# CARDIOVASCULAR VARIABILITY IN OBSTRUCTIVE SLEEP APNEA: A CLOSED-LOOP ANALYSIS

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*Abstract-* **We have developed a model-based approach for estimating the dynamic effects of respiration on heart rate ("RSA") and arterial pressure ("MER"), along with the baroreflex response ("ABR") and the feedforward effect of heart rate on blood pressure ("CID") from a single test procedure. Respiration, heart rate, continuous blood pressure and other polysomnographic variables were monitored in 9 normals and 8 untreated patients with obstructive sleep apnea (OSA). A computer-controlled ventilator was used to vary ventilatory pattern in a randomized breath-to-breath sequence. Using closed-loop model analysis, we estimated the parameters that characterize RSA, ABR, CID and MER. RSA and ABR gains were significantly lower in OSA than normals. During sleep, ABR gain increased threefold in normals but remained unchanged in OSA. CID gain was higher in OSA relative to normals, suggesting increased peripheral vascular resistance. MER gain was also higher in OSA, but only in wakefulness. Apart from increased mean heart rate in OSA, there were no significant differences in other summary and spectral measures of cardiovascular variability. Our approach represents a sensitive, clinically practicable and comprehensive means of assessing autonomic function in OSA during both wakefulness and sleep.**

*Keywords-* **Autonomic control, sleep apnea, system identification, cardiovascular model, blood pressure variability, heart rate variability.**

## I. INTRODUCTION

The intact cardiovascular system maintains arterial blood pressure (ABP) within a fairly narrow range despite a wide variety of physiological perturbations. Although the basic physiological mechanisms involved in short-term cardiovascular regulation are known, relatively few studies have examined the dynamics of ABP control from a quantitative perspective.

Obstructive sleep apnea (OSA) has been linked to hypertension, heart failure, myocardial ischemia and infarction, stroke, and vascular complications. Mechanisms underlying the association between OSA and cardiovascular disease are yet unknown, but abnormalities in autonomic cardiovascular regulation are believed to be implicated. Autonomic function in patients with obstructive sleep apnea (OSA) has been evaluated using cardiovascular reflex tests, which involve subject cooperation (controlled breathing, abrupt change in posture from supine to standing, Valsava maneuver and sustained handgrip) [1]. Therefore, the assessment is limited to autonomic activity during wakefulness. Spectral analysis of heart rate variability (HRV) and arterial blood pressure variability (BPV) has been used to measure autonomic function and can be conducted without subject cooperation, thus allowing the technique to be applied during sleep. However, spectral indexes of HRV and BPV are affected by differences in breathing pattern within and across individuals. Furthermore, as we will demonstrate later, these indices are not sufficiently sensitive to detect changes in the autonomic function across sleep stages. Moreover, spectral analysis of HRV provides only information about the output of the autonomic system, but not the underlying dynamics.

In this paper, an alternative, model-based approach that enables the dynamic effects of respiration on heart rate and arterial blood pressure, and the closed-loop relations between heart rate and blood pressure, to be estimated in both wake and sleep is proposed. The method is based on a four-compartment model of neurocirculatory control of heart rate and arterial blood pressure variability, similar to that published by Baselli [2]. Our model includes a vagally mediated central component of respiratory sinus arrhythmia ($H_{RSA}$); an arterial baroreflex ($H_{ABR}$) component driven by both vagal and sympathetic systems; the feedforward effect of HRV on BPV ($H_{CID}$) [2]; and the mechanical effects of respiration on ABP ($H_{MER}$) due to the alterations in venous return and the filling of intrathoracic vessels and heart chamber associated with changes in intrathoracic pressure (Fig.1).

The goals of the present work were: 1) to estimate and quantify the dynamics of the main physiological mechanism involved in neurocirculatory control of heart rate and arterial blood pressure variability; 2) to investigate how these mechanisms and the autonomic control of HRV and BPV are altered by OSA as well as by changes in wake-sleep state; and 3) to introduce a model-based approach for quantitative assessment of autonomic function in OSA during both wakefulness and sleep.
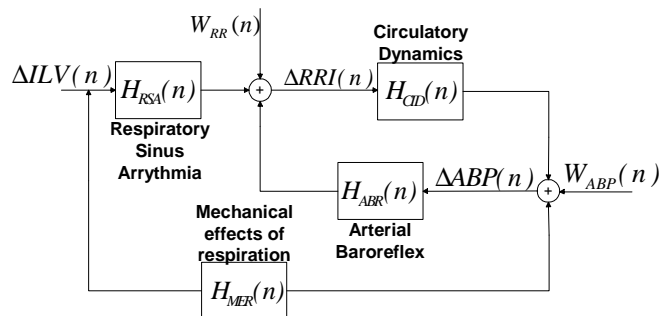


Fig. 1. Minimal closed-loop model of neurocirculatory control of heart rate and arterial blood pressure variability.

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## II. METHODOLOGY

### Subject Pool and Instrumentation

Eight normal subjects (eight males and one female, age: 50.1 ± 1.97 yrs, wt: 179.6 ± 5.5lbs) and nine untreated patients (all males, age: 44.9 ± 2.8 yrs, wt: 244.8 ± 10 lbs) with moderate-to-severe OSA (apnea-hypopnea index = 44.1 + 2.8 $h^{-1}$) participated in overnight sleep studies, conducted at the General Clinical Research Center, LAC/USC Medical Center, Los Angeles, CA. Characteristics of the subjects are shown in Table I. All the subjects were normotensive.

TABLE I
Individual normal subjects and patients characteristics.

| Patient No. | Age (yrs) | BMI (kg/m$^2$) | AHI (1/hr) | Prescribed CPAP (cmH$_2$O) | Subject No. | Age (yrs) | BMI (kg/m2) |
|---|---|---|---|---|---|---|---|
| 1 | 47 | 32.06 | 29.45 | 13 | 1 | 56 | 31.99 |
| 2 | 58 | 26.18 | 12.05 | 10 | 2 | 46 | 28.67 |
| 3 | 40 | 36.50 | 68.09 | 13 | 3 | 46 | 23.92 |
| 4 | 47 | 56.33 | 30.00 | 12 | 4 | 49 | 29.00 |
| 5 | 41 | 36.39 | 19.00 | 13 | 5 | 63 | 24.09 |
| 6 | 44 | 65.48 | 84.00 | 11 | 6 | 45 | 35.39 |
| 7 | 58 | 33.88 | 30.12 | 9 | 7 | 46 | 27.63 |
| 8 | 31 | 44.36 | 55.42 | 20 | 8 | 50 | 26.44 |
| 9 | 38 | 25.87 | 68.00 | 9 | | | |
| Mean | 44.89 | 39.67 | 44.01 | 12.22 | Mean | 50.13 | 28.39 |
| SE | 2.80 | 4.23 | 7.96 | 1.05 | SE | 1.97 | 1.21 |

Each subject was connected via a nasal mask to a bilevel pressure noninvasive ventilator (Model S/T-D 30, Respironics Inc., Murrysville, PA), which was computer-controlled to deliver specific inspiratory and expiratory positive air pressure levels (IPAP and EPAP, respectively). A chin strap was applied to prevent leakage of airflow through the mouth. Pressure within the nasal mask, and inspiratory and expiratory airflow were monitored. Continuous ABP and electrocardiogram (ECG) were also recorded. Other measurements include arterial $O_2$ saturation, two electroencephalogram derivations (central and occipital), chin electromyogram, and left and right electrooculogram.

### Experimental methods

A previous study [3] has shown that parameter estimation accuracy is enhanced when the variability in ventilation assumes a broad-band spectrum. In order to attain this conditions during sleep when voluntary control of ventilation is not possible, we applied the following experimental protocol. A computer-controlled ventilator was used to vary inspiratory mask pressure (and thus, tidal volume) randomly on a breath-to-breath basis. During the ten-minute test sequence, respiration, ABP and ECG were recorded. The ventilator was set in assist mode so that the subject triggered each inspiration on his own effort. Both normals and OSA patients were studied with a minimal amount (2-4 cm H$_2$O)

of continuous positive airway pressure (CPAP) applied during wakefulness. Normals were studied under the same minimal CPAP conditions during sleep. However, in the OSA subjects, CPAP was gradually raised during sleep to the individually prescribed treatment level (9-20 cmH$_2$O) to ensure that there was no upper airway obstruction. The test protocol was first carried out at least 3 times during wakefulness. Subsequently, the test protocol was conducted after attaining a stable sleep stage; the test was repeated at least 3 times in each stable period of stage 2 and REM sleep. Because the subjects were heavily instrumented, most of the total sleep time was spent in stage 2 and REM, with significantly smaller contributions from stages 3 and 4.

### Data Analysis

The cardiorespiratory signals (ECG, ABP, and respiratory airflow, volume and mouth pressure) were recorded and sampled at 200 Hz. In order to obtain the time series of RR intervals (RRI), 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 error 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: 2 Hz). Systolic (SBP) and diastolic (DBP) blood pressure values were also extracted on a beat-by-beat basis via computer algorithm from continuous ABP waveform. Airflow and mask pressure signals were also resampled at 2 Hz so that each respiratory value would be synchronized with the corresponding instantaneous RRI, SBP and DBP values. The instantaneous lung volume (ILV) was integrated from the resampled airflow signal. Each resampled sequence contained 1,200 data points (10 minutes).

In order to ensure the elimination of slow trends, the mean and high-order trend (5$^{Th}$ order polynomial) of the signals were removed prior to further analysis. All the signals were low-pass filtered with a phaseless Kaiser IR filter (passband of 0-0.5 Hz., stopband of 0.85-1 Hz., order of 21, and ripples in the pass and stop bands less than 0.01).

### Analytical Methods

A linear AutoRegressive model representation with eXogenous input (ARX) was used to estimate the impulse responses (IR) and transfer functions (TF) of the four components of the closed-loop model shown in Fig.1:

$$\Delta RRI(n) = -\sum_{i=1}^{p_1} a_i \Delta RRI(n-i) + \sum_{j=0}^{q_1} b_j \Delta ILV(n + D_{RSA} - j)$$
$$\ldots + \sum_{k=0}^{m_1} c_k \Delta SBP(n - D_{ABR} - k) + W_{RRI}(n) \tag{1}$$

$$\Delta SBP(n) = -\sum_{i=1}^{p_2} d_i SBP(n-i) + \sum_{j=0}^{q_2} e_j \Delta ILV(n - D_{MER} - j)$$

$$\ldots + \sum_{k=0}^{m_2} f_k \Delta RRI(n - D_{CID} - k) + W_{SBP}(n) \tag{2}$$

In Equations (1) and (2), $D_{RSA}$, $D_{ABR}$, $D_{CID}$, $D_{MER}$ are the delays associated with the corresponding mechanisms; and the signals $W_{RRI}(t)$ and $W_{SBP}(t)$ represent the variability of HR and SBP not explained by the model.

Since our measurements were recorded under closed-loop conditions, it was necessary to impose causality constraints on the system identification procedure. For this purpose, a delay of 0.5 s or higher was assumed in the baroreflex impulse response. Central regulation in RSA was previously reported to result in an apparent noncausal coupling of respiration and heart rate [4]. Therefore, the model was allowed to adopt negative values of the delay $D_{RSA}$. In order to accommodate this effect, the RRI signal was delayed before the estimation. Shifting the estimated RSA impulse response back in time later compensated for this negative delay.

To select the model with the minimum number of parameters that would best fit the observations, a least squares minimization procedure, similar to that of Kim and Khoo [3], was employed. For a given set of model orders and delays, *Eq. (1)* and *Eq. (2)* were solved by least squares minimization for all combinations of *m, p* and *q* ranging from 4 to 10 [10], with $D_{RSA}$ ranging from -2 to 1 s, $D_{ABR}$, from 0.5 to 2 s, and $D_{MER}$ and $D_{CID}$ from 0 to 2 s. The "optimal model" was selected by searching for the global minimum of the minimum description length [5] over the entire grid of values for *m, p, q,* and the delays. Model adequacy was checked by testing for whiteness of the residuals and the lack of correlation between the corresponding inputs and residuals. Normalized mean squared error and coherence function served as indicators of the prediction accuracy.

From the estimated ARX coefficients, the model component IRs were computed. The corresponding TFs were calculated by taking the Fourier transforms of the IRs. For statistical analysis, scalar indices of the system dynamics were derived from the IRs and TFs. To represent the system gain, the peak magnitude of the IR (Pmag), the peak-to-peak (PPmag) magnitude of the IR and average transfer function magnitude from 0.05 to 0.4 Hz (GTot) were used. The following were used as indices of IR time-course: time to peak IR (Tpeak), and duration of IR (Tir).

Spectral analysis was also applied to the RRI and SBP time-series. From the resulting spectra, we computed the power in the low-frequency region (LFP: 0.04-0.15 Hz), power in the high-frequency region (HFP: 0.15-0.4 Hz), the low-feqency to high-frequency power ratio (LHR), as well as normalized LFP and HFP.

Two-way repeated measures analysis of variance was employed, with state (Wake/Stage 2/REM) being the repeated factor and group (Normals/OSA) being the unrepeated factor. The Student-Newman-Keuls test was employed for post hoc multiple pairwise comparisons if statistical significance was indicated by the ANOVA. Results are presented as mean $\pm$ SE.

## III. RESULTS

### Spectral Analysis

Mean RRI was significantly lower in OSA compared to control subjects (776 $\pm$ 15 vs. 1017 $\pm$ 21 ms; P<0.0001). Mean RRI was also lower in wakefulness vs. sleep in both groups (P<0.01). RRI variability, as quantified by the standard deviation (SD), was lower in OSA subjects during Stage 2 sleep (P<0.05). The LFP of RRI was not significantly different between normal subjects and OSAS, but was significantly lower in stage 2 sleep compared to wake and REM sleep (P<0.025). Mean and SD values of SBP and MBP were not significantly different between normals and OSAS in any wake-sleep state. Normalized LFP and HFP of SBP were respectively lower and higher in wakefulness (P<0.0003), but there were no differences between subject groups.

### Closed-loop model analysis

RSA gain was substantially lower in OSA vs. normals (Gtot; O: 39.3 $\pm$ 3.4 vs. N: 66.1 $\pm$ 5.6 ms L$^{-1}$; P<0.02); it did not change significantly with sleep-wake state in both subject groups. ABR gain was also lower in OSA (PPmag; O: 2.34 $\pm$ 0.4 vs. N: 4.94 $\pm$ 0.7 ms mmHg$^{-1}$; P<0.02). ABR gain was increased approximately threefold in sleep vs. wake in normals, but was unaffected by state changes in OSA (P<0.002). The ABR time-to-peak was significantly lower in OSA vs. normals in both awake and sleep (Tpeak; O: 2.22 $\pm$ .2 vs. N: 3.25 $\pm$ .3 sec). Mean values and SE of the RSA and ABR gains are shown in Fig. 2.
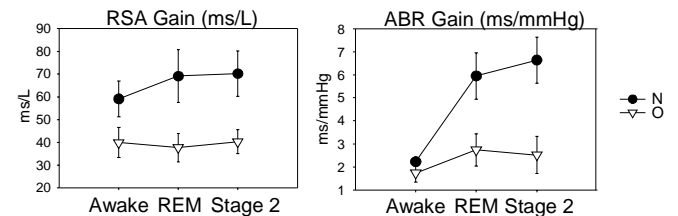


Fig. 2. RSA and ABR gains (mean $\pm$ SE) of the OSA (triangles) and Normal (circles) groups in wakefulness, REM and stage 2 sleeps.

CID gain was marginally higher in OSA vs. normals (Gtot; O: .056 $\pm$ .005 vs. N: .034 $\pm$ .003 ms L$^{-1}$; P<0.052), the

difference being largest in sleep. CID time-to-peak was significantly shorter in OSA vs. normals in all states (Tpeak; O: 2.94 ± .08 vs. N: 3.47 ± .1 sec). CID IR duration was longer in stage 2 sleep than in wakefulness and REM (P<0.008), in both normals and OSA. MER gain was higher in OSA, but only in wakefulness (Pmag; O: 3.36 ± 0.6 vs. N: 0.59 ± 0.7 ms mmHg$^{-1}$; P<0.02). Mean values and SE of the CID and MER gains are shown in Fig. 3.
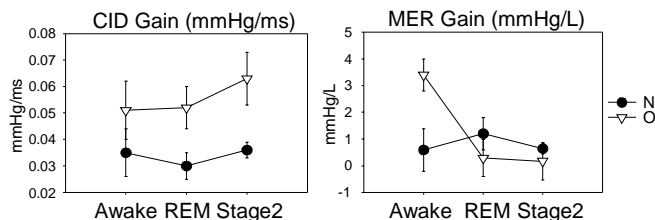


Fig. 3. CID and MER gains (mean ± SE) of the OSAS (triangles) and Normal (circles) groups in wakefulness, REM and stage 2 sleeps.

## IV. DISCUSSION

The lower mean RRI found in the OSA patients is consistent with our previous findings on awake OSA subjects [6]. However, aside from the lower RRI variability in OSA during Stage 2 sleep, none of the other conventional and spectral indices of HRV and BPV showed significant differences between the subject groups.

In contrast, closed-loop analysis of the same data showed that there were significant differences between normals and OSA patients in various descriptors of the dynamic components of the model. The significant reductions in both baroreflex (sympathetic and vagal mediated) and RSA (vagal mediated) gains reflect an impairment of autonomic control in OSA patients, consistent with previous clinical studies [7]. While ABR gain increases almost threefold in sleep vs. wake in normals, in OSA subjects it remains unchanged with sleep. Thus, the impairment of baroreflex control in OSA appears to be much worse during sleep than in wakefulness. The significant reduction of Tpeak of the ABR IR suggests a faster but less effective baroreflex response in OSA.

The larger CID gains in OSA subjects relative to normals indicate that similar fluctuations in RRI lead to larger fluctuations in SBP, another sign that blood pressure regulation is compromised in OSA. This result is consistent with previous findings of elevated sympathetic tone in OSA [6], which can lead to increased peripheral vascular resistance. The higher MER gain in OSA patients during wakefulness (when applied CPAP levels were similar to those used in the normals) may be due to higher upper airway resistance and/or reduced lung compliance in this subject group. During sleep, however, the substantially higher CPAP levels applied in the OSA patients may have offset most of this difference. Further tests are needed to confirm this interpretation of the results.

## V. CONCLUSION

The findings of this study demonstrate that impairment of autonomic control in OSA leads to significant reductions in both baroreflex and RSA gains, particularly during sleep. The higher CID gain in OSA also points to increased peripheral vascular resistance, presumably because of abnormally elevated sympathetic tone. In contrast, summary measures of cardiovascular function and spectral analysis of HRV and BPV were generally not sensitive enough to detect any change in the autonomic function between groups and across wake-sleep stages. The closed-loop modeling approach represents a clinically practicable and comprehensive means of assessing autonomic function in OSA during both wakefulness and sleep.

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