ORIGINAL ARTICLE

Very low frequency component of heart rate variability as a marker for therapeutic efficacy in patients with obstructive sleep apnea: Preliminary study

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Background: Although positive airway pressure (PAP) therapy is effective for treating obstructive sleep apnea (OSA), some patients with severe OSA are intolerable to this treatment, which may lead to an increase in the mortality and morbidity of cardiovascular diseases. We investigated the relationship between heart rate variability (HRV) and sleep parameters during natural sleep and treatment of patients with OSA. **Materials and Methods:** This was the cross-sectional observation study. Patients were 17 males with severe OSA who were unable to accept continuous PAP. Standard polysomnography was performed for two consecutive nights, i.e., during natural sleep and following night with bilevel PAP (BiPAP) treatment. Time-dependent responses of the amplitudes of low frequency (LF), very low frequency (VLF), and high frequency components of HRV were assessed with the technique of complex demodulation. **Results**: Apnea–hypopnea index, oxygen desaturation time, and percentage of stage 1 sleep were significantly reduced, whereas the percentages of rapid eye movement and stages 3 + 4 sleep were increased, by BiPAP treatment. Therapy also reduced the amplitudes of VLF and LF components of HRV. Difference in amplitudes of VLF during natural sleep and treatment with BiPAP was significantly correlated with difference in percentages of stage 1 and stages 3 + 4 sleep. **Conclusion:** Therapy-induced amelioration of OSA and sleep quality was accompanied by decrease in the amplitudes of VLF components of HRV. The VLF component may thus reflect physiological changes in both autonomic activity and sleep structure and serve as an objective marker for therapeutic efficacy in patients with severe OSA.

Key words: Continuous positive airway pressure, heart rate, obstructive sleep apnea, polysomnography, sleep stage

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INTRODUCTION

The high morbidity and mortality rates associated with severe obstructive sleep apnea (OSA) are largely attributable to the coexisting cardiovascular diseases.[1-5] Apnea-hypopnea episodes and these secondary effects can be successfully treated with a positive airway pressure (PAP) treatment.[1,6-8] However, the poor adherence to continuous PAP (CPAP) therapy (generally defined as usage of < 4 h on 70% of nights) ranging from 30% to 74%[9-12] is an urgent issue in the practice of sleep medicine. Age, body mass index, education, smoking, craniofacial index, and nasal resistance are important factors in severity of OSA, treatment follow-up, and adherence of OSA.[10,13,14] Long-term adherence to CPAP is highly associated with initial comfort.[12,15] Bilevel PAP (BiPAP) allows for a

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difference between inspiratory and expiratory pressure, resulting in more efficient and comfortable breathing for some patients. The severity of OSA and concomitant chronic obstructive pulmonary disease may be strong and robust enough to be useful in the decision to use a BiPAP as a first-line therapy.[15] Thus, an objective marker for clinical guide is needed to assess the therapeutic efficacy in patients with OSA.

Heart rate variability (HRV), which has been used to quantify autonomic activity, is receiving increased attention in many clinical and basic research fields.[16,17] It can be broken down into three components such as very low frequency (VLF), low frequency (LF), and high frequency (HF). The HF component is thought to be modulated by parasympathetic activity, whereas the LF component is influenced by both parasympathetic and sympathetic activities. The VLF component, on the other hand, may closely relate to the body temperature regulation,[18] fluctuations in the activity of the renin–angiotensin system,[19] and peripheral chemoreceptor activity.[20]

Here, we have hypothesized that the VLF component of HRV may serve as an objective marker for the efficacy of PAP therapy in patients with OSA. In this context, we investigated the relationship between HRV and sleep parameters during natural sleep and BiPAP night in patients with OSA.

MATERIALS AND METHODS

Subjects

This was the cross-sectional observation study. Participants were recruited from patients who underwent polysomnography at Nagoya University Hospital and diagnosed as OSA. Seventeen males aged 34–70 years (age: 53.2 ± 9.9 years) with severe OSA (apnea–hypopnea index [AHI]: >30/h) (the American Academy of Sleep Medicine, 2005), who were unable to accept CPAP, but could be treated with BiPAP, we also performed BiPAP titration using polysomnography. We also included six healthy males among the same population, aged 30–70 years, who underwent polysomnography and then confirmed AHI <5/h to match the age with OSA patients (age: 46.2 ± 5.9 years). The control group comprised males who were free from medication and had no history of cardiovascular disease or diabetes mellitus. Electrocardiograms, echocardiographic findings, and blood pressure of the controls were normal. The primary endpoint was the efficacy of BiPAP therapy in patients with OSA. The second endpoint was to explore the significant relationship between HRV and sleep indices. The study protocol was approved by the Ethics Review Committee of Nagoya University School of Medicine (Permission number: 238), and patients provided written consent to participate after being informed in detail of the purpose and methods of the study.

Sleep parameters

Standard polysomnography (Alice III instrument; Respironics, Murrysville, USA) with pulse oximetry was performed for all patients. Electroencephalogram (C_3-A_2, C_4-A_1, O_1-A_2, and O_2-A_1), electrooculogram, electromyograms (legs and diaphragm), and electrocardiogram (bipolar CM_5) were recorded, and respiration was monitored with an oronasal thermistor and a thoracoabdominal strain gauge. Apnea was defined as a cessation of airflow through the mouth and nose for ≥10 s, and hypopnea was defined as a reduction in airflow of ≥50%, or a reduction in airflow associated with either an oxygen desaturation of >3% or arousal, also for ≥10 s. AHI was determined as the number of apnea and hypopnea episodes per hour, and OSA was diagnosed when AHI was ≥5 episodes/h and Epworth Sleepiness Scale score ≥11. The total time that nocturnal oxygen saturation was <90% (oxygen desaturation time: ODT), and minimum oxygen saturation was determined by pulse oximetry.[21] Sleep stages were evaluated by visual analysis, and the percentages of stage 1, stage 2, stages 3 + 4, and rapid eye movement (REM) sleep were calculated.[22]

Twenty-four-hour urinary noradrenaline

Sympathetic nervous system activity was estimated by the excretion of noradrenaline in 24-h urine. Samples were collected into acidified containers containing 20 ml of 6 mol/L hydrochloric acid and stored at 4°C prior to analysis. Urinary noradrenaline levels were determined by high-performance liquid chromatography with fluorescent detection.[23]

Data acquisition and analysis of heart rate variability

All patients underwent the standard polysomnography, which was performed on two consecutive nights, i.e., the first night of natural sleep and the following night during treatment with BiPAP. The bipolar CM_5 lead position of the electrocardiogram recorded during polysomnography was used for the analysis of HRV. Time-dependent changes in the amplitudes of VLF (0.0033–0.04 Hz), LF (0.04–0.15 Hz), and HF (0.15–0.45 Hz) components of the R-R interval were assessed with the technique of complex demodulation (CDM) subroutine written in Fortran 77 (developed by the Hayano Biosignal Laboratory (http://hbsl.jp/index.html); the detailed code has been deposited with the National Auxiliary Publications Service).[24] CDM is a nonlinear time-domain method of time series analysis that suits to the investigations of nonstationary/unstable oscillations. In contrast to spectral analysis that provides average features (power and frequency) of oscillatory components in stationary state, CDM provides instantaneous amplitude and frequency as functions of time for oscillations in specified frequency band.

Statistical analysis

Data are presented as means ± standard deviation. The paired Student's *t*-test was used to compare with and without BiPAP data for primary endpoint. We calculated the effect size and the power using G power 3.1 (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Nordrhein-Westfalen, Germany). In general, a statistic power of >0.8 is sufficient to reject the null hypothesis. Data comparing patient with OSA and controls as reference of HRV were analyzed using a nonpaired *t*-test. We performed Pearson's correlation analysis followed by multiple regression analysis to determine independent parameters correlated with HRV parameters in relation to AHI, ODT, and stages 1, 2 or stages 3 + 4. We also performed step-wise multiple regression analysis to determine independent parameters correlated with HRV parameters in relation to AHI, ODT, minimum SpO_2, stages 1, 2, and 3 + 4, and REM. $P < 0.05$ was considered statistically significant. All analyses were performed with StatView statistics and graphing software (Abacus Concepts, Inc., Berkeley, CA, USA).

RESULTS

AHI, ODT, and percentage of stage 1 were significantly decreased; percentages of REM and stages 3 + 4 were significantly increased, in patients with OSA on the night with BiPAP treatment compared with the preceding night of natural sleep [Table 1]. The percentage of stage 2 sleep was not significantly affected by treatment. Urinary noradrenaline excretion (during 24 h) in OSA patients was also significantly decreased by the BiPAP treatment (992 ± 471 vs. 599 ± 259 nmol; $P < 0.05$).

The analysis of HRV during 5-min revealed that the amplitudes of all three frequency components were increased during natural sleep. The decrease in AHI with effective BiPAP treatment was accompanied by a decrease in the amplitudes of all three frequency components of HRV [Figure 1]. The reductions in amplitudes of VLF and LF components with BiPAP treatment were statistically significant, but not the reduction in the amplitude of HF component [Table 1]. The effect size and power for VLF of primary endpoint were 1.30 and 0.99, respectively, between the natural sleep and BiPAP night in patients with OSA. R-R interval also did not significantly differ with and without BiPAP treatment in patients with OSA. There were no significant differences in the amplitude of any of the three frequency components of HRV, and age between patients undergoing BiPAP treatment and the controls as a reference of HRV.

In patients with OSA, the difference in the amplitudes of VLF component during the natural sleep and BiPAP night (⊿VLF) was significantly correlated with the difference in percentages of stage 1 (⊿stage 1) and stages 3 + 4 (⊿stages 3 + 4) [Table 2]. Multiple regression analysis showed that ⊿ stages 3 + 4 was the most significant factor correlated with ⊿ VLF [Table 2]. Step-wise multiple regression analysis including polysomnographic parameters revealed that ⊿ stages 3 + 4 was the most significant factor for ⊿ VLF ($\beta = 0.579$, $P < 0.05$).

Table 1: Sleep and heart rate variability parameters both in controls and in patients with severe obstructive sleep apnea during natural sleep and treatment with bilevel positive airway pressure

	OSA patients		Controls
	Natural sleep	During treatment	
AHI (/h)	52.2±11.2*,†	7.8±4.9	4.6±3.0
ODT (min)	132.7±107.1*,†	6.5±14.1	1.4±1.4
Minimum SpO_2 (%)	70.8±8.7	87.0±4.8	87.7±3.2
Sleep stage (%)			
REM	8.2±5.0*,†	19.6±8.1	18.8±4.6
Stage 1	47.9±17.7*,†	24.4±10.4	19.3±10.6
Stage 2	42.1±17.0	51.5±11.3	57.0±9.5
Stages 3 + 4	1.0±1.9*	4.2±5.9	5.3±5.6
HRV			
R-R interval (ms)	954.6±95.4	959.1±104.5	1048.0±153
VLF (ms)	84.5±29.0*,†	46.7±16.6	56.5±17.3
LF (ms)	38.2±13.6*,†	25.1±11.0	31.5±15.3
HF (ms)	30.1±13.9	18.8±9.6	27.5±16.6

*$P < 0.05$ versus during treatment; †$P < 0.05$ versus controls. OSA=Obstructive sleep apnea; AHI=Apnea–hypopnea index; ODT=Oxygen desaturation time; SpO_2=Arterial oxygen saturation; REM=Rapid eye movement; VLF=Very low frequency; LF=Low frequency; HF=High frequency; HRV=Heart rate variability

Table 2: Simple correlations and multiple regression analysis between polysomnographic and heart rate variability parameters

Simple correlation	⊿VLF		⊿LF		⊿HF	
	r	*P*	*r*	*P*	*r*	*P*
⊿AHI	0.230	0.381	0.108	0.685	−0.156	0.555
⊿ODT	0.227	0.388	−0.376	0.139	−0.216	0.412
⊿Minimum SpO_2	0.100	0.709	−0.231	0.379	−0.230	0.381
⊿Stage 1	0.572	0.015	0.416	0.098	0.275	0.291
⊿Stage 2	0.219	0.406	0.465	0.059	0.275	0.291
⊿Stages 3 + 4	0.579	0.014	0.096	0.719	0.442	0.075
⊿REM	0.431	0.085	0.031	0.908	0.031	0.908
Multiple regression	**⊿VLF**		**⊿LF**		**⊿HF**	
	β	*P*	*β*	*P*	*β*	*P*
⊿AHI	-0.040	0.879	−0.138	0.561	−0.379	0.176
⊿ODT	0.065	0.787	0.548	0.024	−0.341	0.189
⊿Stage 1	0.572	0.051	0.638	0.002	0.549	0.068
⊿AHI	0.122	0.603	0.103	0.688	−0.243	0.285
⊿ODT	0.028	0.909	−0.467	0.099	−0.413	0.929
⊿Stages 3 + 4	0.545	0.042	0.237	0.391	0.632	0.017

⊿=difference between natural sleep and during treatment with bilevel positive airway pressure; AHI=Apnea–hypopnea index; ODT=Oxygen desaturation time; SpO_2=Arterial oxygen saturation; REM=Rapid eye movement; VLF=Very low frequency; LF=Low frequency; HF=High frequency

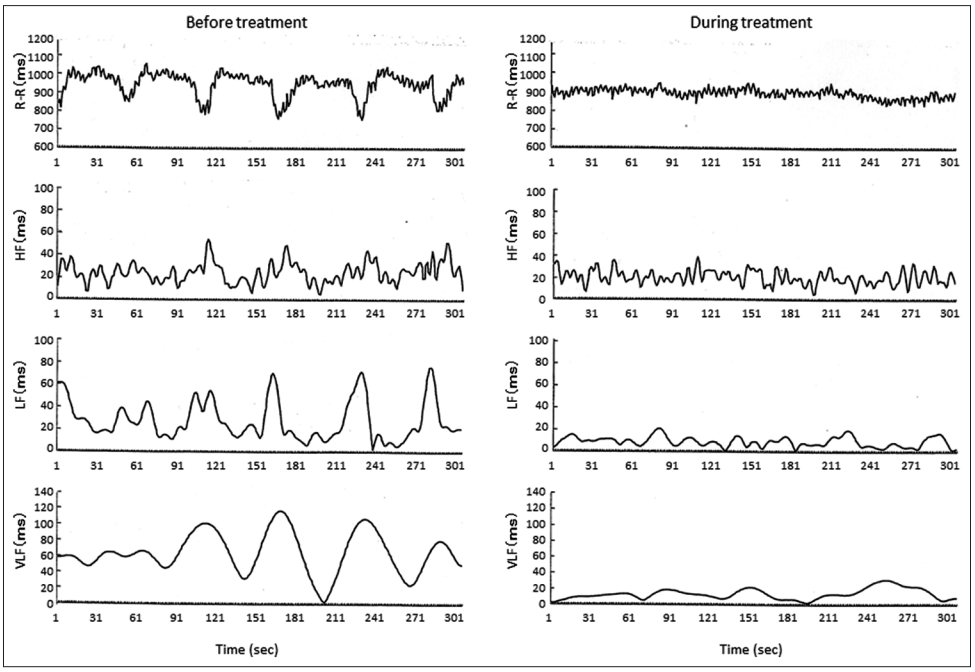

Figure 1: Heart rate variability components with and without treatment. The magnitude of heart rate variability components is presented in amplitude (ms). HF = High frequency; LF = Low frequency; VLF = Very Low frequency

DISCUSSION

This study found that AHI and ODT were markedly reduced, percentages of REM and stages 3 + 4 were increased, and the percentage of stage 1 was reduced, and amplitudes of VLF and LF components of HRV were significantly decreased by treatment with BiPAP in patients with severe OSA who were unable to accept CPAP. The change in VLF was associated with the percentages of stages 3 + 4 and stage 1. Our findings indicate that VLF components of HRV may serve as markers for the efficacy of treatment for OSA and for overall sleep structure.

In this study, the amplitude of VLF component was increased in individuals with severe OSA compared with controls, and it was normalized by BiPAP treatment. Our findings may be supported by the findings of a previous HRV study.[25] The change of this component was associated with not only the improvement of OSA but also sleep quality. VLF component of HRV reflects long-term fluctuations in the R-R interval (25 s to 5 min) and is similar to the frequency of episodes of sleep apnea. Although VLF component of the heart rate power spectrum is reportedly related to temperature regulation[18] and activity of the renin–angiotensin system,[19] as low and respiratory frequency R-R interval rhythms, VLF heart period rhythms depend on the presence of parasympathetic outflow.[26] The previous study demonstrated parasympathetic dominance during slow-wave sleep.[27] Thus, it is possible that VLF component of HRV in these patients reflects transient arousal and bradycardia and tachycardia caused by breathing fluctuations and sleep stages, which suggests that VLF may be a marker for the therapeutic efficacy in patients with OSA.

The LF component, but not the HF component of HRV, as well as urinary noradrenaline excretion was significantly reduced by BiPAP treatment in the present study. Whereas the HF component of HRV is modulated by parasympathetic nervous system activity, the LF component is modulated by both parasympathetic and sympathetic activities.[18] In patients with OSA, the heart rate changes cyclically in response to episodes of apnea and subsequent hyperventilation.[28] The sympathetic nervous system, which can be activated by hypoxia, respiratory acidosis, cortical arousal, and swings in intrathoracic pressure, may contribute to the abrupt increases in heart rate and blood pressure apparent when patency of the upper airway is restored. The sympathetic activity in muscle and blood pressure during sleep were assumed to be higher in patients with OSA than in normal controls. The reduction in amplitude of the LF component induced by BiPAP treatment may thus reflect the normalization of sympathetic activity by this therapy. Analysis of HRV may, therefore, provide information on the balance of autonomic activities during arousal from sleep and the effectiveness of treatment.

Polysomnography is an essential tool for diagnosing OSA as well as for evaluating its severity and the effectiveness of therapy. However, it is still relatively expensive to carry out and time-consuming in many clinical settings.

One drawback of polysomnography is the difficulty of evaluating impairment of autonomic activity in individuals with severe OSA; although OSA is considered to be strongly related to the development of cardiovascular diseases. Abnormal HRV is associated with increased mortality and adverse cardiac events, and the analysis of HRV could present a way to predict sudden arrhythmic death and myocardial infarction.[29,30] Thus, VLF according to the analysis of HRV may provide a simple and useful technique for obtaining information on autonomic activity as well as on sleep structure reflecting the effectiveness of therapy in individuals with OSA.

This study had the limitation that the number of patients with OSA was relatively small. Further intervention trials among a larger sample will be needed to elucidate the physiological relevance of VLF component, especially multiple regression analysis between sleep parameters including AHI of diagnostic criteria and HRV parameters in patients with OSA.

CONCLUSION

This study showed that BiPAP decreased AHI and ODT and improved sleep structure. Successful BiPAP treatment also significantly decreased sympathetic activity indices such as VLF and LF components of HRV in patients with severe OSA. VLF was associated with the therapeutic efficacy of sleep quality. Our findings, therefore, suggest that the VLF component of HRV during sleep may provide insight into the effectiveness of the treatment of OSA and overall sleep structure.

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Conflicts of interest
There are no conflicts of interest.

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