Cardiac Autonomic Control in Obstructive Sleep Apnea
Effects of Long-term CPAP Therapy

MICHAEL C. K. KHOO, VASYL BELOZEROFF, RICHARD B. BERRY, and CATHERINE S. H. SASSOON

Biomedical Engineering Department, University of Southern California, Los Angeles, California; Department of Medicine, University of Florida, Gainesville, Florida; and Department of Medicine, University of California–Irvine/VA Medical Center, Long Beach, California

To determine how long-term treatment with continuous positive airway pressure (CPAP) affects cardiac autonomic function, we measured R-R interval (RRI), respiration, and blood pressure in 13 awake patients with moderate-to-severe obstructive sleep apnea (OSA) in both supine and standing postures, before and after 3 to 9 mo of home therapy. Using visual feedback, the subjects controlled their respiration to track a randomized breathing pattern. From the RRI spectrum, we computed high-frequency power and the ratio of low-frequency to high-frequency power (LHR). To correct for differences in breathing, the average transfer gain relating respiration to RRI changes (Ga) and the modified low-frequency to high-frequency ratio (MLHR) were also derived. CPAP therapy did not change the conventional spectral indices of heart rate variability (HRV). However, Ga increased with average nightly CPAP use in supine (p < 0.01) and standing (p < 0.03) postures, whereas MLHR decreased with CPAP compliance during standing (p < 0.03). Supine mean heart rate decreased with compliance (p < 0.03). None of the estimated parameters was correlated with duration of therapy when actual CPAP use was not taken into account. These results suggest that CPAP treatment improves vagal heart rate control in patients with OSA and that the degree of improvement varies directly with compliance level.

**Keywords:** heart rate variability; autonomic nervous system; spectral analysis; sleep-disordered breathing; cardiovascular control

Current epidemiologic and experimental lines of evidence suggest that obstructive sleep apnea (OSA) may be an independent risk factor for systemic hypertension, as well as acute vascular events such as myocardial infarction and stroke (1, 2). The mechanisms linking OSA to cardiovascular disease remain unclear but recent studies suggest that abnormal autonomic control may be an important factor. For instance, studies using per- oneal microneurography or testing of plasma catecholamines have shown that sympathetic tone is substantially elevated in subjects with OSA in both sleep and wakefulness (3, 4). At the same time, heart rate variability (HRV) is markedly reduced, suggesting impaired parasympathetic control (5, 6). Treatment with nasal continuous positive airway pressure (CPAP) has been shown to reduce muscle sympathetic nerve activity and plasma norepinephrine levels over periods ranging from 1 mo to 1 yr (7–9). Long-term CPAP therapy was also found to lower mean daytime and nocturnal arterial blood pressures in patients with OSA, particularly in those subjects who were hypertensive and who were not receiving medication during the treatment period (10–12). However, an important drawback in many of these studies is that CPAP compliance was either not reported or self-reported, or cardiovascular function was compared before and after the duration of therapy with little attention paid to the quantification of actual CPAP use.

Spectral analysis of HRV is employed frequently as a non-invasive means of assessing cardiac autonomic function (13, 14). The power of the high-frequency band (0.15 to 0.4 Hz) is widely accepted as a measure of parasympathetic activity (13). The ratio of low-frequency (0.04 to 0.15 Hz) power to high-frequency power (LHR) has been used by some workers to represent sympathetic modulation of heart rate (14), but this interpretation is not universally accepted (13). A major limitation of employing these spectral measures is that HRV (in particular, the high-frequency component) is highly sensitive to differences in ventilation and breathing pattern within and across individuals. Recently, we introduced a mathematical algorithm that compensates for these differences in breathing by partitioning the heart rate signal into respiratory-correlated and respiratory-independent components (6). This algorithm led to the introduction of two modified spectral indices that were shown to be more robust for assessing cardiac autonomic control than the corresponding traditional spectral measures of HRV mentioned earlier: (1) the average transfer gain relating respiration to R-R interval (RRI) changes (Ga), representing parasympathetic control; and (2) the modified ratio of low-frequency power to high-frequency power (MLHR).

The primary goal of the present study was to determine how the modified and standard spectral measures of HRV may be altered after long-term CPAP therapy in patients with OSA. Special attention was paid to monitoring nightly CPAP compliance at the prescribed pressure, so that the relationships between actual CPAP use and the corresponding change in each index of autonomic control could be quantified.

**METHODS**

Thirteen male subjects were selected from patients diagnosed by polysomnography to have OSA with apnea–hypopnea index (AHI) > 20 and who were prescribed CPAP therapy. Exclusion criteria were diabetes, significant cardiac arrhythmia, congestive heart failure, and lung disease. Five subjects were hypertensive. For safety, these subjects continued antihypertensive medication between initial and follow-up studies. Three patients were on felodipine; the other two used diltiazem. Informed consent was obtained from all subjects. The study was approved by the Long Beach Veterans Administration Medical Center research committee.

Compliance information was obtained by downloading the time at prescribed pressure from the built-in memory chip of the CPAP device (Respironia Aria LX; Pittsburgh, PA). Duration of CPAP therapy averaged 6 mo. Eleven patients received 4.5 to 7.5 mo of treatment. One patient was restudied only after 3 mo owing to impending relocation of residence; another was restudied in approximately 9 mo after having been temporarily lost to follow-up. Average nightly CPAP use was computed by dividing cumulative CPAP use by treatment duration. Table 1 shows details of patient and individual CPAP characteristics.

Breathing was monitored using respiratory inductive plethysmography, which was calibrated against a spirometer separately in both supine and standing postures. Other measurements included the elec-
trocardiogram (ECG) and blood pressure by finger arterial plethysmography (Finapres, Ohmeda, Boulder, CO). After a familiarization run, the subject controlled his respiration, using visual feedback, to track a waveform with breath durations that varied randomly from breath to breath for 5 min. However, the tidal volumes of the target pattern were selected to maintain average minute ventilation (and thus, chemical drive) constant at the subject’s spontaneous ventilation level. Randomized breathing was used to improve the accuracy with which the modified spectral indices could be estimated (15). The entire set of procedures was performed in supine and standing postures. Respiration was digitized at 2 Hz; ECG and blood pressure were sampled at 200 Hz.

The RRI time-series was resampled at 2 Hz using the Berger algorithm (16). Systolic and diastolic values were extracted beat-by-beat from the blood pressure waveform. After linear detrending, the mean and standard deviation were computed for each dataset. Spectral analysis of RRI was performed using the Welch method with Hanning windowing (17). Low-frequency (0.04 to 0.15 Hz) and high-frequency (0.15 to 0.4 Hz) power were computed by determining the corresponding areas under the power spectrum. RSA was computed as the average magnitude of the transfer function (from 0.15 to 0.4 Hz) relating changes in respiration to changes in RRI (6). MLHR was computed by dividing the respiratory-uncorrelated component of low-fre-
quency power by respiration-normalized high-frequency power (6). $G_{res}$ estimates were checked for reliability by computing the coherence function (respiration $\rightarrow$ RRI) (17). Coherence values in the high-frequency band $>0.5$ were considered significant. Complete details are given in the Appendix (see online data supplement).

Each spectral index was subjected to two-way repeated-measures analysis of variance (ANOVA) (posture $\times$ treatment condition) and tested for dependence on average nightly CPAP use and duration of therapy using multiple linear regression.

RESULTS

Compliance with the prescribed use of CPAP varied widely among individual patients, with average nightly use ranging from 0 to 8.3 h. Only six subjects used CPAP for more than 3 h per night; the other seven patients used CPAP for less than 2 h per night, including two whose average use was close to zero. Body mass index remained unchanged after CPAP therapy.

Figure 1 shows examples of the pre-CPAP versus post-CPAP power spectra derived from respiration and RRI measurements obtained in one of the subjects during spontaneous and randomized breathing. In this particular subject, the mean frequency during spontaneous breathing was approximately 0.25 Hz during pre-CPAP testing. However, during post-CPAP testing, this changed to a significantly lower frequency of approximately 0.1 Hz (Figure 1, top left panel). This led to a corresponding shift of the respiratory peak in the RRI spectrum to 0.1 Hz (Figure 1, lower left panel). Consequently, high-frequency power ($= \text{area under each RRI spectrum between 0.15 and 0.4 Hz}$) was found to decrease from 43.4 to 34.0 ms² after CPAP therapy. However, by computationally accounting for this change in respiratory pattern, $G_{res}$ showed an increase from 26.1 pre-CPAP to 44.7 ms L⁻¹ post-CPAP. Because this subject was able to track the randomized breathing pattern closely during both pre-CPAP and post-CPAP tests, the corresponding respiratory spectra remained relatively unchanged (Figure 1, top right panel). Thus, in this particular subject, controlling for differences in respiration between the first and second studies revealed a post-CPAP increase in high-frequency power of the RRI spectrum (Figure 1, lower left panel). However, this example was not typical of most of the patients, who showed considerable intraindividual variability in ventilation level and in the ability to closely track the displayed randomized pattern. Therefore, computational correction of differences in respiration was always necessary.

Mean RRI increased linearly with average nightly CPAP use ($p = 0.029$) in the supine position (Table 2). There was also a tendency for mean RRI to increase with average nightly CPAP use in the standing posture, but this failed to achieve statistical significance. However, mean RRI was not correlated with duration of therapy per se, suggesting that the decreased heart rate resulted from actual CPAP usage and not by the duration over which each subject was studied. Furthermore, the unknown constant parameter (C) in the multiple regression model was not significantly different from zero (Table 2), suggesting that the increase in mean RRI was unlikely to have been produced by factors other than average nightly use or duration of therapy, such as differences in subject anxiety between the original and follow-up studies. There was no correlation between average nightly use or duration of therapy and any of the measures of HRV (as quantified by the standard deviation of RRI), mean blood pressure, and blood pressure variability. These results are presented in detail in Table 2.

The values of all spectral indices estimated from each individual before and after CPAP therapy and in both supine and standing positions are shown in Figure 2. Repeated-measures ANOVA indicated a strong effect of posture on each of the spectral indices. The conventional and modified ratios of low-frequency to high-frequency power each increased from supine to standing ($p < 0.005$ in both cases) before and after CPAP therapy. At the same time, the change from supine to standing led to decreases in $G_{res}$ and high-frequency power ($p < 0.01$ in both cases). These findings were expected and are in agreement with the widely accepted notion that orthostatic tilt produces sympathetic excitation and vagal withdrawal. Previous studies have shown that this is manifested in the RRI spectrum as a reduction in high-frequency power and some or no increase in low-frequency power (14, 18). Average coherence in the high-frequency band was 0.63 ± 0.03 in the supine posture and 0.55 ± 0.03 upright. These results provided an invaluable check on the consistency and reliability of the estimated spectral indices.

As shown in Figure 3, $G_{res}$ increased significantly with average nightly CPAP use in both supine ($p < 0.01$) and standing ($p < 0.05$) postures, respectively. On the other hand, MLHR decreased with average nightly use ($p < 0.03$) only in the standing posture (Figure 4). High-frequency power and LHR were not significantly correlated with CPAP use (Table 3). None of the spectral indices of HRV was correlated with treatment duration, when the proportion of time using CPAP was not taken into account.

### TABLE 2. DEPENDENCE OF CHANGES IN RRI AND BLOOD PRESSURE ON AVERAGE NIGHTLY CPAP USE AND DURATION OF THERAPY*

| Variable | Dependent | Supine | | Standing | | |
|---|---|---|---|---|---|
| | a (ANCU) | b (DOT) | C (Intercept) | a (ANCU) | b (DOT) | C (Intercept) |
| Mean RRI | 2.88 ± 1.13 | 0.0045 ± 0.0683 | −0.74 ± 14.93 | 2.51 ± 1.20 | 0.001 ± 0.073 | −0.73 ± 15.98 |
| RRI variability | 7.50 ± 5.91 | −0.136 ± 0.359 | 24.78 ± 78.37 | 8.49 ± 4.05 | 0.085 ± 0.246 | −32.26 ± 53.79 |
| Mean SBP | 0.73 ± 1.25 | 0.056 ± 0.076 | −8.76 ± 16.59 | 2.21 ± 1.58 | 0.049 ± 0.096 | −12.38 ± 20.94 |
| SBP variability | −0.48 ± 3.60 | 0.363 ± 0.219 | 59.00 ± 47.79 | −0.37 ± 3.95 | −0.043 ± 0.240 | 22.38 ± 52.39 |
| Mean DBP | −0.64 ± 1.34 | −0.043 ± 0.081 | 4.41 ± 17.73 | 1.11 ± 0.93 | 0.012 ± 0.057 | −11.21 ± 12.36 |
| DBP variability | −2.24 ± 2.38 | −0.026 ± 0.199 | −2.74 ± 43.52 | −1.23 ± 2.54 | −0.102 ± 0.154 | 15.99 ± 33.68 |

*Definition of abbreviations: ANCU = average nightly CPAP use (given in hours); DOT = duration of CPAP therapy (time in days between start of CPAP therapy and follow-up study); RRI = R-R interval (in ms); SBP = systolic blood pressure (in mm Hg).

†Regression coefficients significantly different from zero.

---
DISCUSSION

Several previous studies (5, 6, 19, 20) have applied spectral analysis to heart rate recordings in patients with untreated OSA and found abnormally low levels of overall HRV and high-frequency power. A number of studies have also shown that CPAP treatment leads to reduced sympathetic activity, as measured using microneurography or analysis of plasma catecholamines (7–9). However, apart from our present report, we know of only one other study (21) that has examined the effect of long-term CPAP therapy on HRV and its spectral characteristics. Our finding that $g_{rsa}$ is positively correlated with average nightly CPAP use suggests that treatment of OSA using CPAP also improves vagal heart rate control and that the degree of treatment varies directly with CPAP compliance. These conclusions are clinically important because defective parasympathetic control is known to be an earlier prognostic marker for the development of cardiac arrhythmias (22). Our finding of an inverse correlation between MLHR and average nightly use could be interpreted to imply that CPAP treatment produces a corresponding reduction of sympathetic activity, consistent with previous studies that have employed direct measurements of the latter (7–9). However, a relative shift in RRI spectral power from the low-frequency to high-frequency bands could also result from increased vagal activity alone (18). Thus, the implications of a reduction in MLHR are less clear.

In the present study, we found that the conventional spectral indices of HRV were not affected by CPAP therapy. In contrast, Roche and coworkers (21) found that high-frequency power increased and LHR decreased significantly in a group of 14 patients with OSA after 3 mo of treatment. One possibility for this discrepancy is that Roche’s results were derived from spectral analyses of continuous Holter recordings collected over contiguous periods of 7 h. Averages computed over such a long duration are likely, especially during wakefulness, to reflect RRI spectral characteristics that correspond to regular tidal breathing with mean frequency within the 0.15 to 0.4 Hz range. In contrast, the measurements in our study were collected over a duration of 5 min in each condition. Because variability in ventilation level and breathing pattern can be quite substantial, the comparison of data obtained over a 5-min period between two studies separated several months apart is
more likely to yield HRV spectra that are different (see Figure 1). The randomized breathing protocol, which was employed to enhance the reliability of the parameter estimation procedure (15), was useful in reducing some of these differences of respiration in some subjects. However, by and large, there remained considerable intrasubject variability in the short-term level of ventilation and the ability to closely track the displayed waveform. These differences likely contributed to our finding that high-frequency power and LHR, even when compared under randomized breathing conditions, were not significantly changed after CPAP therapy. These discrepancies highlight the importance of computationally correcting for differences in respiration, unless one can ensure that the breathing pattern is tightly controlled.

One of the strengths of the present study is that compliance with the prescribed CPAP therapy was measured objectively by means of a built-in microchip that stored the time at which the CPAP unit was applied at the prescribed pressure. By contrast, in Narkiewicz’s study (9), CPAP compliance was based on self-reported estimated use, whereas in Roche’s study (21), no details were given as to whether and how compliance was monitored during the 3-mo period of therapy. Objective measurement of compliance is important because self-reported use tends to exceed true use (23). The subjects we studied varied considerably in compliance and treatment duration so that average nightly use was not correlated with duration of therapy. Indeed, none of our indices of HRV showed any correlation with duration of therapy when the level of compliance was not taken into account. The intersubject variability in compliance and treatment duration also allowed us to apply regression analysis to our data. The advantage of this form of analysis is that it has provided, for the first time, a preliminary estimate of the long-term dosage–response effect of CPAP on cardiac autonomic function. This contrasts with the binary outcomes (i.e., does CPAP have a significant effect or no effect?) that one can derive using other methods of paired comparisons, for example, repeated-measures ANOVA.

In the present study, we did not find significant correlations between the measures of blood pressure or blood pressure variability and CPAP use, possibly because most of our subjects were normotensive and because the five hypertensive subjects included in the study were allowed to continue taking their anti-hypertensive medications. On the other hand, hypertensive patients with OSA, who were studied off-medication, were shown in a couple of studies (11, 12) to register significant reductions in systolic and diastolic blood pressures when placed on chronic CPAP therapy, provided a high level of compliance with the treatment was maintained. To determine whether the inclusion of the five hypertensive subjects may have affected our results on HRV, we repeated the regression analyses on each of the spectral indices with these five subjects excluded. Our original conclusions remained unchanged: GRSA was positively correlated with average nightly CPAP use in both supine and standing postures (p < 0.05), and MLHR remained negatively correlated with average nightly use during standing only (p < 0.05).

An interesting finding in the present study is that mean RRI showed a reasonably strong, positive correlation with CPAP use in the supine posture; in other words, long-term CPAP ther-

---

**Figure 4.** Linear regression plots of the changes in MLHR versus average nightly CPAP use in supine (top panel) and standing (bottom panel) postures. MLHR decreased significantly with nightly CPAP use, but only in the standing posture.

---

**TABLE 3. DEPENDENCE OF CHANGES IN SPECTRAL INDICES OF HRV ON AVERAGE NIGHTLY CPAP USE AND DURATION OF THERAPY**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Supine</th>
<th>Standing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>a (ANCU)</td>
<td>b (DOT)</td>
</tr>
<tr>
<td>HFP</td>
<td>13.63 ± 6.75</td>
<td>0.647 ± 0.480</td>
</tr>
<tr>
<td></td>
<td>(0.071)</td>
<td>(0.208)</td>
</tr>
<tr>
<td>G_NA</td>
<td>11.50 ± 3.35</td>
<td>−0.001 ± 0.204</td>
</tr>
<tr>
<td></td>
<td>(0.006)</td>
<td>(0.998)</td>
</tr>
<tr>
<td>LHR</td>
<td>−4.36 ± 4.47</td>
<td>−0.026 ± 0.271</td>
</tr>
<tr>
<td></td>
<td>(0.352)</td>
<td>(0.926)</td>
</tr>
<tr>
<td>MLHR</td>
<td>−4.17 ± 6.25</td>
<td>0.020 ± 0.367</td>
</tr>
<tr>
<td></td>
<td>(0.520)</td>
<td>(0.958)</td>
</tr>
</tbody>
</table>

*Definition of abbreviation: HFP = high-frequency power. See Table 2 for definition of other abbreviations.

* Values in cells represent multiple linear regression coefficients (±SE), with significance levels shown within parentheses.

† Regression coefficients significantly different from zero.
apy led to a decrease in resting heart rate. This increase was independent of the duration of therapy per se. The constant coefficient in the linear regression of mean RRI versus CPAP use and duration of therapy was not significantly different from zero, suggesting that the decrease in heart rate between the baseline study and the follow-up study was not dependent on other extinguating factors, such as changes in level of anxiety between the two studies. Furthermore, this increase in mean RRI is consistent with the increase in $G_{res}$ and decrease in MLHR that we also found, suggesting a treatment-related alteration of the “sympathovagal balance” toward greater parasympathetic and perhaps reduced sympathetic dominance. On the other hand, other studies involving long-term CPAP therapy did not find any change in mean heart rate over time (9, 21); the reason for the discrepancy remains unclear.

A major limitation of this study is that the statistical design did not allow us to investigate the possibility that an interaction effect between CPAP compliance and duration of therapy could have contributed to the changes in autonomic function. The product of average nightly use and duration of therapy represents the cumulative CPAP usage since the start of the therapy. Intuitively, one might expect that, of two patients who are similarly compliant with the prescribed therapy, the one who has been treated with CPAP over a longer duration would show a greater improvement in autonomic function. Our present multiple regression models for $G_{res}$ and MLHR, measured standing, do predict an additional contribution from the difference in duration of therapy between these two hypothetical individuals (Table 3). However, an important question that remains is whether the effect of nightly CPAP use is compounded by treatment duration in more than just an additive manner. Because of the relatively small sample size, the limited range of treatment durations, and the high correlation between average nightly use and cumulative CPAP use in our database, it is impossible for us at this time to dissociate the effects of compliance alone from those that might result from the multiplicative interaction between compliance and duration of therapy. Another limitation of the present approach is derived from our having employed the average use time to quantify CPAP usage. The pattern of CPAP use over a given period of time clearly varies across individuals. For instance, consider two hypothetical patients who are placed on CPAP therapy over a period of 3 mo. The first patient uses CPAP for 4 h every night for the entire three mo, whereas the second uses CPAP only 2 h per night for the first 1 1/2 mo and then for 6 h over the next 1 1/2 mo. Average nightly use would be the same (4 h/night) for both subjects, but there is good reason to suspect that the effects on autonomic function might be different. At this point, however, there is no firm basis for predicting what these differences might be. These fundamental problems would need to be addressed in future studies.

In conclusion, long-term CPAP therapy can lead to significant improvement of cardiac autonomic function, as measured through spectral indices of HRV that incorporate compensation for differences in breathing pattern. However, the degree of change depends strongly on the level of compliance with this treatment modality. The modified spectral index, $G_{res}$, which represents the transfer gain between respiration and heart rate, was found to be strongly correlated with average nightly CPAP use in both supine and standing postures, suggesting that CPAP treatment enhances vagal heart rate control. The fact that this parameter can be derived with relative ease from the noninvasive measurements of heart rate and respiration suggests that it may be useful as a clinical tool for monitoring the changes in the autonomic regulation of cardiac function in OSA that accompany long-term CPAP therapy.

Acknowledgment: The authors thank Edwin Valladarez for technical assistance in the experimental studies and Linda Chen for her help in data analysis.

References