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Fundação Universitária de Cardiologia

ABSTRACT

Objectives: Obstructive sleep apnea (OSA) is an emerging risk factor for cardiovascular disease and is mostly undiagnosed. Sudden changes in heart rate mediated by the autonomic nervous system are observed during sleep apnea episodes. It is not clear whether the presence of cyclic variation of heart rate (CVHR) is useful in predicting OSA. The purpose of the present study was to estimate the diagnostic accuracy of electrocardiographic Holter monitoring to identify patients with significant OSA in a selected population compared to polysomnogram.

Methods: 136 consecutive patients underwent polysomnography (PSG) and electrocardiogram (ECG) Holter monitoring simultaneously for eight hours during sleep-time. All data from the PSG, the ECG Holter recordings and the automated sleep apnea software were evaluated to compare patients with regard to cyclic variation of heart rate, apnea and hypopnea index (AHI) and sleep parameters.

Keywords: sleep apnea, obstructive; electrocardiography, ambulatory; heart rate; sensitivity and specificity; polysomnography.

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The Clinical Utility of Electrocardiographic Holter Monitoring for Detecting Sleep Apnea

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Methods: 136 consecutive patients underwent polysomnography (PSG) and electrocardiogram (ECG) Holter monitoring simultaneously for eight hours during sleep-time. All data from the PSG, the ECG Holter recordings and the automated sleep apnea software were evaluated to compare patients with regard to cyclic variation of heart rate, apnea and hypopnea index (AHI) and sleep parameters.

Results: Patients diagnosed as severe OSA had longer duration of CVHR measured by the Holter monitoring. The likelihood of having significant OSA was directly proportional to the presence and duration of the CVHR. There was a moderate correlation between the duration of the CVHR episodes and the AHI ($r = 0.50$; $P < 0.0001$; 95% CI; $r = 0.36$ to 0.62). The diagnostic utility of CVHR detected on Holter monitoring in the detection of severe OSA was determined using receiver operating characteristic (ROC) curves, assuming $AHI > 15$ as references for severe OSA. We also described the likelihood ratios for OSA stratified by different ranks of CVHR duration.

Conclusion: Electrocardiographic Holter monitoring has good accuracy for the detection of significant OAS in a selected population and therefore can be considered as a valuable simplified technique.

Keywords: sleep apnea, obstructive; electrocardiography, ambulatory; heart rate; sensitivity and specificity; polysomnography.

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1. INTRODUCTION

There is a large amount of recent evidence supporting that obstructive sleep apnea (OSA) is an independent risk factor for cardiovascular disease [1]. The prevalence of OSA appears to be increasing due to epidemic rising rates of obesity. The current prevalence of moderate to severe OSA in the adult population are 10% to 15% in males and 3% to 9% in females when defined as an apnea-hypopnea index (AHI) ≥ 15 events per hour as measured by a polysomnogram accompanied by at least one symptom or sign of OSA [2,3].

Individuals with OSA are at greater risk of stroke [4], hypertension [5,6], atrial and ventricular arrhythmias [7-9], impaired quality of life [10] and has been linked to adverse cardiovascular outcomes including coronary artery disease and congestive heart failure [11,12]. Severe untreated OSA has been associated with increased all-cause and cardiovascular mortality [13-16].

The OSA syndrome is a treatable form of disordered breathing in which the upper airway closes repeatedly during sleep. Evidence suggests that a large proportion of individuals with OSA remain undiagnosed [17]. Effective diagnosis and treatment may reduce the morbidity and mortality associated with OSA [18-20]. The gold standard diagnostic test for OSA is an overnight polysomnography (PSG), but it has several limitations including a prolonged wait time depending on available local resources, inconvenience of an overnight sleep study and expense, especially for lower socioeconomic areas [21]. Portable monitors can be used as an alternative tool to PSG for OSA diagnosis in patients with high pre test probability of having moderate to severe OSA. Portable monitors also can be indicated when critical illness or limited mobility is an issue [22].

Sudden changes in heart rate mediated by the autonomic nervous system are observed during sleep apnea episodes [23]. There is a specific pattern of cyclical variation of heart rate (CVHR) which consists of bradycardia during the apnea followed by an abrupt tachycardia upon its cessation.

The diagnosis of OSA based on electrocardiogram (ECG) recordings during PSG has been evaluated by previous researchers [24-26]. This study proposes an alternative tool to detect sleep apnea using a specific Holter software to detect CVHR.

II. METHOD AND MATERIALS

2.1 Population and study protocol

We conducted a cross-sectional study to evaluate patients with OSA through the presence of CVHR.

Consecutive patients who were specifically referred to PSG for evaluation of suspected sleep-disordered breathing were invited to participate. A full PSG study and ECG Holter monitoring were recorded simultaneously during sleep - time. Two independent physicians, each one blinded to the results of the other, performed heart rate variability analysis and synchronized polygraphic scoring. They completed a questionnaire to provide a measurement of the subject's general level of daytime sleepiness (Epworth sleepiness scale) [27].

Exclusion criteria were permanent or paroxysmal atrial fibrillation during the electrocardiographic Holter monitoring or permanent pacemaker. Participants gave written informed consent before starting the PSG test. The study protocol was approved by the Research Ethics Committee of the *Instituto de Cardiologia – Fundação Universitária de Cardiologia* (protocol number UP4785/12). We followed the STARD statement for studies of diagnostic accuracy [28].

2.2 Polysomnographic Data

A full-night PSG was performed using a digital system (*BMW III PSG Neurovirtual, Brazil*) at *Sonolab* (the sleep laboratory *Hospital Mãe de Deus*, in *Porto Alegre*) during the subject's habitual sleep time. The following physiological variables were monitored simultaneously and continuously: four channels for the Electroencephalogram (EEG); two channels for the electrooculogram (EOG); two channels for the surface electromyogram (EMG) (submentonian region and anterior tibialis muscle); one channel for an ECG; airflow detection via two channels through a thermocouple (one channel) and nasal pressure (one channel); respiratory effort of the thorax (one channel) and of the abdomen (one channel) using inductance plethysmography; snoring (one channel) and body position (one channel); oxy - hemoglobin saturation (SpO₂); and pulse rate. EEG arousals and leg movements were scored according to the criteria established by the AASM Manual for Scoring Sleep and Associated Events [29]. Apneas and hypopneas were scored and classified following the recommended respiratory rules for adults

suggested by the AASM Manual. Sleep staging was performed using *Rechtschaffen* and *Kales* criteria [30]. One trained technician visually scored all PSGs according to standardized criteria for investigating sleep and an experienced blind examiner reviewed and reported all polysomnogram tests. Severity of OSA was categorized as follows: mild (AHI > 5 to 15 events/h); moderate (AHI > 15 to 30 events/h) and severe (AHI > 30 events/h).

2.3 Electrocardiographic Holter Analysis

The software used for the analysis of Holter tracings was a software designed for detecting sleep apnea through analysis of the RR tachogram (graphs of heart rate vs time) and CVHR (*Cardio Sistemas® Comercial e Industrial LTDA, São Paulo, Brazil*). An experienced blind examiner reviewed and reported all Holter tests in order to identify the presence of sleep apnea and CVHR. The Holter ECG signals were scanned on a personal computer using a customized beat-detection and beat-classification algorithm that identified all QRS complexes and labeled the beats as normal, ventricular ectopic, supraventricular ectopic, and artifact. The results were reviewed, and all errors in beat detection and classification were corrected interactively on the computer screen by expert technicians of Holter ECG, who were blinded to the subjects' polysomnographic diagnosis and other characteristics. For the purpose of CVHR detection, the R-R interval time series were interpolated with a horizontal-step function using only N-N intervals and resampled at 2 Hz. The detection of CVHR was performed by a cardiologist with arrhythmias expertise who was blind to both subject characteristics and other polysomnographic data. Duration of CVHR on tachograms was determined. CVHR patterns were characterized as high amplitude (HR changes > or = 20 beats/min per cycle) versus lower amplitude (6-19 beats/min per cycle). Tachograms were classified as having visible HR changes versus not visible (flat) as seen in Figure 1.

III. STATISTICAL ANALYSIS

Continuous variables are expressed as mean $\pm$ standard deviation or as median (with 25th, 75th percentiles), as appropriate. Categorical variables are presented as counts and percentages. Univariate comparisons were made with the χ^2 or the two-sample *t* test, as appropriate [31]. The correlation between total duration of CVHR episodes and the apnea-hypopnea index was assessed with the correlation coefficient analysis. The CVHR on Holter monitoring for the detection of OSA was determined using receiver operating characteristic (ROC) curves, assuming AHI $\geq$ 15 as references for significant OSA. We also described the likelihood ratios for OSA stratified by different ranks of CVHR duration [31]. All statistical analyses were performed using the MEDCALC statistical software version 7.3 (*MedCalc Software, Ostend, Belgium*) and SPSS v.22 (*IBM, Chicago IL, USA*).

IV. RESULTS

Two hundred and eight patients were invited to participate in the study during one year of follow-up. One hundred and thirty-six consented. Three patients (2%) were excluded from our analysis. Two due to atrial fibrillation that makes impossible to measure the CVHR and one had less than 3 hours of Holter recording (figure 2).

The main characteristics of the patients are listed in Table 1. Two thirds were male. The OSA group had a body mass index (BMI) that was greater than the group without significant OSA (33.4 ± 8.1 vs. 28.1 ± 5.2 ; $P < 0.001$). As it was expected the minimum oxygen saturation was lower in the OSA group (73 ± 11.7 vs. 85.3 ± 7.1 ; $P < 0.001$). There was no significant difference in sleep duration, heart rate or autonomic function (SDNN).

There was a moderate correlation between the duration of the CVHR episodes and the AHI ($r = 0.50$; $P < 0.0001$; 95% CI for $r = 0.36$ to 0.62) (Figure 3). Patients diagnosed as severe OSA had longer duration of CVHR measured by the Holter monitoring (Figure 4).

When groups were stratified by the duration of CVHR as shown in table 2, there was a much higher probability of having severe OSA when this duration exceeded 200 minutes of CVHR (+LR=16.28 for severe OSA; CVHR >100-199 min +LR=3.10 for severe OSA).

Additionally, considering a CVHR duration of more than 76 minutes as the diagnostic cutoff point for moderate to severe OSA, we observed that the area under the ROC curve was 0.77 (CI 95% AUR 0.69 to 0.84). These data evidence that CVHF as a good diagnostic discriminant for OSA (figure 5).

V. DISCUSSION

In this study, Holter ECG monitoring was tested for its ability to diagnose OSA and was simultaneously validated against PSG in patients with clinically suspected sleep disordered breathing. The results show that patients with severe OSA have longer duration of CVHR on Holter monitoring. Our results are slightly different to those reported by other authors in studies using similar or alternative methods [23-26].

In the mid 80's *Guilleminault et al.* [23] were the first authors who have demonstrated the presence of CVHR in patients with OSA. At onset of a sleep apnea episode all OSA patients showed progressive bradycardia, followed by abrupt tachycardia on resumption of breathing. *Stein et al.* [24] used heart rate tachogram derived from ECG monitoring during overnight PSG to identify CVHR revealing OSA diagnosis. *Hayano et al.* [26] published an important study to examine the ability of ECG-based automated CVHR detection to estimate the presence and severity of OSA in a large-scale clinical setting. They have observed that the CVHR index closely correlated with the AHI ($r=0.84$) and showed a good performance in identifying patients with moderate-to-severe OSA.

In the last few years, several authors have developed algorithms for the automated ECG detection of OSA. *Khandoker et al.* [32] used a machine learning technique for automated

recognition of OSA from wavelet analysis of R-R intervals and ECG-derived respiratory signal. They developed a classification algorithm using 83 training sets of sleep studies and applied it to 42 test studies selected from the Physionet Apnea-ECG database. The algorithm correctly recognized 24 of 26 OSA subjects and 15 of 16 non -OSA subjects. *Mendez et al.* [33] compared the empirical mode decomposition and the wavelet analysis for detecting OSA from the ECG signal. Using 25 training sets and 25 test sets of sleep studies generated from the Physionet Apnea-ECG database, they reported 85% accuracy for the empirical mode decomposition and 89% accuracy for wavelet analysis in classifying minute-by-minute apnea/non-apnea periods; both methods perfectly discriminated OSA patients from normal subjects. In the present study, we observed comparable performances for the independently optimized ACAT algorithm in the Physionet Apnea-ECG database. Only a few studies, however, have been performed in clinical settings. *Roche et al.* [34] proposed an increase in the relative power of very -low-frequency component (0.01 to 0.05 Hz) of interbeat interval increment (%VLFI) as a marker for OSA. Among a sample of 150 patients referred to a university hospital for clinically suspected OSA, the authors reported an AUC of 0.70 for identifying the patients with an AHI ≥ 15 per hour ($n=100$) and 64% sensitivity and 69% specificity with using %VLFI >4% as the cutoff threshold.

There is a need to improve access to diagnostic and effective treatment strategies for patients with OSA. Although portable monitoring may emerge as a new diagnostic tool, clinical studies to address careful interpretation are needed to continue to advance the field [35].

Patients with OSA are prone to the development of abrupt changes in heart rate. The mechanisms related to this phenomena are not fully understood, but changes in autonomic tone and the coexistence of common shared risk factors are the probable causes [23]. Additionally, the circadian distribution of sudden cardiac death among OSA patients has a peak during the sleeping hours [16]. Holter monitoring is a useful

tool to record such phenomena. There is some evidence suggesting that the occurrence of CVHR indicates the presence of apnea episodes in patients with OSA [24]. In our study we could better understand the association of the CVHR and the presence of severe OSA.

VI. STRENGTHS AND LIMITATIONS

The strengths of the present study include the use of the Holter equipment to demonstrate the presence of moderate to severe OSA. This can change the indications of ECG Holter monitoring. Some limitations of the present study should be noted. First, subjects with atrial fibrillation or implanted pacemakers were excluded because we could not determine the CVHRS in these cases. Second, it is not possible to exclude the effect of periodic leg movements, which may affect CVHR. This is a specific population with high pretest probability of OSA. It is difficult to extrapolate this data to all patients.

6.1 Clinical Implications and Future Research Directions

The results of this study have potentially important clinical implications, because they suggest that many patients submitted to ECG Holter monitoring can be identified as having significant OAS and perhaps could be treated properly.

There is a need to test the sleep apnea software in different populations and perceive its clinical utility in these settings.

VII. CONCLUSION

The high prevalence of untreated sleep apnea and links to serious morbidity and mortality underscore the population burden of this condition and the need for greater clinical recognition and strategies to reduce prevalence.

Electrocardiographic Holter monitoring has good accuracy for the detection of significant OAS in a selected population and therefore can be considered as a valuable simplified technique.

Sources of support

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Conflicts of interest: None

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Table 1. Clinical and demographic characteristics

Variables	All (n=133)	OSA (+) (n=40)	OSA (-) (n=93)	P-value
Age*	49±17	55±15	47±17	0.013
Male gender†	88 (66)	30 (75)	58 (62)	0.169
BMI*	29.7±6.7	33.4±8.1	28.1±5.2	<0.001
Epworth sleepiness scale*	10±5.4	13.4±4.3	8.6±4.6	<0.001
AHI‡	8 (1.5 – 21.8)	37.8±3.4	41.3±5.8	<0.001
Minimum O ₂ Saturation during sleep	81.5±10.4	73±11.7	85.3±7.1	<0.001
Sleep Duration in minutes*	381.3±150	370.80±75	386.26±76	0.281
Heart Rate*				
Minimum	51.9±7.8	52±8	52±8	0.979
Mean	68.8±9.2	71±11	68±9	0.245
Maximum	111.4±19	111±17	112±20	0.861
SDNN*	90.5±37.8	91.1±21.1	90.3±29.6	0.859
CVHR ‡	21 (5.5 – 62.5)	58	15	<0.001

*Mean and Standard Deviation (SD); †Data are n (%); ‡Median (25th to 75th percentile); OSA: Obstructive sleep apnea; BMI: body mass index; AHI: apnea - hypopnea index event/hour; SDNN: standard deviation of NN intervals on Holter; CVHR: cyclic variation of the heart rate

Table 2: Cyclic variation of the heart rate data

CVHR	OSA (+) (n=40)	OSA(-) (n=93)	L.R.
≥ 200	7	1	16.28
100 to 199	8	6	3.10
31 to 99	1 2	25	1.17
0 to 30	1 3	61	0.69

CVHR: cyclic variation of the heart rate in minutes; OSA: obstructive sleep apnea; L.R.: likelihood ratio

A

B

Figure 1: **A)** The Holter tachogram shows high amplitude CVHR during a severe sleep apnea episode. **B)** The Holter tachogram shows usual RR pattern in patient without sleep apnea

Figure 2: Flow diagram of patients included in present study

Figure 3: Relationship between the AHI and the duration of CVHR in minutes

Figure 4: Duration of CVHR in minutes in patients with OSA present and OSA absent

Figure 5: The ROC curve of the CVHR duration in minutes for detecting subjects with moderate-to-severe OSA had an AUC of 0.77 (standard error, 0.050). The ROC curve analysis also indicated that the highest average of sensitivity (51%) and specificity (92%) was obtained with a cutoff threshold of CVHR duration ≥ 76 minutes (95% CI=0.68 to 0.84)