Spectral Indices of Cardiac Autonomic Function in Obstructive Sleep Apnea

Michael C.K. Khoo,[1] Tae–Sun Kim,[1] and Richard B. Berry[2]

[1]*Biomedical Engineering Department, University of Southern California, Los Angeles, CA 90089; and* [2]*Department of Medicine, Veterans Administration Medical Center, Long Beach, and University of California, Irvine, CA 90822*

Summary: Spectral analysis of heart rate variability (HRV) is useful as a noninvasive means of assessing autonomic function in patients with obstructive sleep apnea (OSA). However, standard spectral measures, such as the ratio of low–frequency to high–frequency power (LHR) and normalized high–frequency power (NHFP), can be confounded by the abnormal breathing patterns that occur during sleep. To circumvent this limitation, we employed an autoregressive modeling approach to partition the RR time–series into a component that is correlated with respiration and a respiration–independent component. From these components, we derived two new spectral indices: the modified LHR (MLHR) and the average gain relating respiration to RR changes (G_{RSA}). Six normals and seven OSA patients were studied in relaxed wakefulness and stage 2 sleep; during sleep, the OSA patients were studied without and with continuous positive airway pressure (CPAP) therapy. All four spectral indices showed significant differences between OSA patients and normals in both wakefulness and sleep, although the changes in MLHR and G_{RSA} were substantially larger and less variable: MLHR ($p<0.0003$) and G_{RSA} ($p<0.0001$) vs. LHR ($p<0.005$) and NHFP ($p<0.004$). However, in the OSA subjects, LHR and NHFP were unchanged by CPAP. By contrast, CPAP produced a highly significant increase in G_{RSA} ($p<0.0004$), as well as a decrease in MLHR ($p<0.03$). Thus, by compensating for the effects of breathing pattern differences, MLHR and G_{RSA} unmasked the effects of CPAP therapy, which has been shown in previous studies to reduce sympathetic activity and increase vagal cardiac modulation.

Key words: Heart rate variability; cardiac autonomic control; periodic breathing; continuous positive airway pressure; power spectrum

INTRODUCTION

IN RECENT YEARS, there has been a growing interest in the spectral analysis of heart rate variability (HRV) as a tool for noninvasive assessment of autonomic nervous system function.[1,2] Previous studies have demonstrated the existence of three major periodic components in HRV, each of which is believed to reflect specific physiological processes.[3,4] These are: (1) a high–frequency (HF) oscillation centered around the breathing frequency (~0.15 to 0.4 Hz), commonly referred to as the "respiratory sinus arrhythmia" (RSA); (2) a low–frequency (LF) oscillation (~0.04 to 0.15 Hz), which is believed to be related to baroreflex dynamics; and (3) a very low–frequency (VLF) component (~0.01 to 0.04 Hz), which may be related to thermoregulation as well as low–frequency periodicities in respiration.[5] It is widely accepted that the HF component is mediated primarily through vagal cardiac control; consequently, the

power of the HF band, expressed either in absolute values or normalized against total power, has been used to quantify parasympathetic activity. On the other hand, changes in the LF component can be due to both sympathetic and parasympathetic activity.[1–4] For this reason, the ratio between LF and HF spectral power (LHR) is generally considered to provide a good index of sympathetic modulation.[1,3]

Autonomic function in patients with obstructive sleep apnea (OSA) has been evaluated using cardiovascular reflex tests which involve subject cooperation, such as controlled breathing, abrupt change in posture from supine to standing, the Valsalva maneuver and sustained handgrip.[6–8] As such, the assessment is limited to autonomic activity during wakefulness. Furthermore, each of these tests yields either a positive or negative result, leading the clinician to determine only whether the patient is to be classified as "normal" or "abnormal." In contrast, spectral analysis of HRV yields continuous measures of autonomic function and can be conducted relatively nonintrusively without subject cooperation, thus in principle allowing the technique to be applied during sleep. On the other hand, spectral measures of HRV can be affected by differences in breathing pattern within and across individuals, particular-

ly when these measures are obtained in different sleep–wake states. For instance, the RSA is known to be significantly affected by variations in the rate and depth of breathing.[9,10] In OSA or patients with Cheyne–Stokes respiration, the respiratory modulation of heart rate is not confined to within–breath changes but also takes the form of large cyclical variations that correlate with the episodic apneas or hypopneas.[11] Although these oscillations generally fall into the VLF band, LF and HF power have also been found to increase during OSA episodes.[12]

In this paper, we introduce two new indices, derived from the spectral analysis of HRV, that allow for comparative assessments of autonomic activity within and across subjects. These are: (1) the modified LF–to–HF power ratio, MLHR, and (2) the average gain relating respiration to RR changes in the HF band, G_{RSA}. The underlying premise is that the time series of RR interval fluctuations can be decomposed mathematically into two basic components: one that is independent of respiration and the other that is linearly correlated with present and past fluctuations in respiration.[13] MLHR and G_{RSA} may be thought of as extensions of LHR and HF power, respectively, with the important additional feature that both modified spectral indices contain built–in compensation for differences in breathing pattern. By deriving MLHR and G_{RSA} from data measured during wakefulness and stage 2 sleep in normal subjects and OSA patients (with and without CPAP), we sought to determine whether these new indices would provide a more sensitive assessment of autonomic function than the traditional spectral measures, normalized HF power, and LHR.

METHODS

Experimental Methods

Six normal volunteers (five male and one female, age: 28.5 (mean)+ 1.4 (SE) yrs, wt: 181 + 16 lbs) and seven patients (all male, age: 53.3 + 2.2 yrs, wt: 239 + 13 lbs) with moderate–to–severe OSA (apnea–hypopnea index >20) participated in overnight sleep studies, carried out at the V.A. Medical Center Sleep Disorders Laboratory, Long Beach, CA. Informed consent was obtained prior to each study. The protocol for the studies was approved by the institutional commitee on human experimentation. Although systemic hypertension is highly prevalent in OSA, only two of the patients studied were hypertensive. For safety reasons, these two patients were not asked to discontinue medication for their hypertension prior to the overnight studies. All OSA patients had been on home therapy with continuous positive airway pressure (CPAP) at the time of the study for 377 + 115 days (range: 2–1/2 months to 2–1/2 years). Except for one subject, all other patients had been on home CPAP therapy for more than 16 weeks. Examination of airflow pattern and esophageal pressure

(P_{es}) swings in the normals during the overnight studies confirmed that no subject in this group had any significant sleep–disordered breathing. The individual subject characteristics are displayed in Table 1.

TABLE 1: Subject Characteristics

A: Normal Subjects

Subject	Age (yrs)	Weight (lbs)	Variability in ΔP_{es}*(cm H$_2$O)
N1	24	140	1.4
N2	25	150	1.0
N3	32	248	6.9
N4	32	200	3.0
N5	29	190	6.5
N6	29	160	1.4

B: OSA Subjects

Subject	Age (yrs)	Weight (lbs)	Apnea-Hypopnea Index (hr⁻¹)	Variability in ΔP_{es}* (cmH$_2$O)	Prescribed CPAP level (cmH$_2$O)	Prior CPAP therapy (# days)
O1	55	310	107	34.9	15	525
O2	58	230	75	20.0	7.5	451
O3	48	250	77	23.6	12	171
O4	44	214	48	22.9	10	945
O5	51	225	59	51.3	10	73
O6	59	206	35	10.4	12	118
O7	58	240	50	12.5	13	357

* Variability in ΔP_{es} = Maximum P_{es} deflection - Minimum P_{es} deflection (during Stage 2 sleep)

All subjects breathed through a nasal mask (Soft Series, Healthdyne Technologies, Marietta, GA) and a chin strap was applied to prevent leakage of airflow through the mouth. Pressure within the mask and the pressure difference across the pneumotachograph were measured by using MP45 (Validyne, Northridge, CA) transducers. The port of the nasal mask was connected via a screen pneumotachograph (Model 3700, Hans Rudolph) to measure the inspiratory and expiratory airflow. Arterial O_2 saturation was monitored by pulse oximetry using a finger probe (Model 3700, Ohmeda, Boulder, CO). A 5–Fr polyurethane pediatric feeding tube (Sherwood Medical, St. Louis, MO) was inserted through one nostril after topical administration of lidocaine (1 cc of 4%) so that the tip of the catheter was positioned in the mid–esophagus for measurement of P_{es}. The saline–filled catheter was connected to a disposable Transpac II pressure transducer (Abbot Critical Care, North Chicago, IL), which was subsequently calibrated with a water manometer. The transducer system contained a valve that allowed a slow infusion of saline at 3–4 cc/hr to maintain catheter patency. The other variables monitored included the electrocardiogram (ECG), two elec-

troencephalograph (EEG) derivations (central and occipital), chin electromyogram (EMG), and left and right electrooculograms (EOG).

The distal end of the pneumotachograph was connected to a CPAP device (Respironics, Murraysville, PA). At the start of each study, a small amount of CPAP (2–3 cm H_2O), adequate to reduce most of the resistance of the breathing circuit, was applied. Data collection began with subject lying supine in the bed in relaxed wakefulness. Subsequently, the lights were turned off and the subject was allowed to fall asleep. All subjects were studied under minimal CPAP in wakefulness and sleep. Each OSA subject was also studied during stage 2 sleep (on the same night) after the applied CPAP was gradually raised to the individual's prescribed treatment level (7.5 –15 cm H_2O, see Table 1). All the signals were recorded on a 12–channel Grass (Grass Instruments, Quincy, MA) 78D polygraph using a paper speed of 10 mm/s, digitized on–line at 100 Hz/channel (WINDAQ software, DATAQ Instruments, Akron, OH), and stored in a computer (IBM–compatible 80486) for subsequent processing and analysis. A near–infrared camera and video monitor system allowed continuous visual inspection of the subjects.

Sleep stages were scored according to conventional criteria.[14] Because the subjects were heavily instrumented, most of the total sleep time was spent in stage 2, with significantly smaller contributions from stages 3 and 4 and rapid–eye–movement sleep. Thus, the data segments selected for analysis were limited to periods in which the subjects were in relaxed wakefulness or stage 2 sleep. Selection of data segments representing the CPAP–on condition in the OSA subjects was based on the following criteria: (1) the subject was in stage 2 sleep; (2) there were no arousals or state changes in the interval studied; (3) the prescribed level of CPAP had been administered for at least 15 minutes prior to the start of the selected segment.

Data Analysis

In order to obtain the time series of RR intervals, the time–locations of the QRS complexes in the ECG tracing were first detected using a computer algorithm. The results of this procedure were reviewed manually and edited when necessary to ensure that no detection errors were made. Subsequently, the intervals between successive QRS complexes were computed. Since these spikes occur at irregular intervals, each sequence of RR intervals was converted into an equivalent uniformly spaced time–series (sampling rate: 10 Hz) using a resampling algorithm closely similar to that of Berger et al.[15] P_{es} and airflow were also resampled at 10 Hz so that each respiratory value would be synchronized with the corresponding instantaneous HR value. Each resampled sequence contained 3,000 data points (5 minutes).

Mean RR interval (MnRR) and the standard deviation of HRV (SDRR) were computed from each RR time series. Following removal of the mean and linear trend, power spectral analysis for the P_{es} and RR time series was performed using the Welch method with Hanning windowing.[16] Power in each of the following frequency bands was computed by determining the area under the power spectral density curve bounded by the bandwidth in question: VLF (0.01 – 0.04 Hz), LF (0.04 – 0.15 Hz) and HF (0.15 – 0.4 Hz). Normalized HF power (NHFP) was determined by dividing HF power by the total spectral power of HRV between 0.04 and 0.4 Hz. To compute LHR, LF power was divided by HF power.[1]

Computation of G_{RSA} and MLHR

As in previous cardiovascular modeling studies,[17–19] we used an autoregressive with exogenous input (ARX) model to relate the dynamic fluctuations in RR (denoted as y) to present and past changes in respiration (denoted as x):

$$y(n) = -\sum_{i=1}^{p} a_i\, y(n-i) + \sum_{k=0}^{q} b_k\, x(n-k) + e(n) \qquad n = 1,...,N \quad (1)$$

where N represents the total number of data points being analyzed. The residual error term, $e(n)$, represents that part of $y(n)$ that cannot be accounted for by the ARX model. The unknown ARX model parameters, a_i ($i = 1,...,p$) and b_k ($k = 1,...,q$), were estimated using least–squares minimization. P_{es} was chosen as the variable representing respiration, for reasons to be disclosed later (see Results). Details of the estimation procedure are given in Kim and Khoo.[19]

In Eqn (1), y can be decomposed into two additive components: y_r, representing that portion of y that is correlated with the respiratory input, and y_u, representing the component that is uncorrelated with respiration:

$$y(n) = y_r(n) + y_u(n) \qquad (2)$$

Substituting Eqn (2) into Eqn (1), it can be shown that: and

$$y_r(n) = -\sum_{i=1}^{p} a_i\, y_r(n-i) + \sum_{k=0}^{q} b_k\, x(n-k) \qquad n = 1,...,N \qquad (3)$$

$$y_u(n) = -\sum_{i=1}^{p} a_i\, y_u(n-i) + e(n) \qquad n = 1,...,N \qquad (4)$$

where N represents the total number of points in the data segment being analyzed.

Following estimation of the model parameters, we evaluated y_r and y_u from Eqns (3) and (4), respectively. We also computed the power spectra, $S_{yr}(f)$ and $S_{yu}(f)$, of y_r and y_u, respectively, using the Welch method described earlier. As well, the transfer function, $H(f)$, relating changes in P_{es}

to changes in the respiratory–related component of RR was evaluated as follows:[19]

$$H(f) = \frac{\sum_{k=0}^{q} b_k \exp(-j2\pi fkT)}{1 + \sum_{i=1}^{p} a_i \exp(-j2\pi fiT)} \quad (5)$$

where $j = \sqrt{-1}$ and T represents the sampling interval which, in this case, was 0.1 s. It should be noted that H(f) evaluated at any frequency f yields a complex value consisting of real, Re[H(f)], and an imaginary, Im[H(f)], parts. The absolute magnitude of H(f) was obtained thus:

$$H_{mag}(f) = \sqrt{Re[H(f)]^2 + Im[H(f)]^2} \quad (6)$$

At any frequency, $H_{mag}(f)$ represents the gain with which x is translated into yr. Accordingly, we defined the "RSA gain" (G_{RSA}) to be the average value of $H_{mag}(f)$ in the HF range: 0.15 to 0.4 Hz:

$$G_{RSA} = \frac{1}{0.4 - 0.15} \int_{0.15}^{0.4} H_{mag}(f)\,df \quad (7)$$

If $S_x(f)$ represents the power spectrum of x, it can be shown from linear system theory[16] that:

$$\frac{S_{yr}(f)}{S_x(f)} = H_{mag}(f)^2 \quad (8)$$

Thus, the function $H_{mag}(f)^2$ may be interpreted as the spectrum of the respiratory–related component of RR after normalization for the spectral characteristics of the breathing pattern. We reasoned further that the area under $H_{mag}(f)^2$, between 0.15 and 0.4 Hz, which we will refer to as the "respiration–adjusted high–frequency power" (RHFP), should provide an index of parasympathetic RR modulation that is independent of the breathing pattern:

$$RHFP = \int_{0.15}^{0.4} H_{mag}(f)^2\,df \quad (9)$$

Using a similar line of reasoning, we computed the "respiration–adjusted low–frequency power", RLFP, by computing the area under the respiratory–uncorrelated RR spectrum, $S_{yu}(f)$, between 0.04 and 0.15 Hz:

$$RLFP = \int_{0.04}^{0.15} S_{yu}(f)\,df \quad (10)$$

Finally, we defined the following modified index of sympathovagal balance, which differs from the conventional LHR in that it has discounted for the effects of breathing pattern differences:

$$MLHR = \frac{RLFP}{RHFP} \quad (11)$$

All analytical and data processing procedures, with the exception of the statistical tests (see below), were performed using Matlab software (The Mathworks, Natick, MA).

Statistical Methods

Repeated–measures analysis of variance was employed to determine if condition (Wake vs. Sleep/No CPAP vs. Sleep/CPAP) produced significant effects on the various measures of HRV in the OSA subjects. To determine differences between the OSA subjects and normal controls, we used two–way repeated measures analysis of variance with one factor repeated. The two factors were subject group (Normal vs. OSA) and condition, with condition (Wake vs. Sleep/No CPAP) being the repeated factor. The Student–Newman–Keuls test was employed for post hoc multiple pairwise comparisons if statistical significance was indicated by the analysis of variance. All statistical tests were implemented using SigmaStat/Windows (Jandel Scientific, San Rafael, CA). The level of significance was set at P<0.05, unless otherwise stated.

RESULTS

Cardiorespiratory patterns

Figure 1 shows representative tracings of P_{es}, airflow, and RR from one of the OSA subjects during relaxed wakefulness prior to sleep onset (left column), during stage 2 sleep without CPAP (middle column), and during stage 2 sleep with CPAP application (right column). The corresponding power spectra for the P_{es} and RR signals are displayed in Figure 2. Two types of variation are present in all three RR tracings. The first is the classic pattern of RSA which occurs at approximately the same frequency as the breathing cycle. The spectral peaks that correspond to this oscillation fall between 0.2 and 0.25 Hz (Fig.2). During OSA, the second type of variation appears: this is a VLF oscillation (~ 0.02 Hz, see middle panels of Fig. 2) which is clearly correlated with the apnea–hyperpnea cycle (Fig. 1, middle column). An important observation that should be highlighted is that, during obstructive apnea, the RSA oscillation remains clearly visible even though there is no airflow occurring. The RSA in this case is closely associated with the large and rapid respiratory efforts (Fig.1, top middle panel) that occur during obstructive apnea, and it is for this reason that we chose to use P_{es} and not airflow as the input variable in our model.

Application of CPAP (15 cm H_2O in this subject) eliminated all visible traces of obstructive apnea and led to a substantially regularized breathing pattern (Fig.1, right col-
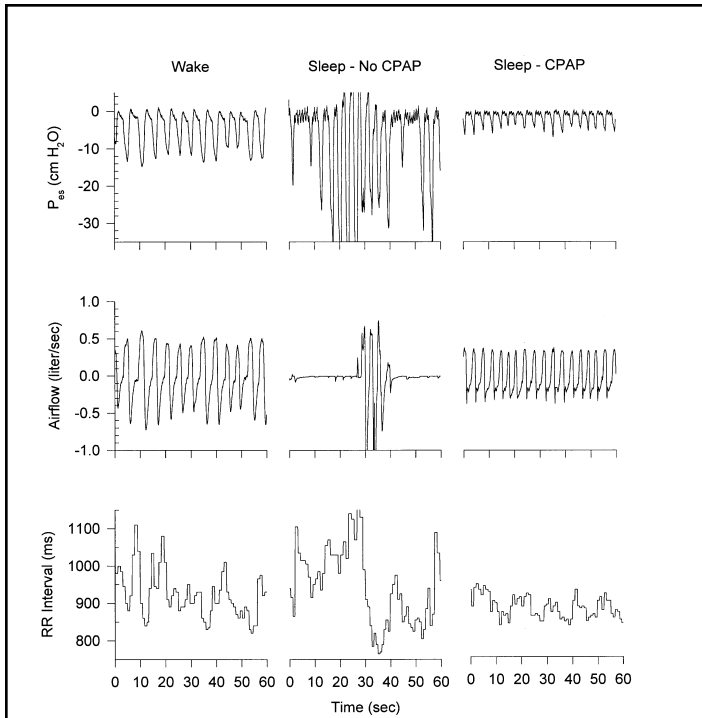
Fig. 1—Sample tracings of Pes (top panels), respiratory airflow (middle panels), and RR interval (bottom panels) in one of the OSA patients during wakefulness (left column), stage 2 sleep without CPAP therapy (center column), and stage 2 sleep with CPAP therapy (right column). See text for details.
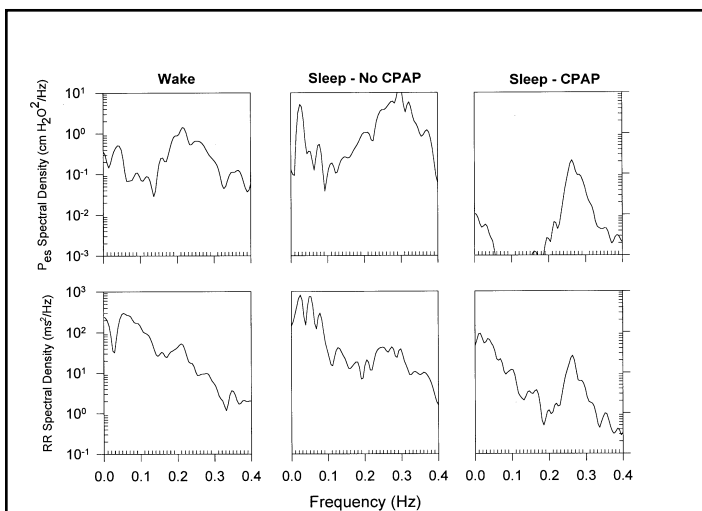

Fig. 2—Power spectra corresponding to the P_{es} & RR signals shown in Fig. 1

umn). However, although this regularization of breathing eliminated most of the VLF variability in the RR time series, we noticed in this patient, as in most of the others, the persistence of a substantial oscillation in the 0.04 to 0.15 Hz range (Figs.1 and 2, bottom right). This LF oscillation in RR was also present in this subject (Figs.1 and 2, bottom left) and most of the other OSA subjects during wakefulness. However, it did not appear to be related to the ventilatory pattern.

It is important to note one other less obvious observation. In addition to an increase of spectral power in the VLF

band, power in the HF band also increased during periods when OSA occurred (Fig. 2, lower middle panel). This was due apparently to the large RSA amplitudes that occurred towards the later part of each apnea when respiratory efforts against the occluded upper airway increased dramatically (Fig.1, top middle panel).

Source–based decomposition of HRV

Figure 3 shows sample results obtained from the application of our technique of source–based decomposition to the RR time–series displayed in Figs.1 and 2. For simplicity, only the Sleep/No CPAP (Fig. 3, left panels) and Sleep/CPAP (Fig. 3, right panels) cases have been presented. For reference purposes, the P_{es} (bold lines) and RR (thin lines) spectra for the two conditions are shown in the top panels of Figure 3. As described previously, the fluctuations in RR were decomposed into a respiration–correlated component, y_r, and a respiration–independent component, y_u. The middle panels of Figure 3 show the corresponding spectra for the respiration–correlated component, S_{yr} (bold lines), and the respiration–independent component, S_{yu} (thin lines). Since the relationship between P_{es} and y_r was assumed to be linear, it is not surprising that the form of the S_{yr} spectrum closely resembles the P_{es} spectrum. In both non–CPAP and CPAP cases, the respiration–correlated component contributed most to the RR signal in the HF and VLF regions. The respiratory contribution to LF power, although not negligible, was relatively small.

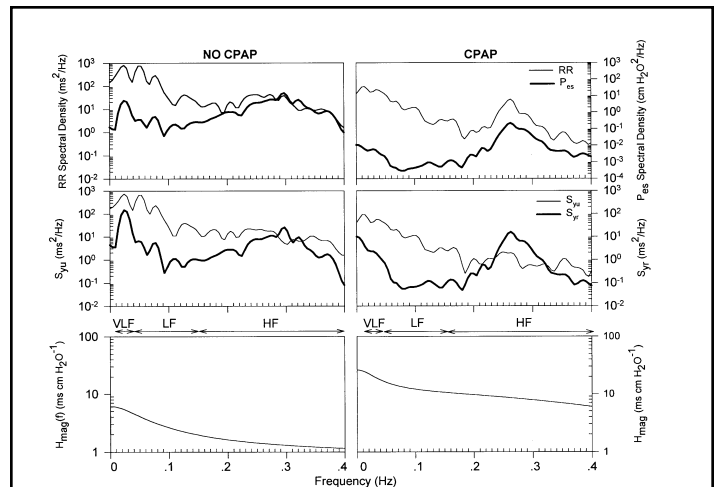The bottom panels of Figure 3 illustrate the behavior of

Fig. 3—Results of source–based decomposition for the sleep/no–CPAP (left column) and sleep/CPAP (right column) data displayed in Figs. 1 and 2. Power spectra for P_{es} (bold tracing) and RR (light tracing) are displayed in the top panels for reference. Middle panels show the corresponding respiration–correlated spectra, S_{yr} (bold tracing), and respiration–independent spectra, S_{yu}. Bottom panels show the magnitude of the transfer function, H_{mag}, relating changes in P_{es} to changes in RR at all frequencies between 0 and 0.4 Hz. G_{RSA} is deduced by taking the average of H_{mag} values between 0.15 and 0.4 Hz.

the magnitude, $H_{mag}(f)$, of the P_{es}–to–RR transfer function as a function of frequency. As indicated previously, $H_{mag}(f)$ represents the gain with which fluctuations in P_{es} are translated into fluctuations in RR at any given frequency, f. The RSA gain, G_{RSA}, given by the average value of H_{mag} between 0.15 and 0.4 Hz, was ~1.4 during OSA (no CPAP) in this subject, compared to ~8.3 when CPAP was applied. In fact, H_{mag} was several–fold higher in CPAP vs. no CPAP over the entire range of frequencies displayed (0–0.4 Hz). This also means that spectral power of the respiration–correlated component of RR, after adjustment for differences in breathing pattern, was considerably smaller in OSA, even though the amplitude of the RSA oscillation in this condition was larger.

Spectral indices of HRV

Table 2 shows the values (mean ± SE) of MnRR, SDRR, VLF power, LF power, and HF power in the OSA patients and normal controls during each of the conditions tested. The change in VLF power across conditions in the OSA patients was significant (p<0.01), with VLF power being highest during OSA and lowest during CPAP therapy. VLF power increased with sleep (p<0.02) in both normals and OSA patients and was also significantly larger in the OSA group compared to normals (p<0.05). MnRR, SDRR, LFP and HFP did not change with state or CPAP application in the OSA subjects and did not display differences when compared to normals. It is interesting to note that although most OSA subjects, such as the individual displayed in Figs.1 through 3, showed markedly higher HF power in sleep without CPAP compared with sleep with CPAP, HF

Fig. 4—Values of NHFP, LHR, G_{RSA} and MLHR in all OSA subjects during relaxed wakefulness (W), stage 2 sleep without CPAP (S), and stage 2 sleep with CPAP therapy (C). Values pertaining to each subject are connected by thin lines, while the closed circles and error bars represent the group means and standard errors. Only G_{RSA} and MLHR showed significant changes when CPAP was applied.

roughly twice as large as that during sleep with CPAP, the difference did not attain statistical significance.

Spectral indices of cardiac autonomic function in OSA subjects

Figure 4 compares the effects of condition (wake vs. sleep/no CPAP vs. sleep/CPAP) on four indices of cardiac autonomic function in the OSA subjects. In each plot, individual responses (segmented lines) are displayed along with the group–averaged means and standard errors for the three conditions. The conventional indices of parasympathetic activity, NHFP, and sympathovagal balance, LHR, did not show significant differences across conditions (top panels, Fig.4). However, there was a highly significant

TABLE 2: Summary of results from Spectral Analysis

	OSA			NORMALS	
	Wake	Sleep	Sleep+CPAP	Wake	Sleep
MnRR (ms)	904 ± 40	922 ± 33	927 ± 41	1030 ± 115	1024 ± 99
SDRR (ms)	55 ± 10	83 ± 11	56 ± 12	66 ± 16	62 ± 10
VLF Power (ms^2)	756 ± 203	2141 ± 618	448 ± 145	286 ± 56	730 ± 264
LF Power (ms^2)	2132 ± 642	2898 ± 865	2184 ± 1153	1000 ± 388	1311 ± 514
HF Power (ms^2)	649 ± 189	887 ± 260	424 ± 140	2640 ±1389	1618 ± 567

Data presented are means ± SE.

Fig. 5—Comparison of group means (± SE) for NHFP, LHR, G_{RSA} and MLHR between normals (light bars) and OSA patients (dark bars). All four spectral indices showed significant differences between the two groups. However, the changes in G_{RSA} and MLHR were substantially larger and less variable.

power was substantially decreased in one subject and increased very slightly in two others. Thus, although the average value of HF power in sleep without CPAP was
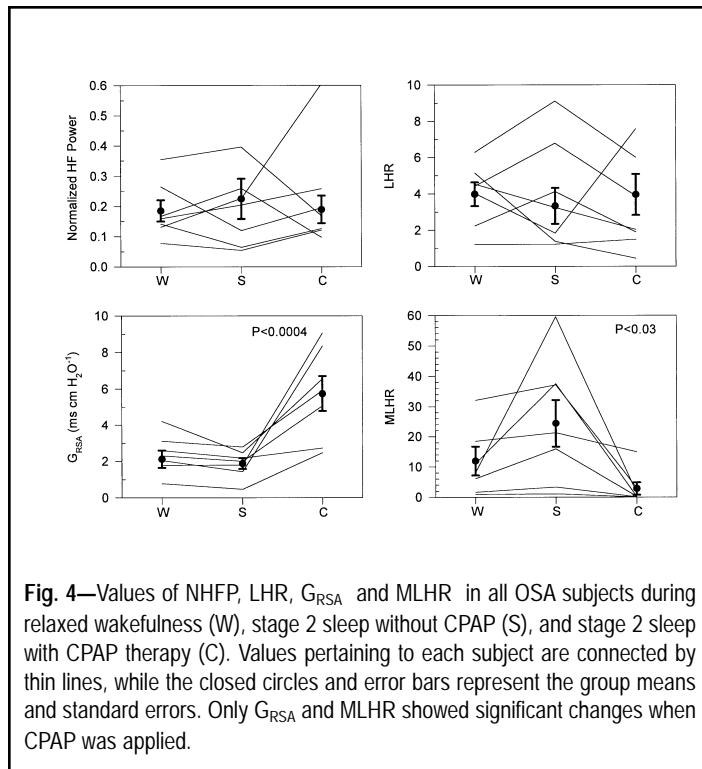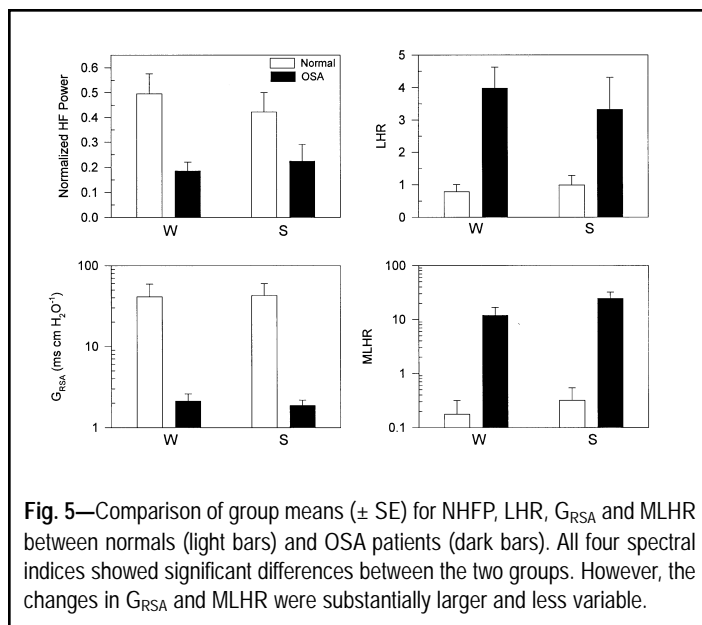
increase ($P < 0.0004$) in G_{RSA} during sleep/CPAP ("C" in Fig.4) compared to wake ("W") and sleep/no CPAP ("S"): on average, G_{RSA} increased roughly threefold. The effect of condition on MLHR was also significant ($p < 0.03$). However, in this case, CPAP therapy significantly reduced MLHR during sleep ($p < 0.05$), but the new MLHR level was not signficantly lower than that in wakefulness.

Spectral indices of autonomic function: OSA vs. normals

In Fig.5, the group means (and SE) for the four spectral indices of autonomic function in normals and OSA subjects are compared in wakefulness ("W") and sleep without CPAP therapy ("S"). There were highly significant differences between the normals and OSA subjects in all four indices, although the differences were considerably more pronounced between groups in G_{RSA} ($p < 0.0001$) and MLHR ($p < 0.0003$), compared to NHFP ($p < 0.004$) and LHR ($p < 0.005$). G_{RSA} was an order of magnitude larger and MLHR an order of magnitude smaller in normals compared to OSA subjects.

DISCUSSION

It is now reasonably well–established that patients with OSA have high sympathetic activity during wakefulness and sleep.[20,21] Consistent with this observation, other studies, using cardiovascular stress tests, have demonstrated abnormal daytime autonomic responses in OSA subjects compared to normal controls.[6–8] In this study, we found that the spectral indices of HRV also point to significant differences between normal subjects and patients with OSA in both wakefulness and sleep. On average, LHR was three to four times higher in OSA compared to normals, suggesting increased sympathetic modulation of heart rate. At the same time, NHFP in OSA was roughly half the normal level, indicating decreased parasympathetic modulation. This latter finding is supported by previous reports that, among the battery of autonomic stress tests generally employed, the controlled deep–breathing test, which assesses parasympathetic activity, is usually the most likely to produce an abnormal response in OSA subjects. This result is clinically important in light of the fact that most studies of autonomic function in OSA have tended to emphasize sympathetic overactivity, whereas defective parasympathetic cardiac control is known to be an earlier prognostic marker for the development of cardiac arrhythmias.[22]

CPAP treatment is known to decrease sympathetic activity in OSA patients[21] as well as in subjects with congestive heart failure who exhibit Cheyne–Stokes respiration during sleep.[23] A recent study has also found that CPAP increases parasympathetic activity in awake subjects with congestive heart failure.[24] In the OSA subjects that we studied, LHR and NHFP were unchanged when CPAP was

applied at individually prescribed levels during stage 2 sleep. We postulated that this apparent absence of change in HRV resulted from the profound differences in spontaneous breathing pattern between the no–CPAP and CPAP conditions, which masked any intrinsic changes in cardiac autonomic control. During periodic episodes of obstructive apnea, the power of the VLF component of HRV increases significantly. This may or may not affect the power of the LF component. In most but not all subjects, HF power is also increased dramatically. Consequently, the differences in the autonomic indices, LHR and NHFP, between no–CPAP and CPAP conditions can be significantly underestimated. This confounding effect of abnormal breathing patterns on the HRV spectrum has been recognized by others[5,12] and has been used by one group as a tool for identifying sleep–related breathing disorders from ECG measurements.[25] To circumvent this problem, we employed a mathematical modeling technique that allowed us to computationally delineate the component of the RR signal that is correlated with respiration from the component that is not. In so doing, we were able to derive two new HRV indices, MLHR and GRSA, that better characterize intrinsic sympathetic and parasympathetic activity, respectively, by compensating for differences in breathing pattern. In contrast to LHR, MLHR showed a several–fold reduction when CPAP was applied during sleep. Unlike NHFP, G_{RSA} was increased approximately by a factor of three during CPAP therapy. MLHR and G_{RSA} also indicated substantial differences in HRV between the OSA group and normals.

There are a number of potentially important issues that need to be investigated in future studies. Since we selected young adult non–snorers to represent our normal controls, it is possible that the difference in age range between the normals (24–32 yrs) and the OSA patients (44–59 yrs) may have accounted for some of the observed differences in HRV. A careful study of 70 normotensive adults by De Meersman,[26] however, found no significant difference in RSA between subjects in the 26–35 year age group compared to subjects who were 46–55 years old, although a large decrease in RSA was noted in subjects >65 years. As mentioned earlier, two of the OSA subjects were hypertensive but were allowed to continue with their blood pressure medication prior to the sleep study. However, the spectral indices of HRV in these individuals fell within the ranges estimated in the other (normotensive) OSA subjects. Another potentially confounding factor is that the OSA patients were signficantly overweight (206–310 lbs) compared to our control subjects (140–248 lbs). It is unclear how this might affect cardiac autonomic function. However, since each OSA patient was his own control during the CPAP portion of the study, these potential complications do not affect our other conclusion: that the new spectral indices G_{RSA} and MLHR were able to detect an improvement in cardiac autonomic function resulting from

CPAP therapy while the more conventional measures, LHR and NHFP, did not. The third important issue that deserves further study is whether the replacement of P_{es} with less "noninvasive" measurements of respiratory effort, such as the change in chest circumference using the respiratory inductive plethysmograph, would affect our present conclusions. The ability to incorporate more traditional measures of respiratory effort would certainly allow our technique to be employed as an additional diagnostic tool in the sleep clinic.

The one finding that was quite surprising to us was the highly substantial difference in all four measures of HRV between the OSA and normal groups during wakefulness, even though all the OSA patients had been undergoing home CPAP therapy prior to the study for durations that varied from 2–1/2 months to 2–1/2 years. However, prior usage of CPAP by each of the patients was not monitored. A recent study has shown that improvement in the response to autonomic stress testing, following one year of home CPAP therapy, depends critically on compliance with the prescribed treatment regimen.[27] Waravdekar et al.[28] found a reduction of daytime sympathetic tone in four of seven OSA patients after the group had undergone compliance–monitored CPAP therapy for >1 month. The three other patients studied did not show any reduction in muscle sympathetic nerve activity. On average, CPAP decreased the baseline sympathetic nerve activity from approximately 69 bursts/min before treatment to 54 bursts/min after treatment. However, one should note that although the baseline level of activity declined after one month of CPAP therapy, sympathetic tone was still substantially higher than the baseline of 34 bursts/min reported in awake normals by Somers et al.[21] These results, taken together, suggest that while home CPAP therapy can improve autonomic function, whether it can completely restore sympathetic activity to normal levels remains unclear. This inference is purely speculative at this time, and future verification in the form of a longitudinal study of a larger OSA population undergoing home CPAP therapy will be required.

ACKNOWLEDGEMENTS

REFERENCES

1. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: Standards of measurement, physiological interpretation and clinical use. Circulation 1996, 93:1043–1065.
2. Stein PK, Bosner MS, Kleiger RE, Conger BM. Heart rate variability: a measure of cardiac autonomic tone. Am Heart J 1994, 127:1376–1381.
3. Malliani A, Pagani M, Lombardi F, Cerutti S. Cardiovascular neural regulation explored in the frequency domain. Circulation 1991, 84:482–492.
4. Parati G, Saul JP, Di Rienzo M, Mancia G. Spectral analysis of blood pressure and heart rate variability in evaluating cardiovascular regulation: a critical appraisal. Hypertension 1995, 25:1276–1286.
5. Mortara A, Sleight P, Pinna GD, Maestri R, Prpa A, La Rovere MT, Cobelli F, Tavazzi L. Abnormal awake respiratory patterns are common in chronic heart failure and may prevent evaluation of autonomic tone by measures of heart rate variability. Circulation 1997, 96:246–252.
6. Sachs C, Kaijser L. Autonomic regulation of cardiopulmonary functions in sleep apnea syndrome and narcolepsy. Sleep 1982, 5:227–238.
7. Veale D, Pepin JL, Levy PA. Autonomic stress tests in obstructive sleep apnea syndrome and snoring. Sleep 1992, 15:505–513.
8. Cortelli P, Parchi P, Sforza E, Contin M, Pierangeli G, Barletta G, Lugaresi E. Cardiovascular autonomic dysfunction in normotensive awake subjects with obstructive sleep apnoea syndrome. Clin Auton Res 1994, 4:57–62.
9. Hirsch JA, Bishop B. Respiratory sinus arrhythmia in humans: how breathing pattern modulates heart rate. Am J Physiol 1981, 241:H620–H629.
10. Brown TE, Beightol LA, Koh J, Eckberg DL. Important influence of respiration on human R–R interval power spectra is largely ignored. J Appl Physiol 1993, 75:2310–2317.
11. Guilleminault C, Connolly S, Winkle R, Melvin K, Tilkian A. Cyclical variation of the heart rate in sleep apnoea syndrome. Lancet 1984,1:126–131.
12. Keyl C, Lemberger P, Dambacher M, Geisler P, Hochmuth K, Frey AW. Heart rate variability in patients with obstructive sleep apnea. Clin Sci 1996, 91 Suppl:56–57.
13. Bianchi A, Bontempi B, Cerutti S, Gianoglio P, Comi G, Natali Sora MG. Spectral analysis of heart rate variability signal and respiration in diabetic subjects. Med Biol Eng Comput 1990, 28:205–211.
14. Rechtschaffen A, Kales R. A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. Los Angeles: BIS/BRI, UCLA, 1968.
15. Berger RD, Akselrod S, Gordon D, Cohen RJ. An efficient algorithm for spectral analysis of heart rate variability. IEEE Trans. Biomed. Eng. 1986; 33:900–904.
16. Rabiner LR, Gold B. Theory and Application of Digital Signal Processing. Englewood Cliffs, NJ: Prentice Hall, 1975. p. 399–419.
17. Triedman JK, Perrott MH, Cohen RJ, Saul JP. Respiratory sinus arrhythmia: time domain characterization using autoregressive moving average analysis. Am. J. Physiol. 1995, 268:H2232–H2238.
18. Baselli G, Cerutti S, Civardi S. Cardiovascular variability signals: toward the identification of a closed–loop model of the neural control mechanisms. IEEE Trans Biomed Eng 1988, 35:1033–1046.
19. Kim TS, Khoo MCK. Estimation of cardiorespiratory transfer under spontaneous breathing conditions: A theoretical study. Am J Physiol 1997, 273: H1012–H1023.
20. Hedner J, Ejnell H, Sellgren J, Hedner T, Wallin G. Is high and fluctuating muscle nerve sympathetic activity in the sleep apnea syndrome of pathogenetic importance for the development of hypertension? J Hypertens 1988, 6:S529–S531.
21. Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. J Clin Invest 1995, 96:1897–1904.
22. Eckberg DL, Drabinsky M, Braunwald E. Defective cardiac parasympathetic control in patients with heart disease. N Engl J Med 1971, 285:877–883.
23. Naughton MT, Benard DC, Liu PP, Rutherford R, Rankin F, Bradley TD. Effects of nasal CPAP on sympathetic acivity in patients with heart failure and central sleep apnea. Am J Respir Crit Care Med 1995, 152:473–479.

24. Butler GC, Naughton MT, Rahman MA, Bradley TD, Floras JS. Continuous positive airway pressure increases heart rate variability in congestive heart failure. J Am Coll Cardiol 1995, 25:672–679.

25. Keyl C, Lemberger P, Pfeifer, Hochmuth K, Geisler P. Heart rate variability in patients with daytime sleepiness suspected of having sleep apnoea syndrome: a receiver–operating characteristic analysis. Clin Sci 1997, 92: 335–343.

26. De Meersman RE. Aging as a modulator of respiratory sinus arrhythmia. J. Gerontol. 1993, 48:B74–B78.

27. Veale D, Pepin JL, Wuyam B, Levy PA. Abnormal autonomic stress responses in obstructive sleep apnoea are reversed by nasal continuous positive airway pressure. Eur Respir J 1996, 9:2122–2126.

28. Waravdekar NV, Sinoway LI, Zwillich CW, Leuenberger UA. Influence of treatment on muscle sympathetic nerve activity in sleep apnea syndrome. Am J Respir Crit Care Med 1996; 153:1333–1338.