV are among major risk factors for arrhythmia in PAH [19].

Study limitations

The study was performed in a single centre due to rare occurrence of PAH, and the number of patients was limited. The group with left ventricular dysfunction included consecutive patients hospitalized in the centre, considering the inclusion and exclusion criteria. Sleep apnea was evaluated using a screening method. However, this method was previously verified against PSG [26], and its good reproducibility in subsequent days was documented [27].

Conclusions

The prevalence of SDB in patients with confirmed pulmonary hypertension is very high, perhaps in as many as more than one third of patients. Several factors have been identified that indicate a higher likelihood of SDB in patients with pulmonary hypertension, including younger age, higher BMI, and PAH due to congenital heart disease and connective tissue disease. Sleep apnea contributes to an adverse modulation of the autonomic nervous system activity in patients with PAH. Our findings should prompt further studies to confirm an association between SDB and PAH, and document the effect of SDB on the prognosis and treatment outcomes in these patients.

Financing

This study was supported by the National Science Centre grant No. 2012/07/B/NZ5/00016.

Conflict of interest(s)

The authors declared no conflicts of interest(s).

Streszczenie

Wstęp. Zaburzenia oddychania w czasie snu (SDB) dotyczą 2–12% ogólnej populacji; jeszcze wyższy odsetek obserwuje się wśród pacjentów z niewydolnością serca spowodowaną dysfunkcją lewej komory (LV–HF). Występowanie SDB w tętniczym nadciśnieniem płucnym (PAH) oraz jego implikacje kliniczne pozostają niejasne. Celem pracy było porównanie relacji między oszacowanym wskaźnikiem bezdechu sennego (eAHI) a parametrami klinicznymi pacjentów z LV–HF i PAH, z uwzględnieniem konsekwencji obecności bezdechu sennego.

Materiał i metody. Do badania włączono 81 chorych, u których wykonano 24-godzinne monitorowanie elektrokardiograficzne metodą Holtera w celu obliczenia eAHI. Populację podzielono na dwie grupy — 39 chorych z LV–HF o etiologii wieńcowej oraz 42 chorych z PAH.

Wyniki. W grupie LV–HF dominowali mężczyźni (87% *v.* 40% w grupie PAH; p < 0,0001), w starszym wieku (63 *v.* 50 lat w grupie PAH; p < 0,001), z wyższymi wartościami wskaźnika masy ciała (BMI) (28 *v.* 25 kg/m^2; p < 0,001) oraz niższą frakcją wyrzutową lewej komory (LVEF) (33 *v.* 56%; p < 0,000001), choć grupy charakteryzowała podobna średnia wartość stężenia N-końcowego fragmenty propetydu natriuretycznego typu B (NT-proBNP). Zaburzenia oddychania w czasie snu, zdefiniowane jako eAHI ponad 15, stwierdzono u 64% chorych z LV–HF i u 36% pacjentów z PAH. Wyższe wartości eAHI występowały w grupie LV–HF (24 *v.* 14; p < 0,001). Pacjenci z LV–HF cechowali się obecnością licznych arytmii komorowych, a przy wartościach eAHI powyżej mediany (> 18,7) potwierdzono zwiększoną częstość występowania arytmii nadkomorowej. W PAH obserwowano istotnie obniżone parametry czasowej zmienności rytmu zatokowego (HRV). W grupie LV–HF wykazano korelację eAHI z wartościami NT-proBNP i odwrotną korelację z LVEF oraz średnią dobową częstotliwością pracy serca. Z kolei eAHI w grupie chorych z PAH nie korelowało z NT-proBNP ani LVEF, ale było odwrotnie proporcjonalne do wieku. Wśród chorych z PAH i wartościami eAHI poniżej 15 przeważali pacjenci z PAH o etiologii idiopatycznej, z wyższymi wartościami rMSSD. Pacjentów z PAH i wartościami eAHI powyżej mediany (> 8,4) charakteryzowały młodszy wiek oraz wyższe wartości BMI.

Wnioski. Zaburzenia oddychania podczas snu u pacjentów z PAH nie były tak częste jak u chorych z LV–HF, ale dotyczyły więcej niż 1/3 populacji. Wyższe wartości eAHI u chorych z LV–HF wskazują na zaawansowaną dysfunkcję hemodynamiczną. U pacjentów z PAH obecność SDB wiąże się z zachorowaniem w młodszym wieku i wskazuje na istotną dysregulację w zakresie autonomicznej kontroli pracy serca.

Słowa kluczowe: zaburzenia oddychania podczas snu, bezdech senny, tętnicze nadciśnienie płucne, niewydolność serca

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