Model-based Assessment of Autonomic Control in Obstructive Sleep Apnea Syndrome during Sleep

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Respiration, R-R interval, blood pressure, and other polysomnographic variables were recorded in eight normal subjects and nine patients with untreated obstructive sleep apnea syndrome in wakefulness and sleep. To increase respiratory and cardiovascular variability, a computer-controlled ventilator delivered randomly modulated inspiratory pressures that were superimposed on a baseline continuous positive airway pressure. A mathematical model allowed heart rate variability to be partitioned into a component mediated by respiratory–cardiac coupling and one mediated by the baroreflexes. Respiratory–cardiac coupling gain was lower in patients versus normal subjects (36.9 ± 3.3 versus 66.1 ± 5.6 milliseconds L⁻¹, p < 0.03). Baroreflex gain in patients was also depressed relative to normal subjects (2.3 ± 0.4 versus 4.9 ± 0.7 milliseconds mm Hg⁻¹; p < 0.02). Baroreflex gain increased two- to threefold from wakefulness to sleep in normal subjects, but was relatively unaffected by state change in patients. Along with results derived from spectral analysis of cardiovascular variability, these findings confirm previous reports that obstructive sleep apnea syndrome is associated with reduced parasympathetic and elevated sympathetic activity. The model-based approach provides a more precise characterization of heart rate variability that can be employed in conjunction with spectral analysis for the noninvasive detection and assessment of autonomic cardiovascular abnormality in obstructive sleep apnea syndrome.

Keywords: baroreflex sensitivity; cardiovascular control; heart rate variability; mathematical model; respiratory sinus arrhythmia

Obstructive sleep apnea syndrome (OSAS) is characterized by repeated episodes of upper airway occlusion during sleep, with each episode resulting in increasing asphyxia until transient arousal restores upper airway patency. The cardiovascular consequences of these events are profound, and thus, it is believed that chronic exposure to obstructive apnea constitutes an independent risk factor for systemic hypertension, heart failure, myocardial infarction, and stroke (1, 2). Given the high prevalence of sleep-disordered breathing, it appears likely that OSAS plays a major role in contributing toward cardiovascular morbidity and mortality in a large segment of the population.

Studies suggest that abnormal autonomic control may be the common factor linking OSAS to these cardiovascular diseases (3–5). For instance, it has been observed that sympathetic drive is elevated to abnormally high levels in OSAS during wakefulness and sleep (3). At the same time, heart rate variability is markedly reduced, suggesting impaired parasympathetic control (4, 5). Autonomic function in patients with OSAS has been evaluated noninvasively, using a variety of cardiovascular reflex tests (6). However, because subject cooperation is required, this approach for assessing autonomic activity is limited to wakefulness. Spectral analysis of heart rate variability has been used to quantify autonomic function in OSAS under spontaneous, resting conditions, allowing the technique to be applied to measurements made during sleep. However, the spectral indices of heart rate variability can be confounded by differences in breathing pattern between individuals and across sleep–wake states (4, 7). Moreover, there remains considerable skepticism as to whether the low-frequency spectral component represents a valid marker of sympathetic activity (8). As well, spectral analysis yields only information about the frequency composition of the “output” (i.e., fluctuations in heart rate) of the underlying system, and provides little insight into the relationships that link heart rate with other companion variables, such as respiration and blood pressure.

We introduced an alternative method of autonomic function assessment in OSAS that allows the dynamic effects of respiration on heart rate and the baroreflex-mediated feedback relations between blood pressure and heart rate to be estimated, using a computational model (9). Our previous study showed the model-based approach to be more sensitive than summary statistical measures of cardiovascular variability in detecting changes in autonomic control resulting from continuous positive airway pressure (CPAP) therapy (9). However, one of the practical drawbacks of this technique was the requirement that the subject control his/her respiration to track a randomized breathing pattern, thus limiting its applicability to wakefulness. In the present study, we have extended the applicability of this method to conditions during sleep by using a computer-controlled ventilator to impose randomly varying changes in tidal volume, thus bypassing the need for voluntary control of the breathing pattern. This modification of our original approach has enabled us to determine how the primary mechanisms that contribute to heart rate variability are altered by OSAS as well as by changes in sleep–wake state.

Some of the findings presented in this article have been previously reported in the form of an abstract (10).

METHODS

Experimental Protocol and Instrumentation

Nine untreated patients with moderate-to-severe OSAS (apnea–hypopnea index, 44.1 ± 2.8 hour⁻¹) and eight normal control subjects participated in overnight sleep studies. Subject characteristics are shown in Table 1. Age was not significantly different between the two groups; however, body mass index was significantly higher in the patients with OSAS (p < 0.05). All subjects were normotensive and were free of diabetes, significant cardiac arrhythmia, congestive heart failure, and lung disease. Informed consent was obtained before each study. The protocol for the studies was approved by the University of Southern California Institutional Review Board.
Each subject was connected via nasal mask to a computer-controlled bilevel pressure ventilator (S/T-D 30; Respironics, Pittsburgh, PA). Measurements of mask pressure and airflow were obtained from the detachable control panel of the S/T-D ventilator. Airflow was electronically integrated in both inspiratory and expiratory phases to obtain the instantaneous lung volume ($V_t$) relative to passive functional residual capacity. Consistent with a previous report (11), we found in initial tests that the tidal volumes derived from the ventilator volume monitor were highly correlated ($r > 0.97$, $p = 0.0001$) with corresponding readings obtained from a reference pneumotachometer (model 3700; Hans Rudolph, Kansas City, MO). A chinstrap was used to keep the mouth closed during sleep, preventing leakage or inspiration through the mouth. Because some degree of CPAP was applied in all subjects, continuous monitoring of mask pressure allowed us to detect abrupt or unusual changes in baseline pressure that could indicate leaks through the mouth.

Blood pressure was monitored continuously from one wrist, using a noninvasive arterial tonometer (model 7000; Colin Medical Instruments, San Antonio, TX). The electrocardiogram, arterial oxygen saturation, central and occipital electroencephalogram, chin electromyogram, left and right electro-oculogram, and nasal thermistor were also monitored. All signals were sampled at 200 Hz. During sleep in the patients with OSAS, a CPAP of 8–15 cm H$_2$O was applied to eliminate all obstructive apneas (defined as episodes of zero airflow lasting 10 seconds or more) and significant hypopnea (defined as periods greater than 10 seconds in duration in which the nasal thermistor signal was reduced to less than 50% of its magnitude during unobstructed breathing and arterial oxygen saturation decreased by more than 4%). A minimal CPAP of 2–3 cm H$_2$O was applied during wakefulness in both groups. In the control subjects, CPAP was maintained at this minimal level during sleep.

During the 10-minute test protocol, the ventilator was set to assist-control, bilevel ventilation mode. Here, the subject was allowed to breathe at his/her own respiratory rate, but the inspiratory pressure was switched randomly breath-to-breath between the CPAP level and CPAP plus 5 cm H$_2$O. Expiratory pressure was kept constant at the CPAP level. Using this experimental setup, tidal volume was modulated from breath to breath without the need for voluntary control by the subject. This allowed the test protocol to be applied during sleep.

After one or two trials to minimize subject anxiety during wakefulness, the test protocol was applied at least three times in each sleep-wake state. Test sequences in which arousals or outright awakening occurred were terminated and were not repeated until the subject returned to a stable sleep state. Sleep stages were scored according to conventional criteria (12).

**Data Analysis**

R-R intervals (RRIs), and systolic blood pressure (SBP) and diastolic blood pressure (DBP) values, were deduced beat-to-beat and resampled at 2 Hz, using the algorithm of Berger and coworkers (13). This algorithm has been shown to be superior to other commonly employed methods in producing RRI spectra that are free from harmonic distortion (13). The resampling frequency of 2 Hz was adequate, given that the average heart rates in our subjects fell in the approximate range of 1 to 1.25 Hz, so that the maximal frequency content would be close to 0.5 Hz (14). On the other hand, it should be recognized that resampling the original RRI time series at an interval approximately half that of the average RRI inevitably introduces a certain degree of spurious correlation between successive values.

Low-frequency oscillatory behavior or baseline drift was observed in some of the data sets. These nonstationary features were removed by detrending the data sets before applying spectral analysis and modeling. The detrending procedure consisted of first fitting a fifth-order polynomial to the signals, and subsequently removing this curvilinear trend from the time series. The power spectrum of the subtracted trend was visually examined to verify that the detrending process had little effect on frequencies above 0.04 Hz.

### Spectral Analysis

After detrending, spectral analysis of RRI, DBP, and SBP was performed by an autoregressive modeling approach (15). Briefly, each of these variables was expressed as a linear combination of its past values. Least-squares minimization of the error between each data point and its corresponding model prediction was employed to determine the number of terms representing past values in the autoregressive model as well as to evaluate the unknown model parameters. After estimation of the unknown parameters, the autoregressive model was transformed into the frequency domain, enabling the corresponding power spectrum to be evaluated (15). From each of the spectra of RRI and blood pressure variability, the powers of the low-frequency (0.04- to 0.15-Hz) and high-frequency (0.15- to 0.4-Hz) bands were determined by evaluating the corresponding areas under the spectrum. The following spectral indices were used for the purposes of this study: high-frequency RRI power, ratio of low-frequency to high-frequency RRI power, low-frequency DBP power, and low-frequency SBP power.

High-frequency RRI power is generally accepted as a measure of vagal modulation of heart rate, because sympathetic stimulation of the sinus node is substantially attenuated at frequencies above 0.15 Hz (16). The question of whether low-frequency RRI power represents only sympathetic activity or a combination of both parasympathetic and sympathetic activity remains controversial (8, 17). The ratio of low-frequency to high-frequency power is used frequently as an index of “sympathovagal balance”: an increase in this ratio would signify an increase in sympathetic activity and/or a reduction in vagal activity (14). However, the underlying premise here is that sympathetic and vagal cardiac influences act in opposite directions; although this is frequently the case, it is by no means a universal rule (8, 16).

Interventions that increase sympathetic drive also lead to increases in SBP and DBP low-frequency power (17). However, cardiac autonomic blockade by pharmacologic agents attenuates heart rate variability profoundly but exerts little effect on blood pressure variability at frequencies below 0.15 Hz (16). Thus, the power of low-frequency

<table>
<thead>
<tr>
<th>TABLE 1. SUBJECT CHARACTERISTICS</th>
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<tbody>
<tr>
<td><strong>Control Subjects</strong></td>
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<tr>
<td><strong>Subject No.</strong></td>
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<tr>
<td>N1</td>
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<td>N2</td>
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<td>N3</td>
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**Definition of abbreviations:** BMI = body mass index (kg m$^{-2}$); OSAS = obstructive sleep apnea syndrome.
SBP or DBP oscillations is commonly used as a quantitative index of sympathetic modulation of the peripheral vasculature. SBP and DBP variabilities also include high-frequency oscillations. The observation that patients with denervated hearts continue to show significant high-frequency blood pressure oscillations suggests that these fluctuations are produced largely by the mechanical effects of breathing on the intrathoracic vasculature (18). Moreover, autonomically mediated fluctuations in systemic vascular resistance or vasomotor tone involve long time constants and, therefore, are unlikely to be the underlying cause of high-frequency blood pressure oscillations. Because it is unclear whether high-frequency SBP and DBP powers provide useful information about autonomic cardiovascular regulation, they have not been reported here.

The Model

On the basis of our knowledge of the underlying physiology (19), RRI, Vt, and SBP are assumed to be interrelated through the closed-loop control scheme illustrated in Figure 1. Respiration influences RRI directly through autonomic respiratory–cardiac coupling. The latter is believed to be the result of central respiratory entrainment of the cardiovagal motor neurons in the medulla as well as vagal feedback from the pulmonary stretch receptors (19–21). Respiration also affects RRI indirectly through changes in intrathoracic pressure, which are translated into changes in blood pressure; the latter subsequently stimulate the baroreceptors, leading to fluctuations in RRI. The totality of these respiratory influences on heart rate variability constitutes what is commonly termed “respiratory sinus arrhythmia.” The closed-loop nature of the control scheme derives from the fact that changes in RRI lead to changes in cardiac output that, in turn, influence blood pressure. Apart from intrathoracic pressure changes and changes in cardiac output, fluctuations in blood pressure can also arise from other sources of spontaneous variability, such as sympathetically driven variations in peripheral vascular resistance.

The focus of this study was limited to the portion of the closed-loop model that accounts for heart rate variability; this corresponds to the area circumscribed by the box (dashed lines) in Figure 1. Fluctuations in RRI were decomposed into three components: the first arising from direct respiratory–cardiac coupling, the second from stimulation of the baroreflexes by variations in blood pressure, and the third from spontaneous variations not related to respiration or the baroreflexes. Using this model, it was possible to estimate the impulse response functions, $h_{\text{ABR}}(t)$ and $h_{\text{RCC}}(t)$, which characterize the gains and temporal properties of the arterial baroreflex (ABR) and respiratory–cardiac coupling (RCC) mechanisms, respectively (Figure 1). $h_{\text{ABR}}(t)$ quantifies the time course of the change in RRI resulting from an abrupt increase in SBP of 1 mm Hg. $h_{\text{RCC}}(t)$ Quantifies the time course of the fluctuation in RRI associated with a rapid inspiration and expiration of 1 L of air. In linear systems theory, the impulse response provides a complete characterization of the dynamic properties of the system in question, because the response of this system to any arbitrary input can be predicted by mathematically convolving the input with the impulse response (20). Details of the computational procedure for estimating $h_{\text{ABR}}(t)$ and $h_{\text{RCC}}(t)$ are given in the Appendix (see the online supplement).

It is imperative to note that the system under study operates in a closed loop (see Figure 1), so that changes in heart rate can subsequently affect SBP through changes in cardiac output. In general, this condition, in which the model input is dependent on its output, can lead to erroneous parameter estimates when conventional analysis techniques are employed. To circumvent this problem, we formulated the model equations in the time domain so that “causality” constraints could be imposed: that is, the model output was constrained mathematically to be dependent on only past values of the inputs. Previous studies have employed similar methodologies that essentially allow the closed loop to be “opened” computationally (22–25).

Statistical Analysis

To facilitate statistical comparison, compact descriptors were derived from each model impulse response and its corresponding transfer function. These included two measures of gain and two measures of temporal behavior of the impulse response. The derived model descriptors were as follows: (1) impulse response (peak-to-peak) magnitude, (2) dynamic gain, (3) response latency, and (4) duration between start of impulse response and its first major peak or valley. The computational procedures used for evaluating these compact descriptors are detailed in the Appendix (see the online supplement).

Each estimated parameter was subjected to two-way repeated measures analysis of variance (subject group × sleep–wake state). Post hoc multiple pairwise comparisons (Student–Newmans–Keuls test) were performed if statistical significance was indicated.

RESULTS

Sample Time Series

A representative segment of data obtained from one of the subjects with OSAS is displayed in Figure 2. A CPAP level of
about 7 cm H2O was applied throughout the duration of sleep. Figure 2 (top panel) shows the randomly timed increases in inspiratory pressure delivered during the test procedure. The consequent variability imposed on the breathing pattern is evident in both tidal volume and breath duration (Figure 2, second panel down). These respiratory variations, in turn, lead to corresponding fluctuations in SBP (Figure 2, third panel down) and RRI (Figure 2, bottom panel). However, it should be noted that spontaneous fluctuations in SBP and RRI, which are largely independent of the respiratory changes, also occur (e.g., at about 40 seconds).

Because the subjects were heavily instrumented, total sleep time was spent primarily in Stage 2 and rapid eye movement (REM) sleep. Thus, comparisons of the results were made across only three states: wakefulness, REM sleep, and non-REM Stage 2 sleep.

**Summary Statistical Measures**

The means and standard errors of the cardiovascular variables in both subject groups are shown in Table 2. Mean RRI was significantly lower in patients with OSAS relative to control subjects (p < 0.005); in both groups, mean RRI increased from wakefulness to sleep (p < 0.02). DBP variability showed a slight tendency to be higher in the patients with OSAS, but this group difference failed to attain statistical significance. There were no group or state differences in any of the other summary statistical measures of heart rate and blood pressure. Average minute ventilation during the test protocol in the control subjects was 9.0 ± 0.5, 7.4 ± 0.4, and 7.2 ± 0.3 L/minute in wakefulness, REM sleep, and Stage 2 sleep, respectively. The corresponding values for the OSAS group were 9.9 ± 0.6, 7.5 ± 0.4, and 6.8 ± 0.5 L/minute, respectively. Thus, in both subject groups, ventilation decreased significantly (p < 0.05) from wakefulness to sleep.

**Spectral Measures of Cardiovascular Variability**

High-frequency RRI power demonstrated a clear tendency during sleep to increase in the control subjects but to decrease in the subjects with OSAS (p < 0.03). The ratio of low-frequency to high-frequency power was significantly higher in the subjects with OSAS relative to control subjects (p < 0.05). In the control subjects, this ratio tended to be lower in REM and Stage 2 sleep relative to wakefulness, whereas in the patients with OSAS it showed a tendency to be highest in REM sleep. However, these state-related differences were not statistically significant. Both low-frequency SBP power and low-frequency DBP power were higher in subjects with OSAS versus control subjects in all states (p < 0.05). Thus, spectral analyses of heart rate and blood pressure variability indicated an elevation of sympathetic influence on cardiovascular control and reduced vagal activity in patients with OSAS. The changes in autonomic activity with sleep were also different between subjects with OSAS and control subjects. The results are displayed in detail in Table 3.

**Dynamics of the Estimated Model Components**

The left-hand side of Figure 3 shows sample tracings of the estimated RCC impulse responses [hRCC(t)] corresponding to wakefulness (top), REM sleep (middle), and Stage 2 sleep (bottom) in a control subject (dark tracings) and one of the patients with OSAS (light tracings). Each impulse response represents the time course in RRI after a rapid inspiration and expiration of 1 L of air. In both subjects, hRCC(t) displays a biphasic form in which there is an initial large negative overshoot followed by a smaller positive overshoot. The initial negative dip is consistent with the well-accepted notion that the respiratory sinus arrhythmia consists of an acceleration of heart rate (or, equivalently, a reduction in RRI) during inspiration. The subsequent positive overshoot in the RCC impulse response reflects the decrease in heart rate during expiration (19). Throughout all states, hRCC(t) is clearly smaller in magnitude in the patient with OSAS relative to the control subject. A further interesting feature displayed by hRCC(t) is that the initial negative phase starts before time zero, implying that RRI begins decreasing toward the end of

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**Table 2. Summary Cardiovascular Measures**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control Subjects</th>
<th>Subjects with OSAS</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Wakefulness</td>
<td>REM</td>
<td>Stage 2</td>
</tr>
<tr>
<td>Mean RRI, ms</td>
<td>980 ± 44</td>
<td>1,027 ± 39</td>
<td>1,045 ± 39</td>
</tr>
<tr>
<td>RRI variability, ms</td>
<td>49.9 ± 8.3</td>
<td>49.1 ± 7.5</td>
<td>44.4 ± 7.1</td>
</tr>
<tr>
<td>Mean SBP, mm Hg</td>
<td>127.1 ± 6.3</td>
<td>122.8 ± 5.7</td>
<td>117.9 ± 4.0</td>
</tr>
<tr>
<td>SBP variability, mm Hg</td>
<td>4.9 ± 0.3</td>
<td>4.1 ± 0.5</td>
<td>4.5 ± 0.3</td>
</tr>
<tr>
<td>Mean DBP, mm Hg</td>
<td>69.2 ± 4.6</td>
<td>70.9 ± 4.8</td>
<td>66.6 ± 2.5</td>
</tr>
<tr>
<td>DBP variability, mm Hg</td>
<td>3.5 ± 0.7</td>
<td>2.7 ± 0.3</td>
<td>2.8 ± 0.3</td>
</tr>
</tbody>
</table>

*Definition of abbreviations: DBP = diastolic blood pressure; OSAS = obstructive sleep apnea syndrome; REM = rapid eye movement; RRI = R-R interval; SBP = systolic blood pressure.

* Statistically significant (p < 0.05)
the previous expiration, before the current inspiration (see Discussion).

The estimated baroreflex impulse responses from the same control and subjects with OSAS are displayed in Figure 3 (right panels). \( h_{\text{RCC}}(t) \) Quantifies the time course of the change in RRI resulting from an abrupt increase in SBP of 1 mm Hg. In this case, there is an initial large positive overshoot and a subsequent smaller negative undershoot, consistent with the notion that the net baroreflex response to an increase in blood pressure is a slowing of heart rate (or, equivalently, an increase in RRI). In all three states, \( h_{\text{RCC}}(t) \) was substantially smaller in magnitude in the subject with OSAS relative to the control subject. Another important feature is that \( h_{\text{RCC}}(t) \) was roughly twice as large in magnitude during sleep compared with wakefulness in the control subject; in contrast, the baroreflex impulse response of the subject with OSAS did not show much change in magnitude with changes in sleep–wake state.

**Statistical Comparison of Model Parameters**

Table 4 displays the group-averaged results for all compact descriptors derived from the RCC and ABR impulse responses. Both descriptors of RCC gain were on average lower in the subjects with OSAS relative to control subjects; however, statistical significance was attained only in the group difference in RCC dynamic gain (\( p < 0.03 \)). In both subject groups, there was little change in RCC dynamic gain across sleep–wake states (Figure 4, right panel). There were no differences between subject groups or across sleep–wake states in the time course descriptors.

Both descriptors of ABR gain increased from wakefulness to sleep (\( p < 0.01; \) Table 4). However, this increase was clearly much greater in the control subjects: the interaction between state and subject group was significant (\( p < 0.05 \)). For instance, ABR impulse response magnitude was more than twice as large in Stage 2 sleep relative to wakefulness in the normal subjects; in contrast, this parameter was not significantly dependent on state in the OSAS group (Figure 4, right panel). ABR impulse response magnitude was lower in the patients with OSAS versus control subjects in all states (\( p < 0.02 \)). Baroreflex latency was significantly smaller in the subjects with OSAS (\( p < 0.05 \)). Both descriptors of temporal behavior of baroreflex dynamics were not dependent on sleep–wake state.

**DISCUSSION**

**Noninvasive Assessment of Autonomic Function during Sleep**

In this article, we have introduced a new noninvasive method for assessing autonomic cardiovascular control in patients with OSAS during wakefulness and sleep. The method combines an experimental protocol, in which a randomly modulated breathing sequence is used to induce fluctuations in both heart rate and blood pressure, with a computational model, which allows the temporal relationships between pairs of these signals to be estimated. In previous studies by our group, random modulation of the breathing pattern was achieved through voluntary control, thereby limiting the application of the technique to wakefulness (9, 26). It is well known in the field of system identification that randomized inputs are superior in enhancing the accuracy of parameter estimation, because they stimulate the system under study with a broad range of frequencies (20). Previous theoretic (27) and experimental (28) studies have demonstrated the validity of this notion in the analysis of heart rate variability. In the present study, we extended the technique to make it applicable for use during sleep, by having the subject breathe from a ventilator in which the timing of ventilatory assist was programmed to vary randomly on a breath-to-breath basis. Application of the test protocol in general did not provoke arousals in the patients with OSAS. During wakefulness, each subject was given one or two trial runs of the test protocol before the start of the experiment, so that the imposition of the variable amount of ventilatory assistance would not provoke anxiety or voluntary efforts to “fight” the ventilator. However, we cannot dismiss the possibility that, in some cases, subject anxiety during the tests may have elevated sympathetic activity above levels normally found in quiet wakefulness. Another possible limitation is that the ventila-

### Table 3. Spectral Indices of Heart Rate and Blood Pressure Variability

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control Subjects</th>
<th>Subjects with OSAS</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Wakefulness</td>
<td>REM</td>
<td>Stage 2</td>
</tr>
<tr>
<td>HFP, ms²/Hz</td>
<td>242 ± 66</td>
<td>327 ± 151</td>
<td>503 ± 188</td>
</tr>
<tr>
<td>LHR</td>
<td>1.51 ± 0.27</td>
<td>0.82 ± 0.22</td>
<td>0.72 ± 0.28</td>
</tr>
<tr>
<td>LFP&lt;sub&gt;SBP&lt;/sub&gt;, mm Hg²/Hz</td>
<td>2.82 ± 0.66</td>
<td>1.50 ± 0.29</td>
<td>1.86 ± 0.41</td>
</tr>
<tr>
<td>LFP&lt;sub&gt;DBP&lt;/sub&gt;, mm Hg²/Hz</td>
<td>1.37 ± 0.37</td>
<td>1.46 ± 0.52</td>
<td>1.40 ± 0.60</td>
</tr>
</tbody>
</table>

**Definition of abbreviations:** HFP = high-frequency power of RRI variability; LFP<sub>SBP</sub> = low-frequency power of DBP variability; LFP<sub>ABR</sub> = low-frequency power of SBP variability; LHR = ratio of low-frequency to high-frequency RRI power; OSAS = obstructive sleep apnea; REM = rapid eye movement.

* Statistically significant (\( p < 0.05 \)).
tory assistance may have produced occasional periods of mild hypopapnia and thus led to unintended alteration of autonomic activity.

**Delineation of Major Components of Heart Rate Variability**

Heart rate variability is composed primarily of contributions that arise from the neural and mechanical coupling of the respiratory and cardiovascular systems, lung vagal feedback, as well as baroreflex feedback (19). Central to the method introduced in this study is the mathematical model that allows the respiratory and baroreflex contributions to be delineated. Although respiration and blood pressure are treated as though they are mutually independent inputs, these variables and heart rate are part of a larger closed-loop control system (see Figure 1). However, the presence of delays in this closed-loop system allows us to computationally partition the feedforward and feedback portions, so that each portion of the system can be treated as though it is operating under open-loop conditions (20). For instance, in the baroreflex portion of the closed-loop system, present changes in RRI are constrained in the mathematical model to be influenced by only past, but not present or future, fluctuations of blood pressure. This imposed constraint (termed “causality” in systems engineering terminology) forces the estimation scheme to converge toward a solution that reflects the effect of blood pressure on RRI (i.e., the baroreflex) rather than one reflecting the effects of RRI on blood pressure (i.e., the feedforward component). This approach of “temporal delineation” can only be applied by employing a model that has been formulated in the time domain. In contrast, frequency domain methods, such as techniques that employ cross-spectral analysis, do not allow the implementation of causality constraints. The application of this type of computational approach to cardiovascular control has appeared in publications by other researchers (22–25).

In principle, the estimation of $h_{\text{bar}}(t)$ and $h_{\text{RCC}}(t)$ is best achieved when the corresponding inputs, SBP and $V_t$, are independent of each other (20). However, as illustrated in Figure 1, respiration can indirectly influence heart rate, because inspiration generally produces a reduction in SBP by making intrathoracic pressure more negative; this decrease in SBP leads subsequently to a baroreflex-mediated decrease in RRI. Fortuitously, other influences, such as variations in cardiac output and peripheral resistance, also contribute to spontaneous fluctuations in SBP. In our study, application of the test protocol helped to further decorrelate $V_t$ and SBP, because on any given breath, inspiration could result in either a decrease or increase in SBP. Which way SBP was affected depended on the relative amounts of active breathing and assistance provided by the ventilator during that breath.

**Potential Confounding Effects of CPAP**

While the subjects with OSAS were sleeping, CPAP was applied at individually prescribed levels to ensure upper airway patency throughout the test procedure. We believe that this was an important part of the experimental procedure, because it enabled us to assess autonomic control across different sleep–wake states and across individuals under relatively similar patterns of respiration and under stable stages of sleep. In contrast, previous investigations of autonomic control in subjects with OSAS during sleep were performed under uncontrolled conditions in which the episodes of obstructive apnea were associated with profound swings in sympathetic and parasympathetic activity as well as transient state changes (29, 30). The occurrence of large swings

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**TABLE 4. MODEL PARAMETER ESTIMATES**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control Subjects</th>
<th>Subjects with OSAS</th>
<th>p Value</th>
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<tbody>
<tr>
<td></td>
<td>Wake REM Stage 2</td>
<td>Wake REM Stage 2</td>
<td></td>
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<tr>
<td>RCC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IR magnitude, ms L⁻¹</td>
<td>40.6 ± 7.6</td>
<td>46.7 ± 9.1</td>
<td>45.8 ± 6.6</td>
</tr>
<tr>
<td>Dynamic gain, ms L⁻¹</td>
<td>59.1 ± 7.9</td>
<td>69.1 ± 11.6</td>
<td>70.2 ± 10.0</td>
</tr>
<tr>
<td>Latency, s</td>
<td>−1.12 ± 0.10</td>
<td>−1.12 ± 0.20</td>
<td>−1.03 ± 0.20</td>
</tr>
<tr>
<td>Time to peak, s</td>
<td>1.12 ± 0.10</td>
<td>1.34 ± 0.20</td>
<td>1.37 ± 0.20</td>
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<td>ABR</td>
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<tr>
<td>IR magnitude, ms mm Hg⁻¹</td>
<td>2.23 ± 0.20</td>
<td>5.95 ± 1.60</td>
<td>6.64 ± 1.10</td>
</tr>
<tr>
<td>Dynamic gain, ms mm Hg⁻¹</td>
<td>2.22 ± 0.30</td>
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<td>5.01 ± 1.00</td>
</tr>
<tr>
<td>Latency, s</td>
<td>0.86 ± 0.20</td>
<td>1.18 ± 0.20</td>
<td>1.21 ± 0.20</td>
</tr>
<tr>
<td>Time to peak, s</td>
<td>1.94 ± 0.30</td>
<td>2.18 ± 0.50</td>
<td>2.34 ± 0.40</td>
</tr>
</tbody>
</table>

*Statistically significant (p < 0.05).

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**Figure 4.** RCC gain (left panel), represented by the dynamic gain of the RCC impulse response ($D_{\text{RCC}}$), was significantly higher in normal control subjects (filled circles) than in subjects with OSAS (open triangles), but was unchanged with sleep–wake state. Baroreflex gain (right panel), represented by the peak-to-peak magnitude of the ABR impulse response ($IR_{\text{A}}$), was also higher in normal subjects versus patients with OSAS. During sleep, baroreflex gain increased substantially in control subjects, but was only slightly elevated in subjects with OSAS.
in respiration and the cardiovascular variables can lead to severe distortions of the heart rate and blood pressure variability spectra, and thus contribute to interpretational difficulties if these spectral measures are used for making inferences about autonomic function (31).

On the other hand, CPAP application in the patients with OSAS during sleep may have led inevitably to some confounding influences. For example, in subjects with normal heart function, acute application of CPAP is known to decrease left ventricular preload more than left ventricular afterload, leading to a reduction in cardiac output (32). However, our subjects with OSAS did not show any change in SBP or DBP during sleep relative to wakefulness when only minimal CPAP was applied. The CPAP-induced increase in lung volume may have contributed to some increase in vagal activity and reduction in sympathetic drive (33). Therefore, our technique is likely to have underestimated the extent of autonomic abnormality in the subjects with OSAS during sleep.

To determine whether CPAP application may have exerted some unexpected effects on our findings, we performed correlation analyses between CPAP levels and the spectral and model-based indices of autonomic function estimated from the OSAS group during sleep. No significant correlations were found, except for baroreflex gain (r = −0.42, p < 0.02) during Stage 2 sleep. It should be noted that the correlation between CPAP level and baroreflex gain in Stage 2 sleep was negative, whereas we would have expected an increase in CPAP to augment vagal outflow and thus increase baroreflex sensitivity as well. This suggests that the underlying cause of the negative correlation was not the direct effect of CPAP application but the fact that the patients who needed higher levels of CPAP were also those who had more severe upper airway obstruction, and these were the subjects who likely had greater autonomic impairment (and thus, lower baroreflex sensitivities).

Spectral Indices of Heart Rate Variability

Previous studies employing spectral analysis of heart rate variability have reported significantly diminished high-frequency power and enhanced low- to high-frequency ratio in awa"ke patients with OSAS relative to normal control subjects (4, 5, 34). Consistent with these results, we found the ratio of low-frequency to high-frequency power and mean heart rate to be higher in our subjects with OSAS across all sleep–wake states. Low-frequency SBP and DBP power were also higher in the subjects with OSAS. These findings strongly support the notion that sympathetic tone is higher and parasympathetic activity is reduced in OSAS, as would have been expected on the basis of previous studies (3, 34). An important contribution of the present study is that we have shown that sympathetic activity in OSAS remains abnormally elevated in sleep even after CPAP has been applied to stabilize respiration.

In normal humans, a number of studies have reported that the magnitude of respiratory sinus arrhythmia, quantified as high-frequency RRI power, increases during sleep (35–37). We observed similar trends in the high-frequency power of our control subjects, although the relatively intrusive nature of our protocol did not allow us to obtain sufficient data to study these effects in Stages 3 and 4. Our subjects with OSAS demonstrated the opposite trend: high-frequency power was substantially decreased in REM or Stage 2 sleep versus wakefulness. The decrease in average ventilation during sleep was probably responsible for the reduction in high-frequency power observed in the subjects with OSAS. However, the contradictory trends in high-frequency power between control subjects and subjects with OSAS were unlikely to be due to differences in the state dependence of respiration, because mean ventilation decreased during sleep in the control subjects as well. Because RCC gain did not change with sleep–wake state in either group, the likely source of increase in high-frequency power in the control subjects was the large increase in baroreflex gain in these subjects during sleep. In the subjects with OSAS, sleep was not accompanied by a significant elevation of baroreflex gain. Thus, in normal subjects, it appears that the sleep-related increase in respiratory sinus arrhythmia is largely baroreflex mediated.

Baroreflex Gain: Patients with OSAS versus Normal Subjects

A number of previous studies have demonstrated a significant reduction in baroreflex sensitivity in subjects with OSAS (38, 39), although others have suggested that it is not different from that in normal subjects (40, 41). There are a number of possible reasons for this discrepancy. First, the difference between subjects with OSAS and normal subjects in baroreflex sensitivity may be small during wakefulness, relative to the variability across individuals. Because the foregoing studies were conducted on patients with OSAS only during wakefulness, the group difference in baroreflex sensitivity may have been difficult to detect in some cases. Parati and coworkers (42) found no difference in baroreflex sensitivity between a group of patients with severe OSAS and a normal control group during wakefulness; however, during sleep, baroreflex sensitivity in the subjects with OSAS was about 25% lower than normal. Similarly, in the present study, we found our estimates of baroreflex gain to be much lower in the OSAS group than in the normal group during sleep compared with wakefulness. This finding of reduced baroreflex gain in OSAS is consistent with our spectral analysis results, which implicate increased sympathetic activity, because it is well known that, in general, baroreflex sensitivity is inversely correlated with sympathetic drive (43).

Some of the discrepancy in results across different studies may also have been due to the use of different methodologies for estimating baroreflex sensitivity. For instance, in the study by Carlson and coworkers (38) bolus doses of sodium nitroprusside were injected to transiently lower blood pressure, during which the corresponding decreases in RRI were measured. Parati and coworkers (42) employed the “sequence technique,” which relates spontaneous fluctuations in blood pressure to corresponding fluctuations in RRI. The drawback of both these techniques is that they do not take into account the contribution of respiration to the fluctuations in RRI. One study has shown that excluding the effect of respiration on RRI can lead to the introduction of a significant amount of bias in the computation of baroreflex sensitivity (44). In our model-based approach, the component of the RRI fluctuations linearly correlated with respiration is removed before the remaining values are related to SBP fluctuations for the estimation of baroreflex gain. As well, our model makes the more realistic assumption that baroreflex action is associated with dynamic characteristics (e.g., response time); the aforementioned pharmacologic and sequence techniques do not take into account baroreflex dynamics.

Temporal Characteristics of the Model Components

One of the advantages of our method of analysis is that it enables a quantification of not only the gains but also the temporal characteristics of the model components. However, by and large, there were no differences between groups in the descriptors of time course. Baroreflex latency was significantly shorter in subjects with OSAS versus control subjects for the same sleep–wake state. This difference was on the order of 20–30% and, therefore, may have been largely related to the difference in heart rate between subjects with OSAS and control subjects, because mean RRI was about 30% shorter in subjects with OSAS compared with normal subjects. These observations suggest that,
on a beat-to-beat basis, the latency with which baroreflex-mediated changes in heart rate first begin to occur, after a change in arterial blood pressure, is similar in subjects with OSAS and normal control subjects.

We consistently found the RCC impulse response \[h_{RCC}(t)\] to be associated with a negative latency, implying that during the average breathing cycle the heart rate begins accelerating in the last segment of the preceding expiratory phase, before the start of the current inspiration. This finding is consistent with previously published figures of ensemble-averaged intrabreath changes in RRI, which show a short lead in RRI relative to the start of inspiration (19, 21). Katona and coworkers (45) found in recordings of cardiac vagal efferent fibers of anesthetized dogs that vagal firing ceased 0.5 seconds before the onset of respiratory activity. The average lead of about 1 second found in both of our subject groups is similar in magnitude to the latencies reported by others employing similar computational analyses (23–25). Although the RRI time series were resampled at 0.5-second intervals, the effective time resolution of our delay estimates was one beat. Moreover, in the resampling process, the RRI estimate in any given beat may have been affected by the RRI value of the following beat.

Conclusion

In the present study, we have employed a model-based approach to assess the autonomic control of heart rate in OSAS. The model allows for the partitioning of heart rate variability into a component mediated by the baroreflexes and a component mediated by respiratory–cardiac coupling. A computer-controlled ventilator was used to randomly modulate the breathing pattern of the subject, allowing this technique to be applied under conditions in which subject cooperation is not possible, such as during sleep. Both RCC and ABR gains were found to be substantially lower in the subjects with OSAS relative to normal control subjects in all sleep–wake states. Baroreflex gain increased two- to threefold from wakefulness to sleep in the control subjects, but was relatively unchanged in the patients with OSAS. In both groups, RCC gain was relatively independent of sleep–wake state. The present findings confirm previous reports that OSAS is associated with reduced parasympathetic and elevated sympathetic activity. The model-based approach provides a more precise characterization of the autonomic control of heart rate variability than does spectral analysis. As such, the application of this technique, in conjunction with the spectral analysis of cardiovascular variability, constitutes an improved, comprehensive approach for the detection and assessment of abnormal autonomic function in OSAS during wakefulness and sleep.

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