Heart Rate Variability in Obstructive Sleep Apnea: A Prospective Study and Frequency Domain Analysis

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Background: Cyclic variation of the heart rate is observed during apneic spells in obstructive sleep apnea (OSA). We hypothesized that autonomic changes would affect frequency-domain measures of heart rate variability (HRV).

Methods: We studied 20 patients (15 men, 5 women, mean age 47.2 ± 12.2 years) with suspected OSA undergoing overnight polysomnography, and five patients (4 men, 1 woman, mean age 49.2 ± 8.6 years) with recently diagnosed sleep apnea undergoing polysomnography while wearing continuous positive airway pressure (CPAP). Holter monitors were applied during sleep studies and data were analyzed in 5-minute blocks over the course of the night. Using spectral analysis, low frequency (LF) and high frequency (HF) powers were calculated for each interval. Overall mean and standard deviation (SD) for LF power, HF power, and the LF:HF ratio were recorded for each patient. Comparisons were made between patients with severe OSA (apnea hypopnea index (AHI) > 30, n = 8), moderate OSA (AHI 1–30, n = 5), without OSA (AHI < 10, n = 7), and patients wearing CPAP (n = 5).

Results: Assessment of overnight LF or HF power revealed no significant difference between the four groups. The LF:HF ratio, which represents sympathovagal balance, was higher among those with moderate disease compared to normals and those with severe OSA (both P = 0.037). The standard deviation of the LF:HF ratio was higher among those with moderate disease compared to normals (P = 0.0064) and those with severe OSA (P = 0.0006). OSA patients receiving CPAP behaved like patients with moderate OSA, with increased SD of the LF:HF ratio.

Conclusions: The observed changes in the LF:HF ratio and its SD suggest an increased sympathetic tone and discordance in sympathovagal activity in moderate OSA, which is blunted in severe OSA. CPAP may restore autonomic defects, characteristic of severe OSA, to moderate levels.

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Altered heart rate variability has been demonstrated in association with several disorders that affect autonomic tone including recent myocardial infarction,[1,2] congestive heart failure,[3,4] and diabetic neuropathy.[5,6] Obstructive sleep apnea (OSA) has been associated with characteristic heart rhythm disturbances[7,8] with recent focus on heart rate variability in OSA.[9–15] Roche et al[15] have demonstrated that a number of time-domain measures are diminished in patients with OSA, reflecting a loss of naturally occurring periodic changes in heart rate. Previous studies have provided insight into heart rate periodicity changes at particular frequency ranges by examining individual apneic episodes,[12] individual sleep stages,[14] or very low frequency ranges.[10] We set out to examine overnight heart rate variability in OSA using frequency-domain analysis with special attention to high frequency and low frequency ranges. We hypothesized that an increase in sympathetic tone relative to vagal tone in patients with OSA would be reflected in an augmented overnight low frequency

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(LF) power and diminished high frequency (HF) power, resulting in a greater overnight LF:HF ratio with progressively worse OSA.

METHODS

Study Population

We prospectively studied 25 consecutive patients (19 men, age 47.6 ± 11.5 years) in normal sinus rhythm undergoing overnight sleep studies. Twenty patients were referred to the sleep laboratory for clinically suspected OSA, and five had overnight trials of continuous positive airway pressure (CPAP) for a recent diagnosis of OSA.

Sleep Studies

Each patient underwent overnight sleep studies with continuous polysomnography. Recordings included electroencephalogram, electro-oculogram, submental electromyogram (EMG), left and right anterior tibialis EMG, electrocardiogram (ECG), thoracoabdominal motion, oronasal airflow (expired carbon dioxide), and arterial oxygen saturation with pulse oximetry using an ear probe sensor. The studies were scored manually, blind to Holter and heart rate variability (HRV) results, and the total apnea and hypopnea index (AHI) was calculated by determining the average number of events (apneas or hypopneas) per hour of sleep. Obstructive apneas were defined as the cessation of airflow for at least 10 seconds accompanied by ongoing respiratory effort. Obstructive hypopneas were defined as a reduction in airflow of at least 50% for at least 10 seconds accompanied by a reduction in thoracoabdominal movement and by an arousal or an arterial oxygen desaturation of at least 3%. Severe OSA was defined as an AHI >30 per hour, mild-to-moderate OSA as an AHI 10–30, and normal as an AHI < 10.

Patients who had previously been diagnosed with obstructive sleep apnea (AHI > 10) were studied during a trial of continuous positive airway pressure (CPAP). CPAP was titrated in a standard fashion for all patients and was started via a nasal mask selected and sized to optimize patient comfort. The starting pressure was 5 cm of water (cm H_2O). The CPAP pressure was increased in 1 cm H_2O increments if the patient was still snoring, having arousals from sleep, or having obstructive events associated with arousal or an oxygen desaturation > 3%. The pressure was not increased if respiratory events occurred without an associated arousal or oxygen desaturation >3%.

All polysomnography recordings were divided into 5-minute intervals. Each interval was analyzed for corresponding sleep stage. If rapid eye movement (REM) sleep persisted through the entire 5 minutes, the interval was designated "REM; '' if stage 2 non-REM sleep persisted through the entire 5 minutes, the interval was designated "non-REM.'' Intervals during which the patient was awake for the full 5 minutes were also assessed.

Holter Monitoring and HRV Analysis

One investigator (LG) applied Holter monitors to all patients prior to sleep study in a standard manner. Recordings were made throughout the duration of the sleep study, and time readings were synchronized between the Holter and the polysomnography computer. Holter tapes were analyzed on a Marquette MARS v4.0a (Marquette Incorporated, Madison, WI) by the same investigator who was blind to the polysomnography results. Beats were excluded from HRV analysis if they occurred immediately before or after ventricular, junctional, or ectopic supraventricular beats. R-R intervals greater than 5 seconds were also excluded. The recording was divided into 5-minute intervals, corresponding to the 5-minute intervals of the polysomnography study, and power spectral analysis was performed for each interval and graphed as power in milliseconds squared (ms^2) versus frequency in hertz (Hz). Frequency ranges of interest were defined as low frequency (LF) (0.04–0.15 Hz), and high frequency (HF) (0.15–0.40 Hz) and were recorded for each interval, along with the LF:HF ratio. For each patient the following measures were obtained: mean LF power (μLF), mean HF power (μHF), mean LF:HF power (μLF:HF), standard deviation of LF power (sdLF), standard deviation of HF power (sdHF), and standard deviation of LF:HF power (sdLF:HF). The resulting values were used to calculate a mean for each of the above six variables according to sleep apnea status. For example, for the severe OSA group an overall mean LF was calculated by averaging the mean overnight LF values for patients found to have severe OSA. A mean LF standard deviation for the same group was calculated by averaging the overnight LF standard deviation of each patient with severe OSA. The latter result was intended to indicate the degree of

Table 1. Minimum Oxygen Saturation Data

	n	Mean Minimum O_2 Saturation, REM Sleep	Mean Minimum O_2 Saturation, Non-REM Sleep
Severe OSA	7	79.8 ± 15.0	86.1 ± 6.02
Moderate OSA	4	92.5 ± 1.73	94.0 ± 1.63
Normal	5	93.4 ± 1.34	94.6 ±.548
CPAP	4	93.5 ±.577	94.2 ± 1.50
ANOVA P-value		.052	.0032

ANOVA, analysis of variance; CPAP, continuous positive airway pressure; O_2, oxygen; OSA, obstructive sleep apnea; REM, rapid eye movement.

variability of low frequency power, according to OSA status.

Statistical Analysis

ANOVA testing was used to compare baseline characteristics among groups, and two-tailed Student *t*-tests were used to compare HRV variables. Independent variables were severe OSA, moderate OSA, normal, and CPAP. Dependent variables were μLF, μHF, μLF:HF, mean sdLF, mean sdHF, and mean sdLF:HF. Data were further examined using the nonparametric Mann–Whitney test in light of the small study population. Differences were considered statistically significant if $P < 0.05$.

RESULTS

The study population consisted of 20 patients (15 men, age 47.2 ± 12.2 years) with suspected OSA, and 5 patients (4 men, age 49.2 ± 8.6 years) with recently diagnosed OSA undergoing a repeat sleep study for CPAP titration. Eight patients were diagnosed with severe OSA, five with moderate OSA, and seven were normal. Oxygen saturation data were available according to sleep stage for 20 patients(5 normal, 4 moderate, 7 severe, 4 CPAP), and are shown in Table 1. Age and body mass index did not differ significantly among the groups ($P = 0.69$ and 0.56, respectively) (Table 2). Eight patients had comorbidities for which they were taking medications (Table 3).

Analysis revealed no difference between any two of these groups with regard to mean LF, mean HF, standard deviation of LF, or standard deviation of HF (Table 2). The LF:HF ratio was greater in patients with moderate OSA than normals ($P = 0.037$) and those with severe OSA ($P = 0.037$). The standard deviation of the LF:HF ratio was, likewise, greater in patients with moderate OSA than normals ($P = 0.006$) and those with severe OSA ($P = 0.0006$). Patients with CPAP had a greater standard deviation of the LF:HF ratio than those with severe OSA ($P = 0.045$).

When data were analyzed using nonparametric tests, LF:HF ratio was higher in patients with moderate OSA than those with severe OSA ($P = 0.040$). There was a trend toward higher ratio among patients with moderate OSA compared to normals ($P = 0.062$). The standard deviation of the ratio was again higher in patients with moderate OSA than normals ($P = 0.012$) and those with severe OSA ($P = 0.005$). A trend toward greater standard deviation of the LF:HF ratio persisted when patients with

Table 2. Characteristics of Patients and Heart Rate Variability Results According to Sleep Apnea Status

	n	age	BMI	μLF	μHF	mean LF:HF	sdLF	sdHF	sd LF:HF
Severe OSA	8	50.8	35.0	2610	1283	2.723 ± 0.966	1685	853	1.463 ± 0.398
Moderate OSA	5	46.6	28.9	999	326	5.186 ± 2.722	813	259	3.854 ± 1.353
Normal	7	43.6	32.4	2121	1084	2.656 ± 0.648	1586	632	1.730 ± 0.799
CPAP	5	49.2	34.6	691	461	3.382 ± 1.614	813	250	2.341 ± 1.002

BMI, body mass index; CPAP, continuous positive airway pressure; LF:HF, ratio of low to high frequency power; μLF, mean low frequency power; μHF, mean high frequency power; OSA, obstructive sleep apnea; sdHF, standard deviation of high frequency power; sdLF, standard deviation of low frequency power; sd LF:HF, stand deviation of ratio of low to high frequency power.

Table 3. Details of the Eight Study Patients with Comorbidities and Using Medications

Patient	OSA Status	Comorbidity	Medications
1	Severe	Hypertension	Amlodipine
2	Severe	History myocardial infarction	Aspirin, coumadin
3	Severe	Hypertension	Atenolol, amiloride
4	Severe	Hypertension, gout	Amlodipine, allopurinol
5	Normal	Hypertension, depression	Amlodipine, zoloft
6	CPAP	Hypertension	Enalapril
7	CPAP	Hypothyroid	L-thyroxine
8	CPAP	Gastroesophageal reflux	Ranitidine

CPAP, continuous positive airway pressure; OSA, obstructive sleep apnea.

CPAP were compared to those with severe OSA ($P = 0.079$).

When data were analyzed according to sleep stage, the LF:HF ratio during REM sleep was greater in moderate OSA than in normals ($P = 0.048$), and showed a trend toward an increased value in moderate OSA compared to severe OSA ($P = 0.055$) (Table 4). There was also a trend toward increased LF:HF during REM sleep with CPAP compared to severe OSA ($P = 0.078$). The LF:HF ratio was not significantly different among any of these groups during non-REM sleep.

DISCUSSION

Our results demonstrate an overnight LF:HF ratio which is higher among patients with moderate OSA than severe OSA patients and normals. The same pattern holds true for standard deviation of the LF:HF ratio. High frequency power is generally regarded as a reflection of vagal tone and LF power as a reflection, albeit less pure, of sympathetic tone. The LF:HF ratio can therefore be regarded as the ratio of sympathetic to vagal tone as measured by periodic fluctuations in heart rate. The standard deviation of the LF:HF ratio reflects the degree of change in heart rate at low frequency with respect to that at high frequency (Fig 1). A low LF:HF ratio standard deviation would therefore indicate congruous changes in sympathetic and vagal tone, whereas a high standard deviation would indicate incongruous changes over time.

Our finding that patients with moderate OSA have higher LF:HF ratios than normals suggests a higher proportion of sympathetic tone with moderate OSA, which is likely induced by repetitive apneic events. A number of mechanisms may be responsible for this finding. Relative hypoxemia may act upon central chemoreceptors to increase sympathetic tone. Repeated awakening from sleep may also result in vagal withdrawal and high relative sympathetic activity. The finding that the LF:HF standard deviation is also increased suggests that overnight changes in vagal tone are not congruous with changes in sympathetic tone. Five-minute intervals encompass numerous apneic episodes in patients with OSA. Therefore, the disparity of autonomic influences seen in our study was not likely due to the influence of individual apneic episodes on vagal and sympathetic tone, but rather due to more infrequently occurring events. These may

Table 4. LF:HF Ratios According to Sleep Stage and Sleep Apnea Status

	Normal	Moderate OSA	Severe OSA	CPAP	P Value
	2.380 ± .763	5.896 ± 3.222			0.048
REM		5.896 ± 3.222	2.759 ± 1.132		0.055
LF:HF			2.759 ± 1.132	5.980 ± 3.752	0.078
	1.505 ± .509	3.565 ± 3.299			0.20
Non-REM		3.565 ± 3.299	2.352 ± 1.131		0.38
LF:HF			2.352 ± 1.131	2.189 ± 2.009	0.86

CPAP, continuous positive airway pressure; LF:HF, low to high frequency ratio; OSA, obstructive sleep apnea; REM, rapid eye movement.

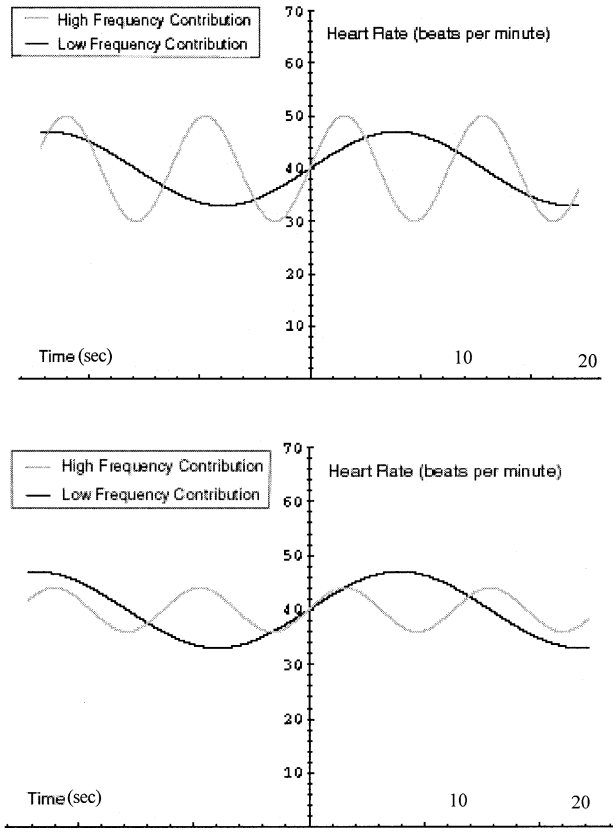

Figure 1. Illustration of heart rate fluctuations separated into high and low frequency contribution. Two curves are shown, representing high and low frequency periodic change in heart rate, and the amount these oscillations contribute to overall heart rate change (amplitude). The sum of the two sine waves would represent the overall heart rate over time. The upper image reflects a periodic high frequency change in instantaneous heart rate of approximately 20 beats per minute (BPM). The lower image demonstrates a subsequent high frequency change of 10 BPM, thus illustrating an decrease in high frequency power. The low frequency change in instantaneous heart rate of 15 BPM remains constant from the first to the second interval. Therefore, there is an overall increase in LF:HF power. If the LF power had concomitantly decreased by the same proportion as the HF power, the LF:HF ratio would have remained constant. Whereas each time interval contains an LF:HF ratio, the standard deviation of LF:HF is determined by the relative change of low frequency to high frequency heart rate oscillations among several intervals.

have included awakenings, as mentioned above, which occur more often in OSA patients than normals. Changes in sleep stage may also have been an important factor. Indeed, REM sleep, which typically occurs at 90-minute intervals, is associated with significantly more apneic episodes in OSA patients than non-REM sleep. Analysis of our data according to sleep stage suggested that the significant differences in LF:HF ratio among groups, as described above, were observed in REM intervals and absent in non-REM intervals.

Our finding that the group with severe OSA had lower LF:HF ratios and standard deviations than those with moderate OSA was unexpected. Since the LF and HF power did not differ significantly among these groups, this finding can be attributed to the relationship between the two. There was a trend toward increased LF and HF power with severe OSA, with a greater increase in the HF power. These findings may suggest further increase in sympathetic tone with more advanced disease, with a concomitant increase in vagal tone, perhaps due to a more frequent and exaggerated Mueller maneuver. It is also possible that the profound change in respiratory pattern in severe OSA patients has a direct influence on the HF power, since respiration itself is known to contribute to this measure. The diminished LF:HF standard deviation suggests that the low and high frequency power change in a more congruous manner in patients with severe OSA. Since there is a trend toward an increased standard deviation of both LF and HF, a possible explanation may be a persistently elevated sympathetic tone that is less dynamic than in moderate OSA, and a vagal tone that is elevated due to the reasons described above, and remains relatively elevated due to the increased frequency of apneic events.

The increased LF:HF standard deviation in the group on CPAP compared to those with severe OSA suggests that treatment with CPAP has an effect on the heart rate variability of OSA patients. By preventing apneic episodes and the resulting arousals, oxygen desaturations, and large negative intrapleural pressure swings caused by inspiratory effort against a closed upper airway, the use of CPAP could prevent alterations in autonomic tone that give rise to the HRV characteristics we saw in our severe OSA patients. Some effect on autonomic tone may persist even in the absence of apneas, and HRV variables of patients on CPAP were not significantly different from normals or those with moderate OSA. Some difference may have been detected with larger sample sizes.

It is interesting to note that all significant findings described above with regard to LF:HF ratio approached significance when only REM intervals were considered, but not when non-REM intervals

were examined. This suggests an influence of sleep stage on heart rate variability in OSA.

Limitations to our study include the small sample size, and the comparison of patients using CPAP to others with disease, rather than using the CPAP patients as their own controls by analyzing their previous sleep studies. This would not have been compatible, however, with our prospective approach. There were possible confounding factors in the severe OSA group with regard to comorbidities and medications. With the exception of gout, the comorbidities that were observed, however, are all known complications of OSA and therefore their impact on HRV may be relevant to the assessment of the OSA patient. In fact, this may be an argument in favor of the use of HRV as an adjunctive tool for the stratification of patients with OSA. We could not address the question of the impact of CPAP therapy on HRV after varying lengths of treatment period. It would be interesting to investigate several patients at a given stage of OSA, and their HRV before CPAP, with first administration of CPAP, and after various intervals of use.

Obstructive sleep apnea is a disease with numerous potential complications, including hypertension, myocardial infarction, cerebrovascular accidents, and arrhythmias.[16] We have further delineated the HRV characteristics of OSA patients in various stages of disease while being treated with CPAP. We suggest that the LF:HF ratio is the most useful measure for comparison, and its value during REM sleep had a greater impact on overall trends than its value during non-REM sleep. We have introduced the notion of LF:HF standard deviation as a means of comparing the activity of the vagal and sympathetic nervous systems over time. Further study of these variables could be useful to determine if a threshold exists which, with reasonable sensitivity, provides a diagnosis of OSA or a stratification of moderate versus severe OSA. Such a test, which requires only Holter monitoring, could provide a simple and inexpensive diagnostic step before polysomnography studies. It could also be performed in the comfort and convenience of the patient's own home.

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