Possibility of Applying Heart Rate Variability as a Screening Method to High-Risk Obstructive Sleep Apnea Patients

Abstract

Background: Altered heart rate variability (HRV) has been associated with a number of disorders affecting autonomic tone, including recent myocardial infarction, congestive heart failure, and diabetic neuropathy. Furthermore, obstructive sleep apnea (OSA) has been shown to be associated with characteristic disturbances in heart rhythm. In this study, using HRV frequency analysis, an attempt has been made to diagnose or possibly diagnose OSA. **Materials and Methods:** Using Somnologica version 3.3.1 software (Medcare-Embla), polysomnographic recordings were done. Electrocardiographic signals were digitalized with a sampling rate of 250 Hz. Using the HRV analysis report of this software, low-frequency (LF) and high-frequency (HF) information and LF to HF ratio (LF/HF) were obtained at 5-min intervals, then at cutting points 30, 35, 40, 45, and 50, which indicate the intensity of the apnea and hypopnea index (AHI), were analyzed with mean and standard deviation of HRV frequencies. **Results:** According to the results reported in this study, comparison of mild, moderate, and severe cases led to no significant differences, while frequency-domain analysis displayed significant LF/HF increase in more severe AHI cases. This can probably be applied in screening high-risk patients, reducing the application of PSG in high probable cases, and providing an estimate of prognosis of potentials patients for the physicians. **Conclusions:** In the study of frequency-domain analysis, LF/HF increases in more severe AHI cases. These can probably be applied in screening high-risk patients, reducing the application of PSG in high probable cases.

Keywords: *Heart rate control, obstructive, sleep apnea*

Majid
Malekmohammad,
Parisa Adimi
Naghan[1],
Batoul Khoundabi[2],
Shideh Omidian[3]

Tracheal Diseases Research Center, National Research Institute of Tuberculosis and Lung Diseases, Shahid Beheshti University of Medical Sciences, [1]Chronic Respiratory Disease Research Center, National Research Institute of Tuberculosis and Lung Diseases, Shahid Beheshti University of Medical Sciences, [2]Iran Helal Institute of Applied-Science and Technology, Red Crescent Society of the Islamic Republic of Iran, Tehran Research Center for Health Management in Mass Gathering, [3]Omidian Shideh, Qazvin University of Medical Sciences, Qazvin, Iran

Introduction

Obstructive sleep apnea (OSA), as a prevalent respiratory disorder, is typically characterized by recurrent episodes of interruption in normal breathing as a result of total or partial collapse in pharyngeal muscles.[1] OSA shares similar risk factors with cardiovascular diseases, while OSA acts as a predisposing factor for cardiovascular morbidities, regardless of other demographic characteristics or risk markers. As one of the noninvasive methods for evaluating the regulation of autonomic nervous system, heart rate variability (HRV) is also a promising index of health and disease, including but not limited to cardiovascular and respiratory diseases.

Altered HRV has been associated with a number of disorders affecting autonomic tone, including recent myocardial infarction,[2] congestive heart failure,[3-5]

and diabetic neuropathy.[6,7] Furthermore, OSA has been shown to be associated with characteristic disturbances in heart rhythm,[8,9] leading to a slur of research focusing on HRV in OSA.[10-15]

According to Roche *et al.*,[14] a number of time-domain measures seem to diminish in OSA patients, which is a reflection of naturally occurring periodic changes in heart rate.

A number of previous studies have dealt with heart rate periodicity changes at particular ranges via examination of individual apneic episodes,[16] individual sleep stages,[11,13] or very low-frequency (VLF) ranges, providing valuable insight into those changes.[11] Some studies have examined overnight HRV in OSA applying frequency-domain analysis, while paying special attention to high-frequency (HF) and low-frequency (LF) ranges. It is hypothesized that this study could be a simpler method of diagnosis and assist in screening.

How to cite this article: Malekmohammad M, Adimi Naghan P, Khoundabi B, Omidian S. Possibility of applying heart rate variability as a screening method to high-risk obstructive sleep apnea patients. Adv Biomed Res 2022;11:22.

Materials and Methods

Participants

For this study, 49 OSA syndrome patients were recruited from two sleep laboratory centers in Tehran, with mean ± standard deviation (SD) age of 51 ± 12 years. The following inclusion criteria were applied to have the target patients: (1) <65 years old, (2) normal electrocardiogram at wakefulness, and (3) apnea–hypopnea index (AHI) >5 later on, while those patients receiving the antihypertensive treatment or having a diagnosis of hypertension were excluded. Other exclusion criteria included either previous or current cardiovascular diseases, pulmonary disorders, diabetes mellitus, substance abuse, history of taking alcohol or other drugs within 7 days before polysomnographic study, diagnosis of periodic limb movements during sleep, disorders of the autonomic nervous system or endocrine system with the potential of changing blood pressure, and history of operations or continuous positive airway pressure treatment for OSA. Having obtained informed consent from the patients before the study, the researchers defined and categorized the participants according to their AHI into three major categories of 5–15, 15–30, and higher than 30. The last category, in its own term, was divided into five distinct groups of AHI = 30, AHI = 35, AHI = 40, AHI = 45, and AHI = 50 in terms of AHI. Ultimately, the institutional ethical committee approved the protocol.

Polysomnography

Using Somnologica version 3.3.1 software (Medcare-Embla Natus Medical Incorporated, CA, USA), polysomnographic recordings were done with Embla N7000 system (Medcare-Embla) during the time when the patient' bedtime from light-off to light-on. Electroencephalography was monitored using F3/A2 (Right Frontal Area) and F4/A1(Left Frontal Area), C3/A2(Left Central area) and C4/A1(Right central Area) leads, and O1/A2(Left Occiput Area) and O2/A1(Right Occiput Area) leads were also used to smoothly detect alpha waves useful to see onset of sleep and arousal. Two pairs of electrooculography leads were used. Electromyography leads were put on the submentalis and the tibialis anterior muscles. Airflow was continuously measured by a thermistor and a nasal pressure cannula. The respiratory movements were monitored using the respiratory inductive plethysmography belts around chest and abdomen. Oxygen saturation was measured by a pulse oximeter sensor which was put on the left second finger.

The oxygen desaturation event index (ODI) was defined as the number of events per hour in which oxygen saturation decreases by 3% or more. Hypopnea was defined as a reduction of airflow by 30% for at least 10 s associated with either oxygen desaturation of at least 3% or arousals. Apnea was defined as an airflow reduction of 90% or more for at least 10 s. AHI was calculated by dividing the total number of apneas and hypopneas by the number of hours of sleep. The evaluation of sleep stages was based on the AASM 2018 study.[17]

Data acquisition and analysis

Electrocardiographic signals acquired by the polysomnographic machine were digitalized with the sampling rate of 250 Hz. Artifacts were eliminated, and the analysis was done only for normal beats. Time-domain variables were mean of RR (the interval between successive Rs), NN (beat-to-beat interval), the SD of NN intervals, NN50 count (the number of pairs of successive NNs that differ by >50 ms), and RMSSD (square root of the mean of the sum of the squares of differences between adjacent RR intervals). SDANN is the SD of the averages of RR intervals in all 5-min segments. The percent NN or RR intervals >50 ms different from the prior interval is often available on commercial Holter.[18] In frequency-domain analysis, the power was calculated VLF (0.0033–0.04 Hz), LF (0.04–0.15 Hz), and HF (0.15–0.40 Hz) bands. The LF/HF ratio was also included in the statistics. Sleep events in the analysis were AHI, ODI, average O_2 saturation, arousal index, limb movement, and snoring time. The significance level was defined as $P < 0.1$.

Statistical analysis

The data were analyzed using the statistical package IBM SPSS version 24.0 (Statistical Package for the Social Sciences, Chicago, IL, USA). The qualitative variables are expressed as proportions and frequencies. The quantitative variables with normal distribution are summarized as mean ± SD. Kolmogorov–Smirnov test was applied to test the normality distribution. To explore the independency of some categorical variables, Chi-square or Fisher's exact test was used. The comparison of the distribution variables between two groups was done by independent or paired *t*-test and Mann–Whitney U-test for normal and nonnormal, respectively.

Results

Of 49 patients participating in the study, 28 (57%) were male and the rest were female. Their average age was 52 ± 12 years. Table 1 presents other demographic information on the participants in the study.

The results of the investigation of different frequencies are presented in Table 2. Regarding Table 3 on comparing cutoff points, with AHI increasing, LF/HF approaches significance level. There was no significant difference between mild, moderate, and severe groups in terms of frequencies [Table 2]. Therefore, in the severe group, analysis was defined based on the severity of AHI in the following cutoffs and the results are presented in Table 3.

Discussion

OSA, as a nocturnal interruption in breathing, is considered as one of the risk factors of cardiovascular diseases, which frequently lead to morbidity and mortality. One of its

typical disorders is its effect on autonomous system (ANS) disorders. This stems more from changes in sympathetic system as a result of arousal and hypoxia compared with parasympathetic system. As in pathophysiology of sleep breathing disorders, either arousal or intermittent hypoxia occurs, leading to the release of norepinephrine and other somnocytokines, this leads to inflammatory pathways and subsequent cardiovascular vessel injuries. Furthermore, these factors collectively lead to some changes in the ANS that intensifies HRV.

While various studies have dealt with ANS disorders in-depth, they seem to have failed to provide a clear-cut answer in most cases to the question of which frequency or analysis shows the changes in the ANS more tangibly. This fact can be rooted in a number of causes, and according to previous studies, these root causes might be of higher significance. Variation in terms of phenotypes of the disease

Table 1: Demographic Variables

Variable	Mean±SD/*n* (%)
Age (Year)	51.6±12.3
BMI (Kg/m^2)	29.0±4.2
Neck (cm)	36.8±8.9
Sex (Male)	28 (57.14)
ESS	12.51±9.8

Table 2: Comparison of Frequency Domain Analysis between Three Groups

Frequency	Severity	Mean	SD	*P*
VLF	Mild	3147.9	2005.4	0.635
	Moderate	3623.6	1282.1	
	Severe	4409.5	3780.9	
LF	Mild	2339.5	1472.1	0.537
	Moderate	2757.0	873.5	
	Severe	3374.0	2600.1	
HF	Mild	1796.8	1410.4	0.960
	Moderate	1913.5	1100.8	
	Severe	2038.8	2241.4	
LF/HF	Mild	1.9	1.3	0.354
	Moderate	2.6	2.5	
	Severe	3.5	2.7	

**:Significant at 0.10 level SD: standard Deviation

Table 3: Comparison of LH/HF by Different AHI Cut-Off Points

Cut-Off Points	Mean±SD		*P*
	≤ Cut-Off Points	> Cut-Off Points	
30	2.48±2.18	3.50±2.11	0.133
35	2.42±2.12	3.50±2.11	0.100
40	2.46±2.00	3.55±2.16	0.088**
45	2.46±2.00	3.55±2.17	0.088**
50	2.55±1.91	3.68±2.25	0.066**

**:Significant at 0.1 level

including reaction type to hypoxia and arousal can be of extreme importance as an inclusion criterion, although this has not been taken into account in the present study. OSA is a complex and heterogeneous disease and the AHI alone cannot capture the different range of this circumstance. Consideration of phenotype in patient selection improves prognosis for clinical trials result. Understanding of mechanisms might personalize treatments.[19] Moreover, HRV analysis and methods for measuring changes vary in different studies.

Considering the fact that the severity of OSA can be identified via using AHI index, the present study aims at comparing AHI state and disorders in the ANS, i.e., participants with mild, moderate, and severe were studies initially in linear and nonlinear analyses.

According to the results reported in this study, comparison of mild, moderate, and severe cases led to no significant differences, while frequency-domain analysis displayed significant LF/HF increase in more severe AHI cases. This can probably be applied in screening high-risk patients, reducing the application of PSG in high probable cases, and providing an estimate of prognosis of potentials patients for the physicians. Based on the findings of a number of studies conducted so far, the power of LF and the power of LF/HF show triggering sympathetic autonomous system which can be accompanied with cardiovascular diseases, leading to a relatively poor prognosis.

One of the limitations of this study is application of EMBLA software in analyzing HRV changes. Using MATLAB (software Digital Equipment Corporation, VAX, Sun Microsystem) could have provided 2-min interval analyses instead of 5-min ones of EMBLA. However, the fact is that data analysis using EMBLA seems to be more user-friendly and much easier and can aid the physicians and clinicians to obtain the results rather rapidly. Yet, other limitations of the study include ignoring the OSA phenotype in the patients as mentioned above, lack of investigating the reaction to the respiratory events, and robustness of ANS before participating in the study. Nucleoli involved in controlling autonomous system in the brain are impacted by hypoxia stemming from OSA that can lead to functional disorder. These are the cases that prevent us from observing the changes.

Conclusions

In the study of frequency-domain analysis, LF/HF increases in more severe AHI cases. This can probably be applied in screening high-risk obstructive sleep apnea patients, reducing the application of PSG in high probable cases.

Acknowledgments

Financial support and sponsorship

Conflicts of interest

There are no conflicts of interest.

References

1. Rundo JV. Obstructive sleep apnea basics. Cleve Clin J Med 2019;86:2-9.
2. Buccelletti E, Gilardi E, Scaini E, Galiuto L, Persiani R, Biondi A, *et al.* Heart rate variability and myocardial infarction: Systematic literature review and metanalysis. Eur Rev Med Pharmacol Sci 2009;13:299-307.
3. Bigger JT Jr., Fleiss JL, Rolnitzky LM, Steinman RC, Schneider WJ. Time course of recovery of heart period variability after myocardial infarction. J Am Coll Cardiol 1991;18:1643-9.
4. Casolo G, Balli E, Taddei T, Amuhasi J, Gori C. Decreased spontaneous heart rate variability in congestive heart failure. Am J Cardiol 1989;64:1162-7.
5. Besnier F, Labrunée M, Richard L, Faggianelli F, Kerros H, Soukarié L, *et al.* Short-term effects of a 3-week interval training program on heart rate variability in chronic heart failure. A randomised controlled trial. Ann Phys Rehabil Med 2019;62:321-8.
6. Pagani M, Malfatto G, Pierini S, Casati R, Masu AM, Poli M, *et al.* Spectral analysis of heart rate variability in the assessment of autonomic diabetic neuropathy. J Auton Nerv Syst 1988;23:143-53.
7. Benichou T, Pereira B, Mermillod M, Tauveron I, Pfabigan D, Maqdasy S, *et al.* Heart rate variability in type 2 diabetes mellitus: A systematic review and meta-analysis. PLoS One 2018;13:e0195166.
8. Guilleminault C, Connolly SJ, Winkle RA. Cardiac arrhythmia and conduction disturbances during sleep in 400 patients with sleep apnea syndrome. Am J Cardiol 1983;52:490-4.
9. Patel N, Donahue C, Shenoy A, Patel A, El-Sherif N. Obstructive sleep apnea and arrhythmia: A systemic review. Int J Cardiol 2017;228:967-70.
10. Ferini-Strambi L, Oldani A, Zucconi M, Smirne S. Cardiac autonomic activity during wakefulness and sleep in REM sleep behavior disorder. Sleep 1996;19:367-9.
11. Shiomi T, Guilleminault C, Sasanabe R, Hirota I, Maekawa M, Kobayashi T. Augmented very low frequency component of heart rate variability during obstructive sleep apnea. Sleep 1996;19:370-7.
12. Narkiewicz K, Montano N, Cogliati C, van de Borne PJ, Dyken ME, Somers VK. Altered cardiovascular variability in obstructive sleep apnea. Circulation 1998;98:1071-7.
13. Khoo MC, Kim TS, Berry RB. Spectral indices of cardiac autonomic function in obstructive sleep apnea. Sleep 1999;22:443-51.
14. Roche F, Gaspoz JM, Court-Fortune I, Minini P, Pichot V, Duverney D, *et al.* Screening of obstructive sleep apnea syndrome by heart rate variability analysis. Circulation 1999;100:1411-5.
15. Lombardi C, Pengo MF, Parati G. Obstructive sleep apnea syndrome and autonomic dysfunction. Autonomic neuroscience. Basic Clin 2019;221:102563.
16. Vanninen E, Tuunainen A, Kansanen M, Uusitupa M, Länsimies E. Cardiac sympathovagal balance during sleep apnea episodes. Clin Physiol 1996;16:209-16.
17. Berry RB, Albertario CL, Harding SM, Lloyd RM, Plante DT, Quan SF, *et al.* The AASM manual for the scoring of sleep and associated events: Rules, terminology and technical specifications: American Academy of Sleep Medicine; 2018.
18. Mietus JE, Peng CK, Henry I, Goldsmith RL, Goldberger AL. The pNNx files: Re-examining a widely used heart rate variability measure. Heart 2002;88:378-80.
19. Zinchuk AV, Gentry MJ, Concato J, Yaggi HK. Phenotypes in obstructive sleep apnea: A definition, examples and evolution of approaches. Sleep Med Rev 2017;35:113-23.