

## Correlation between the Severity of Obstructive Sleep Apnea and Heart Rate Variability Indices

The risk of cardiovascular disease is known to be increased in obstructive sleep apnea syndrome (OSAS). Its mechanism can be explained by the observation that the sympathetic tone increases due to repetitive apneas accompanied by hypoxias and arousals during sleep. Heart rate variability (HRV) representing cardiac autonomic function is mediated by respiratory sinus arrhythmia, baroreflex-related fluctuation, and thermoregulation-related fluctuation. We evaluated the heart rate variability of OSAS patients during night to assess their relationship with the severity of the symptoms. We studied overnight polysomnographies of 59 male untreated OSAS patients with moderate to severe symptoms (mean age  $45.4 \pm 11.7$  yr, apnea-hypopnea index [AHI]= $43.2 \pm 23.4$  events per hour, and AHI >15). Moderate (mean age  $47.1 \pm 9.4$  yr, AHI=15-30, n=22) and severe (mean age  $44.5 \pm 12.9$  yr, AHI >30, n=37) OSAS patients were compared for the indices derived from time and frequency domain analysis of HRV, AHI, oxygen desaturation event index (ODI), arousal index (Ari), and sleep parameters. As a result, the severe OSAS group showed higher mean powers of total frequency (TF) ( $p=0.012$ ), very low frequency (VLF) ( $p=0.038$ ), and low frequency (LF) ( $p=0.002$ ) than the moderate OSAS group. The LF/HF ratio ( $p=0.005$ ) was higher in the severe group compared to that of the moderate group. On the time domain analysis, the HRV triangular index ( $p=0.026$ ) of severe OSAS group was significantly higher. AHI was correlated best with the LF/HF ratio ( $r_s=0.610$ ,  $p<0.001$ ) of all the HRV indices. According to the results, the frequency domain indices tended to reveal the difference between the groups better than time domain indices. Especially the LF/HF ratio was thought to be the most useful parameter to estimate the degree of AHI in OSAS patients.

Key Words : Sleep Apnea, Obstructive; Heart Rate; Spectrum Analysis; Polysomnography

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Received : 2 April 2007

Accepted : 14 August 2007

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\*This paper was supported by Konkuk University in 2006.

## INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is a condition of sleep-disordered breathing, which is characterized by the repetitive complete or partial collapses of the pharyngeal airway during sleep. It has been known to frequently involve middle-aged people and to be found in 2% of women and 4% of men (1). Patients with OSAS usually present excessive daytime sleepiness, unrefreshing sleep, fatigue, and even depression, and these symptoms may lead them to serious work or car accidents (2, 3). It has been reported that OSAS has numerous comorbidities, such as obesity, diabetes mellitus, coronary heart disease, stroke, congestive heart failure, cardiac arrhythmia, and gastroesophageal reflux (4-7). In addition, it is also an independent risk factor for hypertension (6, 8) and has a close relationship with atherosclerotic cardiovascular disease (7). Although the exact pathophysiological mechanisms are not yet fully understood, repetitive reduction of blood oxy-

gen saturation, increased efforts to breathe, increased sympathetic tone and subsequent rennin-angiotension-aldosterone system are considered to be involved in the development of cardiovascular diseases (7). Therefore, the assessment of cardiac functions in OSAS patients is an essential step in clinical settings.

Heart rate variability (HRV) analysis has been widely used to non-invasively evaluate cardiac autonomic functions. Investigators have demonstrated that abnormal HRV is associated with increased mortality or adverse cardiac events and that the analysis of HRV can be a way of predicting sudden arrhythmic death, myocardial infarction, angina pectoris, stroke mortality, and even rapid progression of atherosclerosis in animals (9-12). Changes of HRV parameters were also reported in OSAS patients (13-15), and HRV analysis has been proposed as a screening tool for OSAS (16). However, there are numerous indices or variables in time or frequency domain analysis of HRV, and researchers have reported slightly different findings

in their studies. If there is a good index which correlates well with the severity of OSAS symptoms and also reflects increased cardiac risk, it helps us better understand the pathophysiology of increased cardiovascular morbidity in OSAS, and can be a useful tool for clinicians. We examined the nocturnal HRV of OSAS patients to find what parameter in time or frequency domain analysis is the best to reflect the severity of symptoms.

## MATERIALS AND METHODS

### Subjects

Fifty-nine untreated male OSAS patients were recruited from two university hospitals in Seoul, and their mean  $\pm$  SD age was  $45.4 \pm 11.7$  yr. All subjects met the following inclusion criteria: 1) male, 2) less than 61 yr old, 3) normal electrocardiogram at wakefulness, and 4) apnea-hypopnea index (AHI) greater than 15. The patients who were on the antihypertensive treatment or had a diagnosis of hypertension were excluded. Other exclusion criteria were 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 (PLMS), disorders of autonomic nervous system or endocrine system that can change blood pressure, and history of operations or CPAP treatment for OSAS. Informed consent was obtained prior to the study. The protocol was approved by the institutional review board.

The subjects were categorized into two groups, moderate OSAS group ( $n=22$ ) and severe OSAS group ( $n=37$ ). The former was defined as the subjects with the AHI greater than 15 but less than 30, and the later with the AHI equal to or greater than 30.

### Polysomnography

Polysomnographic recordings were done with Embla N7000 system (Medcare-Embla®, Reykjavik, Iceland) using Somnologica version 3.3.1 software (Medcare-Embla®, Reykjavik, Iceland) during the time when the subjects were in bed from light-off to light-on. Electroencephalography was monitored using C3/A2 and C4/A1 leads pairs, and O1/A2 and O2/A1 leads were also used to easily detect alpha waves that are useful to see onset of sleep and arousal. Two pairs of electro-oculographic leads were used. Electromyographic 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 plethysmographic 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 4% or more. Hypopnea was defined as a reduction of airflow by 50-80% for at least 10 sec associated with either oxygen desaturation of at least 4% or arousals. Apnea was defined as an air flow reduction 80% or more for at least 10 sec (17). 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 Rechtschaffen and Kales' study, and episodes of arousals were assessed according to the guidelines in the previous studies (18).

### 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 RR, SDNN, SDNN index, RMSSD, NN50 count, NN50 of total HR (%), SDANN, and HRV triangular index. SDNN is the standard deviation of all RR intervals. RMSSD is the square root of the mean of the sum of the squares of differences between adjacent RR intervals. SDANN is the standard deviation of the averages of RR intervals in all 5-min segments. The SDNN index is the mean of the standard deviation of all RR intervals for all 5-min segments. NN50 count means the number of pairs of adjacent RR intervals differing by more than 50 ms in the entire analysis interval. NN50 of total HR (%) is the NN50 count divided by the total number of all RR intervals. The HRV triangular index means the total number of RR intervals divided by maximum height of the histogram excluding boundaries. In frequency domain analysis, the power was calculated for very low frequency (VLF, 0.0033-0.04 Hz), low frequency (LF, 0.04-0.15 Hz), and high frequency bands (HF, 0.15-0.40 Hz). The LF/HF ratio was also included in the statistics.

Comparisons between the two groups, moderate and severe OSAS groups, were made for demographic data, sleep parameters and events, and HRV indices by independent *t*-test. Sleep events in the analysis were AHI, ODI, average O<sub>2</sub> saturation, arousal index, limb movement and snoring time. Partial correlations controlling age and Body Mass Index (BMI) were evaluated for AHI versus HRV indices. The significance level was defined as  $p < 0.05$ .

## RESULTS

The differences of mean age ( $47.1 \pm 9.4$  vs.  $44.5 \pm 12.9$  yr) and BMI ( $26.1 \pm 3.9$  vs.  $27.8 \pm 3.8$  kg/m<sup>2</sup>) were not significant between the moderate and the severe OSAS groups. The sleep profiles and sleep event data of the subjects were shown in Table 1. The proportion of stage 1 sleep was greater in the severe OSAS group than in the moderate OSAS group

**Table 1.** Sleep profiles and events of the subjects with obstructive sleep apnea syndrome

Variable	Moderate OSAS (n=22)		Severe OSAS (n=37)		t	p
	Mean	SD	Mean	SD		
TIB (min)	456.75	69.68	460.67	66.16	-0.216	0.830
SPT (min)	441.39	68.98	450.02	66.81	-0.474	0.637
TST (min)	394.35	95.96	403.15	82.53	-0.372	0.711
SL (min)	15.35	35.49	10.64	12.10	0.742	0.461
SE (%)	86.96	15.98	88.32	12.50	-0.363	0.718
Awakenings	7.18	6.01	7.57	6.64	-0.223	0.824
S1 (%)	17.66	6.43	28.25	15.23	-3.090	0.003
S2 (%)	45.96	13.08	40.51	13.92	1.485	0.143
S3 (%)	4.74	3.52	5.26	6.76	-0.297	0.768
S4 (%)	8.18	6.18	5.31	8.02	0.879	0.389
REM (%)	18.17	7.10	14.71	6.99	1.817	0.075
Wake (%)	11.58	12.87	10.50	12.41	0.319	0.751
AHI	21.2	4.7	56.4	19.8	-8.20	<0.001
Snoring (min)	167.49	109.20	154.02	116.43	0.422	0.675
Snoring (%)	40.60	24.48	34.34	25.06	0.907	0.368
ODI	14.66	6.32	48.06	22.51	-6.781	<0.001
Average SpO <sub>2</sub>	95.05	1.23	92.40	3.13	3.794	<0.001
LM	85.81	73.65	157.15	108.11	-2.662	0.010
Arl (respiratory)	10.73	4.89	35.92	20.75	-5.584	<0.001
Arl (spontaneous)	6.93	3.66	6.88	9.58	0.022	0.983
Arl (total)	18.80	6.16	43.26	17.67	-6.252	<0.001

OSAS, obstructive sleep apnea syndrome; TIB, time in bed; SPT, sleep period time; TST, total sleep time; SL, sleep latency; SE, sleep efficiency; S1, stage 1 sleep; S2, stage 2 sleep; S3, stage 3 sleep; S4, stage 4 sleep; REM, REM sleep stage; Wake, wakeful state; AHI, apnea-hypopnea index; ODI, oxygen desaturation event index; LM, limb movements; Arl, arousal index.

**Table 2.** Time and frequency domain variables of the heart rate variability of the subjects with obstructive sleep apnea syndrome

Variable	Moderate OSAS (n=22)		Severe OSAS (n=37)		t	p
	Mean	SD	Mean	SD		
RR Interval (ms)	971.23	154.37	903.19	117.90	1.907	0.062
SDNN (ms)	94.14	26.52	109.19	63.98	-1.048	0.299
SDNN index (ms)	71.86	24.58	90.14	66.23	-1.241	0.220
RMSSD (ms)	57.32	31.18	64.97	85.40	-0.404	0.688
NN50 count	4796.14	4464.33	5132.14	4329.50	-0.285	0.777
NN50 of total HR (%)	18.53	17.52	18.01	15.62	0.118	0.906
SDANN (ms)	57.36	28.29	53.86	23.78	0.509	0.613
HRV TI	17.36	4.72	21.60	7.84	-2.292	0.026
Total power (ms <sup>2</sup> )	13,682	4,643	19,270	9,429	-2.592	0.012
VLF power (ms <sup>2</sup> )	8,523	3,615	12,038	7,216	-2.126	0.038
LF power (ms <sup>2</sup> )	3,135	1,145	5,292	3,059	-3.169	0.002
HF power (ms <sup>2</sup> )	1,885	1,108	1,738	1,523	0.396	0.694
LF/HF ratio	2.03	1.08	4.38	3.67	-2.922	0.005

OSAS, obstructive sleep apnea syndrome; SDNN, standard deviation of NN interval; RMSSD, square root of the mean squared differences of successive NN intervals; NN50, the number of interval differences of successive NN intervals greater than 50 ms; SDANN, standard deviation of average NN interval; HRV TI, heart rate variability triangular index; VLF, very low frequency; LF, low frequency; HF, high frequency.

( $p=0.003$ ). Other variables of the sleep profile revealed no difference. The mean AHI for the moderate OSAS group was  $21.2 \pm 4.7$ , and  $56.4 \pm 19.8$  for the severe OSAS group. There was no a significant difference in snoring time between the two groups. The severe OSAS group showed a significantly higher ODI ( $p<0.001$ ), lower average SpO<sub>2</sub> ( $p<0.001$ ), and higher total number of episodic limb movements ( $p=0.010$ )

than the moderate OSAS group. The severe OSAS group showed higher respiratory ( $p<0.001$ ) and total arousal indices ( $p<0.001$ ) with no difference of spontaneous arousal index as compared to the moderate OSAS group.

Time domain variables did not demonstrate any differences between the groups except for HRV triangular index (Table 2). The HRV triangular index of the moderate OSAS group

**Table 3.** Partial correlation of apnea-hypopnea index (AHI) and heart rate variability (HRV) indices controlling age and body mass index of the subjects with obstructive sleep apnea syndrome

Variable	AHI	
	$r_p$	$p$
Total power (ms <sup>2</sup> )	0.313	0.018
VLF power (ms <sup>2</sup> )	0.286	0.031
LF power (ms <sup>2</sup> )	0.395	0.002
HF power (ms <sup>2</sup> )	-0.196	0.143
LF/HF ratio	0.610	<0.0001
RR Interval (ms)	-0.370	0.005
SDNN (ms)	0.035	0.799
SDNN index (ms)	0.079	0.561
RMSSD (ms)	-0.030	0.825
NN50 count	-0.021	0.880
NN50 of total HR (%)	-0.093	0.491
SDANN (ms)	-0.159	0.237
HRV triangular index	0.153	0.254

VLF, very low frequency; LF, low frequency; HF, high frequency; SDNN, standard deviation of NN interval; RMSSD, square root of the mean squared differences of successive NN intervals; NN50, the number of interval differences of successive NN intervals greater than 50 ms; SDANN, standard deviation of average NN interval.

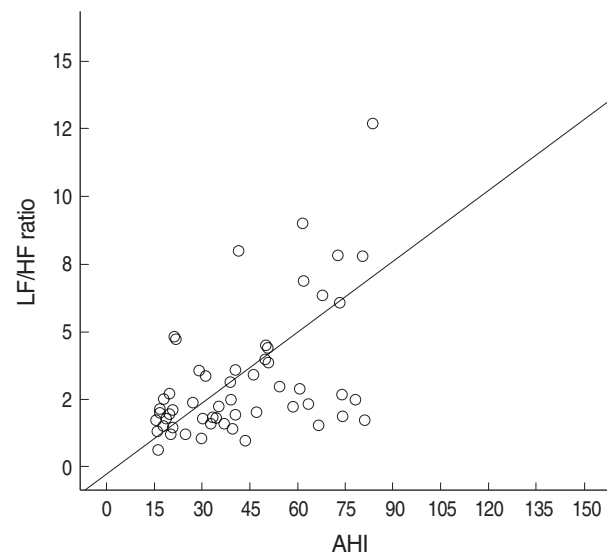
was significantly lower than the severe OSAS group ( $17.4 \pm 4.7$  and  $21.6 \pm 7.8$  respectively,  $p=0.026$ ). In frequency domain analysis, total power ( $p=0.012$ ), VLF power ( $p=0.038$ ), LF power ( $p=0.002$ ), and LF/HF ratio ( $p=0.005$ ) were greater in the severe OSAS group than in the moderate OSAS group with no difference of HF power (Table 2).

In the correlation analysis between AHI and HRV indices controlling age and BMI (Table 3), AHI showed positive correlations with total power ( $r_p=0.313$ ,  $p=0.018$ ), VLF power ( $r_p=0.286$ ,  $p=0.031$ ), LF power ( $r_p=0.395$ ,  $p=0.002$ ) and LF/HF ratio ( $r_p=0.610$ ,  $p<0.0001$ ), but a negative correlation with RR interval ( $r_p=-0.370$ ,  $p=0.005$ ). The most significantly positive relationship with AHI was found in the LF/HF ratio (Fig. 1).

## DISCUSSION

It is quite proper that the severe OSAS group had greater oxygen desaturation, arousal indices and lower SpO<sub>2</sub> than the moderate symptom group because the mean AHI was completely different from each other according to the definition of the groups. The increased ventilatory effort that results from obstructed breathings in apneic or hypopneic episodes causes frequent arousals (7). More frequent arousals in the patients with severe symptoms might prevent them from falling into deep sleep, and it can also explain increased limb movements in this group.

In time domain analysis, most parameters failed to make significance in the statistical comparison between the groups. The only time domain variable demonstrating the difference



**Fig. 1.** The correlation between AHI and LF/HF ratio controlling age and body mass index is shown by positive relationship ( $r_p=0.610$ ,  $p<0.0001$ ) in the subjects with obstructive sleep apnea syndrome. AHI, apnea-hypopnea index; LF, low frequency; HF, high frequency.

was the HRV triangular index. The HRV triangular index can be calculated by the integral of the density distribution divided by the maximum of the density distribution of normal-to-normal (NN) interval. The HRV triangular index tends to correlate with total power in frequency domain analysis. It also reflects the overall amount of variability and has known to be affected by both sympathetic and parasympathetic activity but more influenced by lower bands than higher bands (19). The significant difference of the HRV triangular index in this study can be interpreted to have been affected by the influence of lower frequency component, because HF did not show the difference. Although the LF component has been regarded as a parameter reflecting sympathetic activity, it is far from conclusive whether this result about the HRV triangular index means increased sympathetic tone, because not only LF but also VLF power contributed to the significance of total power. In spite of a few previous studies that reported increases of VLF component in OSAS patients (20, 21) and synchronized VLF behavior with hypoxemia (22), the exact physiological meaning of VLF still remains in debate. One of the possible explanations for the reason why most time domain variables were not better than frequency domain variables in differentiating the two groups in this study is that frequency domain techniques may be better than time domain analysis in the precise evaluation of changes of sympathovagal balance (19).

In the frequency study, all variables but HF power were found to be significantly greater in the patients with severe symptoms. The difference between the groups depended on the power of very low and low frequency bands. It can account



for the greater total power in the patients with severe symptoms because HF power revealed no difference. Parasympathetic control for heart rate has a very short latency enabling a beat-to-beat basis change, but synaptic norepinephrine mediating sympathetic influence is metabolized relatively slowly (19). In different way from respiratory sinus arrhythmia that occurs at a high frequency, baroreceptor-mediated heart rate variation has a lower frequency variation about 0.10 Hz and can be significantly diminished by sympathetic blockade (19, 23). The HF component has been known to be associated with parasympathetic activity, and LF power was proposed as an index that is affected by the activity of sympathetic nervous system. However, there has been no complete agreement about the meaning of the LF component. Mostly sympathetic activity or both sympathetic and parasympathetic activities are thought to contribute to the LF component of HRV. The LF finding without a HF change in this study can be thought to implicate increased sympathetic tone in the severe patients compared with the moderate symptoms group.

The LF/HF ratio was found to have a better statistical significance for differentiating the two study groups and to have better correlation with OSAS severity than other variables in frequency analysis. One possible reason for this is that the LF/HF ratio with less contribution of parasympathetic activity would reflect sympathetic activity better than the LF component itself. Another possible reason that can explain why the LF/HF ratio demonstrated a better significance than LF power is that the LF/HF ratio is a normalized parameter without an effect of total power that can be variable with experimental conditions.

There were some previous studies in which investigators tried to find a relationship between OSAS severity and HRV parameters. Narkiewicz and colleagues found a increased LF/HF ratio, HF power, and normalized LF power in patients with moderate-to-severe OSAS patients compared to normal controls, and a greater LF/HF ratio compared to mild OSAS patients (24). Gula and colleagues reported that the LF/HF ratio was higher among patients with moderate OSA compared to normals and interestingly those with severe OSA (25). Aydin and colleagues reported that total power, VLF, LF, and LF/HF ratio were higher in patients than those in controls, and that LF and LF/HF ratio were increased in severe OSAS group compared with mild OSAS group (21), but Yang and colleagues' study did not find any difference of time or frequency variables between mild-to-moderate and moderate-to-severe OSAS patients (26). Because their methods were different in the criteria for patients classification, length of time series, hours for getting signals, and ways of analysis, direct comparisons of the results cannot be justified. However, the increased LF power and LF/HF ratio in OSAS patients are relatively consistent findings. The temporary reduction of the oxyhemoglobin level in apnea or hypopnea episodes is known to result in the activation of sympathetic nervous system and subsequent stimulation of

the rennin-angiotension-aldosterone system. The relationship of OSAS and systemic hypertension can be attributed to these physiological mechanisms (27). Because LF power and LF/HF ratio have been regarded as indices indicating sympathetic tone or sympathovagal balance, it is plausible to assume that the greater AHI, the greater LF or LF/HF ratio.

This study suggests that the LF/HF ratio can be an appropriate index estimating the severity of OSAS symptoms and that it can be a good candidate for a screening tool with an oximetry for apnea-hypopnea syndrome. Regardless of its usefulness, there have been continuous efforts to find appropriate screening methods for OSAS (28-30). The reduction of the arterial oxygen level is a direct consequence of apnea and hypopnea, but a screening only with oximetry does not have a good sensitivity (29). The LF/HF ratio may be useful because this study showed that it has a linear correlation with AHI.

Frequency analysis has been done usually for short-term HRV data because there is a stationary problem in the long-term data, and it often makes the meaning of the data obscure. However, this result found that the LF/HF ratio still has a meaningful relationship with the severity of the symptoms in the long-term HRV. A limitation is that there was not a normal control group in this study, but there seemed to be no disagreement about the increased LF/HF ratio in the patients through previous studies. Verification of its usability as a screening method needs further studies.

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