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Original Article

Nocturnal heart rate variation in diabetic and non-diabetic patients with sleep apnea syndrome

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ABSTRACT

Objectives: Heart rate variability (HRV) analysis is used for the evaluation of autonomic function in the cardiovascular system. Decreased HRV is associated with disorders affecting the autonomous system such as diabetes mellitus (DM) and obstructive sleep apnea (OSA). Previous studies have shown an association between OSA and DM. However, the interrelationships of HRV with OSA and DM are not well known. The aim of this study was to assess nocturnal HRV in patients who suffered from OSA with and without DM.
Methods: Sixty patients with OSA (27 with DM and 33 non-DM) underwent polysomnography for eight hours starting at midnight. From electrocardiogram (ECG) recordings taken as a part of polysomnography, time-domain and frequency-domain HRV parameters were evaluated to compare patients with regard to nocturnal HRV components such as low frequency (LF) and high frequency (HF), apnea–hypopnea index (AHI) and sleep parameters.
Results: In the non-DM group, a direct relationship was observed between AHI and HRV rather than very low frequency (VLF) and LF/HF variables. This relationship was just significant between AHI and standard deviation of five-min average of normal R–R intervals and adjacent R–R intervals differing by 0.50 ms over 24 h ($p < 0.05$). In the DM group, the correlation between AHI and HRV parameters except HF and waking frequency was direct and non-significant. Intergroup comparison showed a significant difference between groups regarding AHI and HRV-index, LF and VLF ($p < 0.05$).
Conclusions: DM can affect HRV; however, this is not the case in OSA patients. This means that in the presence of OSA, the DM effect on HRV disappears.

1. Introduction

Heart rate and blood pressure are under the tight regulation of the autonomous nervous system [1]. Heart rate variability (HRV), as a measure of the autonomic effect of the heart, is associated with sympathetic and parasympathetic activity [2]. In normal subjects, different heart rate regulation has been seen in various sleep stages during nocturnal increase in mean R–R intervals [3].

According to cardiac cycle and blood pressure oscillation, three main frequency components of HRV could be recognized synchronously with respiration as follows: a very-low-frequency component (VLF), a low-frequency component (LF), and a high-frequency component (HF). The LF component may be an index of both sympathetic and parasympathetic activity, while the HF component represents parasympathetic activity [4].

HRV is a physiologic variable which is affected by the interaction of the sympathetic and the vagal autonomous systems [5]. Decreased HRV as an abnormal adaptability of cardiac autonomic system is shown to be associated with different disorders such as diabetes mellitus (DM), obstructive sleep apnea (OSA), heart failure, and myocardial infarction [6–10]. The impact of these disorders on

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HRV parameters might be different due to different physiological mechanisms. Modulation of HRV in OSA is specifically influenced by the cyclic occurrence of apnostic events even if it lasts for one min [11]. This modulation is reflected at lower band variations and at VLF. Thus, this parameter is considered as an indirect and alternative measure for evaluation of OSA [12].

OSA, a disorder originated in sleep, strongly modulates autonomous nervous system and consequently heart rate variations [11]. OSA with enhanced sympathetic activity results in development and progression of cardiovascular diseases [13]. Repeated obstruction of the airway for over 10 s during sleep, despite respiratory effort, imposes a great clinical impact on health status [14]. Marked variations in HRV and blood pressure have been seen in patients with OSA, which increase the risk of cardiovascular diseases [15]. Uncontrolled cardiovascular autonomic function (CAF) is also seen in cases with DM [16].

Impaired autonomic regulation has been seen both in cases with DM and in cases with OSA, but it is unknown whether the presence of DM in cases with OSA can affect the HRV parameters or not. Thus, we aimed to evaluate the parameters of HRV including VLF, LF, HF, LF/HF ratio, and HRV index, Standard deviation of all intervals (SDN), SD of the normal-to-normal R–R intervals (SDNN), SDNN index, SD of five-min average of normal R–R intervals (SDANN), adjacent R–R intervals differing by 0.50 ms over 24 h (NN50 of total heart rate), and root mean square of differences between adjacent normal R–R intervals (RMSSD) in the setting of OSA in cases with and without DM.

2. Methods and materials

The methodology was approved by the ethical committee of the Institutional Board Review of Isfahan University of Medical Sciences, Isfahan, Iran. All participants signed informed consent forms prior to taking part in this study. DM and OSA were defined by self-history and polysomnography, respectively. All participants underwent eight hours of nocturnal sleep polysomnography starting at midnight in a temperature- and light-controlled, sound-attenuated room in the Bamdad Sleep Clinic, Isfahan, Iran. The polysomnography equipment was Embla® N7000 Recording System polysomnography. The recorded parameters included electroencephalography (EEG), electro-occulography (EOG), electromyography (EMG), electrocardiography (ECG), respiratory effort, oronasal airflow, oxygen saturation, snoring sounds, and body position. Sleep scoring was performed by a trained technician according to the American Academy of Sleep Medicine (AASM) scoring criteria 2012 [17]. The reported parameters include apnea–hypopnea index (AHI) and arousal index.

ECG was recorded at nighttime, together with polysomnography. An HRV analysis was performed through Somnologica software. Heart rate time and frequency domain parameters were measured during sleep. The measured parameters include: SDN, SDNN, SDNN index, SDANN, NN50 of total heart rate, HRV, VLF, LF, HF, LF/HF ratio, HRV index, and RMSSD. Inter-group comparison between mean values of each parameter was performed by *t*-test. To evaluate the correlation between AHI and HRV parameters in DM vs non-DM cases, the Z-Fischer test was used.

Statistical analysis was performed using SPSS ver. 18. Numerical measures are reported as mean ± SD. K^2 was used to define differences between groups. To determine evaluation of variables, multiple regression analysis was performed. Data are expressed as odds ratio (OR) with 95% confidence interval.

3. Results

A direct relationship was observed between AHI and HRV rather than VLF and LF/HF variables in the non-DM group. This correlation was just significant between AHI and NN50 of total heart rate in non-DM cases ($p < 0.05$). A similar relationship was observed between AHI and SDANN in the non-DM group ($p < 0.05$). In the DM group, the correlation between AHI and HRV parameters except HF

Table 1
Heart rate variability analysis in diabetics and non-diabetics.

Parameter	Measures	Total			Non-diabetic			Diabetic			Inter-group correlation (*p*-value)		
		AHI	HI	AI	AHI	HI	AI	AHI	HI	AI	AHI	HI	AI
HRV index	Pearson correlation	0.16	−0.24	0.26	0.16	−0.30	0.13	0.27	−0.10	0.49	0.695	0.463	0.149
	p-value	0.23	0.08	0.05	0.39	0.11	0.48	0.18	0.61	0.01			
HF	Pearson correlation	−0.03	−0.23	−0.05	0.06	−0.36	−0.04	−0.09	−0.01	−0.04	0.593	0.187	0.981
	p-value	0.84	0.09	0.70	0.75	0.05	0.85	0.66	0.97	0.83			
LF	Pearson correlation	0.13	0.12	0.16	0.16	0.28	0.01	0.23	0.08	0.40	0.782	0.456	0.134
	p-value	0.32	0.37	0.23	0.40	0.13	0.98	0.24	0.70	0.04			
ln.SDANN	Pearson correlation	0.24	0.16	0.02	0.37	0.23	0.05	0.08	0.03	−0.04	0.273	0.476	0.744
	p-value	0.06	0.24	0.89	0.04	0.22	0.77	0.68	0.87	0.86			
ln.NN50_of.total.HR	Pearson correlation	0.35	0.17	0.12	0.48	0.13	0.15	0.28	0.29	0.13	0.401	0.547	0.918
	p-value	0.01	0.21	0.37	0.01	0.51	0.42	0.16	0.15	0.53			
ln.RMSSD	Pearson correlation	0.18	0.01	0.01	0.24	−0.19	0.05	0.09	0.17	−0.06	0.575	0.203	0.704
	p-value	0.17	0.95	0.94	0.19	0.32	0.81	0.66	0.41	0.77			
ln.SDNN	Pearson correlation	0.14	−0.12	0.12	0.18	−0.21	0.11	0.11	−0.01	0.13	0.799	0.483	0.929
	p-value	0.28	0.36	0.38	0.32	0.26	0.56	0.57	0.94	0.51			
ln.OD	Pearson correlation	0.82	0.71	0.66	0.75	0.77	0.70	0.88	0.61	0.60	0.138	0.283	0.506
	p-value	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00			
ln.LF vs HF	Pearson correlation	−0.02	0.03	0.00	−0.13	0.04	−0.12	0.19	0.14	0.22	0.252	0.732	0.225
	p-value	0.86	0.80	0.97	0.50	0.81	0.53	0.35	0.49	0.28			
ln.VLF	Pearson correlation	0.08	0.00	0.49	0.02	0.43	0.43	0.24	−0.28	0.66	0.429	0.011	0.251
	p-value	0.55	0.99	0.00	0.93	0.02	0.02	0.26	0.19	0.00			
Number of awakenings	Pearson correlation	0.14	0.07	−0.02	0.30	0.24	0.08	−0.01	−0.12	−0.12	0.257	0.188	0.458
	p-value	0.29	0.59	0.91	0.11	0.20	0.67	0.96	0.54	0.53			
BMI	Pearson correlation	0.13	0.23	−0.03	0.25	0.34	−0.14	0.03	0.12	0.04	0.421	0.392	0.531
	p-value	0.32	0.08	0.82	0.17	0.06	0.46	0.87	0.55	0.86			
Age	Pearson correlation	0.26	0.19	0.21	0.42	0.19	0.30	−0.09	0.06	0.00	0.054	0.633	0.276
	p-value	0.05	0.16	0.11	0.02	0.30	0.10	0.67	0.77	0.98			

AHI, apnea–hypopnea index; AI, apnea index; BMI, body mass index; HF, high frequency; HI, hypopnea index; HR, heart rate; HRV, heart rate variability; LF, low frequency; OD, oxygen desaturation; RMSSD, root mean square of differences between adjacent normal R–R intervals; SDANN, standard deviation of five-min average of normal R–R intervals; SDNN, standard deviation of the normal-to-normal R–R intervals; VLF, very low frequency.

Table 2
Heart rate variability parameter analysis comparison in diabetics and non-diabetics.

Parameter	Non-DM (mean ± SD)	DM (mean ± SD)	*p*-value
HRV index	16.80 ± 6.95	13.22 ± 6.41	0.049
HF	1116.29 ± 874.25	947.18 ± 770.94	0.441
LF	3214.58 ± 1618.22	2167.78 ± 1817.95	0.024
VLF	8.79 ± 0.63	8.35 ± 0.88	0.040
NN50-of total HR	2.13 ± 2.03	1.68 ± 1.91	0.400
RMSSD	3.67 ± 0.74	3.90 ± 0.84	0.273
SDNN index	63.51 ± 32.98	67.96 ± 43.63	0.661
SDANN	4.16 ± 1.29	4.19 ± 0.92	0.929
SDNN	4.40 ± 0.38	4.39 ± 0.38	0.898
BMI	32.97 ± 5.43	33.76 ± 7.41	0.643
Number of awakenings	15.87 ± 9.90	20.11 ± 14.39	0.192
LF/HF	1.22 ± 0.98	0.72 ± 0.90	0.052
Age	51.84 ± 14	58.15 ± 8.80	0.05
AI	1.30 ± 1.33	1.65 ± 1.47	0.05
HI	2.75 ± 0.74	3.01 ± 0.68	0.05

AI, apnea index; BMI, body mass index; DM, diabetes mellitus; HF, high frequency; HI, hypopnea index; HR, heart rate; HRV, heart rate variability; LF, low frequency; NN50, adjacent R–R intervals differing by 0.50 ms over 24 h; RMSSD, root mean square of differences between adjacent normal R–R intervals; SDANN, standard deviation of five-min average of normal R–R intervals; SDNN, standard deviation of the normal-to-normal R–R intervals; VLF, very low frequency.

and the waking frequency (or put simply, the number of awakenings) was direct and non-significant. In general, the correlation between AHI and HRV parameters rather than HF and LF/HF was direct. The degree of correlation between AHI and HRV parameters rather than HF and NN50- of total heart rate was non-significant ($p > 0.05$) (Table 1).

Intergroup comparison showed a significant difference between groups regarding AHI and HRV-index, LF, and VLF ($p < 0.05$). Other parameters showed a non-significant difference between groups ($p > 0.05$) (Table 2). Disregarding AHI, there was a significant difference in LF and VLF values between groups ($p < 0.05$) (Table 3). There was a non-significant difference between the percentage of apnea index and hypopnea index compartments of AHI and their comparison in diabetic vs non-diabetic cases ($p > 0.05$) (Table 4).

4. Discussion

It has been previously recognized that apnea and hypopnea events are accompanied by concomitant cyclic variations in heart rate [18]. Ongoing investigations demonstrated that sleep apnea could be recognized though evaluation of HRV changes with a good reliability [19]. It is well known that both sympathetic and parasympathetic activity are increased at the end of each apnostic episode, followed by a subsequent fall during the short period of compensatory hyperventilation [20]. HRV analysis showed different sympathetic and parasympathetic responses in cases with sleep apnea compared with normal population [21]. The association between OSA and DM is well known. The possibility of the occurrence of sleep apnea in diabetic patients is very high [22]. Cardiovascular autonomic neuropathy is a major contributing factor for the development and progression of cardiovascular complications of DM [23]. Furthermore, recent studies have evaluated the benefits of HRV analysis for sleep apnea diagnosis in patients with metabolic syndrome [24].

Table 3
High-frequency, low-frequency and very-low-frequency measures in diabetic vs non-diabetic cases disregarding apnea–hypopnea index.

Parameter	Non-diabetic	Diabetic	*p*-value
High frequency	1115.13 ± 151.10	984.51 ± 162.08	0.459
Low frequency	3268.72 ± 306.70	2105.62 ± 328.98	0.013
Very low frequency	8.805 ± 0.14	8.335 ± 0.15	0.029

Table 4
Percentage of apnea index and hypopnea index compartments of apnea–hypopnea index and their comparison in diabetic vs non-diabetic cases.

Parameter percentage	Non-diabetic	Diabetic	*p*-value
Apnea index	31 ± 13.4	27 ± 11.07	0.742
Hypopnea index	31 ± 25.22	27 ± 25.67	0.800

The major finding of this study is the similar relationship between AHI and HRV parameters in OSA cases with and without DM. This suggests that altered HRV in the setting of DM could be mainly due to OSA per se. Thus, we suggest that HRV can be considered as an indirect screening of OSA in patients with DM.

The only differences between the two groups were LF and HRV parameters. The HRV difference between the two groups is explained by the impact of DM on cardiac autonomic function. The precise physiological concept of the LF parameter is not well understood but it could pass through increased sympathetic activity. The LF parameter is generally derived from a mixture of sympathetic and vagal modulation [25]. Only a few previous studies have stated that a higher apnea index is associated with a higher vagal modulation during NREM sleep.

Although our study demonstrated that HRV analysis could be helpful in the diagnosis of sleep apnea in diabetic patients, there are some limitations. The limited number of cases and controls, and the application of only one-lead electrocardiography are among our limitations. Indeed, the analysis of HRV during sleep is modified artificially by the presence of repetitive apneas, leg movements, or arousals due to the impact of 'rhythmic' biological noise on cardiovascular autonomic oscillations.

Conclusions

DM can affect HRV in non-OSA cases; however, DM can not affect HRV in OSA patients. Therefore, in the presence of OSA, this DM effect would no longer exist.

Conflict of interest

The authors have no conflicts of interest to declare.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2016.11.003.

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