Relationship of Arousals From Sleep to Sympathetic Nervous System Activity and BP in Obstructive Sleep Apnea*

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Study objective: Obstructive sleep apnea (OSA) patients have a high frequency of arousals. We hypothesized that arousals significantly influence tonic sympathetic nervous system function.

Design: We examined the association of 11 variables measuring sympathetic activity, including plasma norepinephrine (NE), urinary NE, and BP measurements, with movement and cortical arousals.

Patients: Sixty-seven subjects with various degrees of hypertension and OSA were evaluated. All patients were free from antihypertensive medications.

Results: The age (range, 35 to 60 years), weight (range, 100 to 150% of ideal body weight), and diet of the subjects were similar. The movement arousal index was correlated with daytime baseline plasma NE (BNE), daytime urine NE, mean daytime diastolic BP, and systolic BP during rapid eye movement sleep ($r = 0.39$ to $0.53$; $p < 0.002$). Cortical arousals did not correlate with any of the variables. A multiple regression procedure was performed to examine how well movement arousals predicted those variables with significant correlations. The respiratory disturbance index (RDI) and nighttime pulse oxyhemoglobin saturation were included in the regression equation due to their close association with movement arousals. Movement arousals independently predicted BNE ($t_{[48]} = 2.06; p < 0.05$). No other variable independently predicted any of the measurements of sympathetic activity.

Conclusions: These findings suggest that movement arousals may influence daytime sympathetic tone independently of RDI and nighttime saturation.

(t) CHEST 1999; 116:655–659

Key words: arousals; BP; norepinephrine; obstructive sleep apnea; sympathetic nervous system

Abbreviations: BNE = daytime baseline plasma norepinephrine; CAI = cortical arousal index; EMG = electromyography; MAI = movement arousal index; MDBP = mean resting diastolic BP; NE = norepinephrine; OSA = obstructive sleep apnea; RDI = respiratory disturbance index; REM = rapid eye movement; SBP = systolic BP; SNS = sympathetic nervous system; SpO2 = pulse oxyhemoglobin saturation; TST = total sleep time

Transient increases in heart rate, BP, ventilation, and surges in sympathetic output often accompany arousals from sleep. These autonomic changes appear to be out of proportion to the physiologic needs of the sleeping individual.1 Animal and human studies support the notion that arousals from sleep lead to transient activation of the sympathetic nervous system (SNS),2,3 which could have cardiovascular implications.4

Increases in SNS activity is a frequently invoked hypothesis for the mechanism of the development of hypertension in patients with obstructive sleep apnea (OSA).5–7 Hypoxia increases sympathetic nerve firing,8 especially in the presence of upper airway obstruction such as during an apneic event.4,9 Measurement of plasma and urinary catecholamines also support higher sympathetic activity in sleep apnea patients.10–13 One of the characteristics of sleep apnea patients is their high frequency of arousals from sleep. However, it is not known if arousals contribute to the tonic activation of the SNS described in OSA.

The measurement of arousals is not well standardized. In recent work, we found that two categories of...
arousals (increases in EEG frequency > 3 s in duration, and arousals associated with muscle activity) were particularly reliable on test-retest and between readers. The possible association of arousals from sleep and SNS function in normal subjects or sleep apnea patients has not been fully evaluated. We set out to determine if arousals influenced SNS function in a heterogeneous group of patients with and without OSA and with and without hypertension. We hypothesized that arousals significantly influence tonic SNS function.

**Materials and Methods**

**Subjects**

All subjects gave informed consent to the protocol approved by the Institutional Review Board. Sixty-seven subjects (12 women and 55 men) were studied at the University of California San Diego Clinical Research Center. Subjects responded to public service advertisements, were referred from community physicians, or were referred by previous subjects. Subjects ranged in age from 35 to 60 years old, and their weight was between 1.0 and 1.5 times the ideal body weight, as determined from Metropolitan Life tables. Patients receiving antihypertensive medication had their treatment tapered for 3 weeks prior to the study. A resting BP while sitting was obtained three times on two separate occasions. Subjects with a systolic BP (SBP) consistently > 140 mm Hg and/or a diastolic BP > 90 mm Hg were considered hypertensive. Subjects with a respiratory disturbance index (RDI) ≥ 20 were considered to have OSA. Subjects were excluded if they were receiving medications known to affect sleep or if they had congestive heart failure; symptomatic obstructive pulmonary, coronary, or cerebral vascular disease; history of life threatening arrhythmias; cardiomyopathy; history of psychosis; narcolepsy; or current alcohol or drug abuse.

**Experimental Design**

Subjects were admitted to the Clinical Research Center at 5:00 PM and were immediately placed on an isocaloric diet providing 170 mEq Na and 100 mEq K per day. Sleep was recorded on 2 consecutive nights with polysomnography (model 4412P; Nihon Koden; Irvine, CA) that recorded central and occipital EEG, bilateral electro-oculography, submental and tibialis anterior electromyography (EMG), ECG, nasal/oral airflow using a thermistor, and respiratory effort using chest and abdominal inductance belts. Pulse oxyhemoglobin saturation (SpO2) was monitored using a pulse oximeter (Biotrack 3740; Ohmeda; Louisville, CO) and analyzed using appropriate software (Profox Version PFD 6/97; Profox Associates; Escondido, CA). Sleep records were scored according to the criteria of Rechtschaffen and Kales.

Apneas were defined as decrements in airflow ≥ 90% from baseline for a period ≥ 10 s. Hypopneas were defined as a decrement in airflow ≥ 50% but < 90% from baseline for a period ≥ 10 s. The number of apneas and hypopneas per hour were calculated to obtain an RDI.

On both nights, BP measurements were taken every hour using a BP monitor (Dinamap 1846 SX-P; Critikon; Tampa Bay, FL). On night 2, venous blood samples were obtained hourly via a heparinized catheter from an adjoining room. Blood samples were immediately placed in crushed ice and were then spun down in a refrigerated centrifuge. Plasma was stored at −80°C until the time of assay. Plasma norepinephrine (NE) was measured using a radioenzymatic assay.

On the second hospitalization day, two 12-h urine collections (6:00 AM to 6:00 PM and 6:00 PM to 6:00 AM) for NE were completed. Urine collections were stored appropriately until the time of assay. NE was measured using a radioenzymatic assay, and it is expressed in nanograms excreted per 12 h or 24 h as appropriate.

**Arousal Definitions**

The definition of an arousal from sleep was based on the criteria published in the 1992 American Sleep Disorders Association report on EEG arousals. However we stratified arousals by the presence or absence of increased chin EMG and/or leg movement. Two different definitions of arousal were used: (A) shifts in EEG frequency to alpha or theta ≥ 3 s but < 15 s duration (cortical arousals); (B) shifts in EEG frequency ≥ 3 s but < 15 s duration, associated with a rise in chin EMG amplitude and/or a rise in leg EMG activity (movement arousals). Before an arousal could be scored, the subject had to have been sleeping for a minimum of 10 s in the same or the contiguous sleep epoch. A minimum of 10 s of intervening sleep was necessary to score a second arousal. Shifts in EEG frequency were scored from either or both of the EEG derivations (occipital or central). The abrupt appearance of K complexes was scored as an arousal only if accompanied by an obvious shift in EEG frequency. Arousal indexes were calculated by dividing the number of arousals by the total sleep time (TST). Arousal preceded by a leg movements or occurring within 30 s of a BP measurement or blood sampling were excluded. Changes in EEG frequency > 15 s duration were considered awakenings rather than arousals, and they were not counted.

**Statistical Analysis**

To eliminate first night effect, all sleep and BP measurements used in the analyses reflect the values obtained during night 2. Due to missing values, only variables with > 50 measurements were included. Differences among the subject groups at baseline were assessed using two-way analyses of variance. Post hoc analyses were done using the independent sample t test.

Pearson correlations with Bonferroni corrections were performed using all subjects to examine the association between cortical arousals and movement arousals, and 11 different variables related to the following: (1) urinary NE; (2) plasma NE; and (3) BP. A multiple regression procedure was then performed to examine how well arousals predicted those variables with significant correlations from each of the above three groups. RDI and nighttime SpO2 were included in the regression analysis because of their close association to arousals. Statistical analyses were performed using appropriate statistical software packages (SPSS for Windows 7.0; SPSS, Chicago, IL).

Sample size estimation was done based on several variables measured in our previous studies using a t test with a pooled estimate of the variance. Our calculations suggested that a sample size of 15 subjects per group would be adequate to detect differences in plasma NE of 0.068 ng/ml with 80% power (α = 0.05; two-tailed).

**Results**

Table 1 provides the subject’s characteristics. The sample was composed of roughly equal numbers of...
subjects with and without sleep apnea, and with and without hypertension. Sleep apnea subjects were slightly older than the nonapneic subjects (50.7 vs 44.5 years old). On average, the subjects were mildly obese (average weight, 122% of ideal body weight using Metropolitan Life norms), and there was no difference between groups in body mass index, cortical arousal indexes (CAIs), TST, or sleep efficiency indexes. In general, apneic subjects had higher mean (SD) plasma NE (daytime baseline NE \([BNE]\), 0.470 [0.178] ng vs 0.369 [0.157] ng; \(p = 0.02\)) and urine NE (24-h urine NE, 36.2 [11.3] ng vs 26.0 [10.9] ng; \(p = 0.001\)) levels than nonapneic subjects. Apneic hypertensive subjects had higher movement arousal indexes (MAIs) than apneic normotensive subjects, and apneic normotensive subjects had higher MAIs than nonapneic hypertensive or normal subjects (apnea \(x\) hypertension interaction; \(p = 0.023\); Table 1).

Table 2 presents the univariate correlations between MAI and variables reflecting SNS activity, including plasma NE, urine NE, and BP measurements. Significance was adjusted using Bonferroni’s correction. A significant \(p\) value was determined to be \(< 0.0023\). In terms of plasma NE, only BNE was related to MAI (\(r = 0.41; p = 0.001\)). Daytime urine NE was the measurement from this group related to MAI (\(r = 0.39; p = 0.002\)). Mean resting diastolic BP (MDBP), as well as SBP during rapid eye movement (REM) sleep (REM SBP) were also correlated with MAI (\(r = 0.39\) and 0.53 respectively; \(p = 0.001\)). The CAI did not correlate with any of the variables examined, regardless of the collection or measurement schedule.

A multiple regression procedure was performed to examine how well MAI predicted those variables with significant correlations (BNE, daytime urine NE, MDBP, and REM SBP). Because of the tight association between MAI and RDI (\(r = 0.92; p < 0.001\)), and MAI and mean nighttime \(\text{SpO}_2\) (\(r = -0.38; p = 0.003\)), these were included as independent variables together with MAI in the regression equation. No one variable independently predicted daytime urine NE or REM SBP, except for MAI, which independently predicted BNE (See Table 3; \(t [48 \text{ degrees of freedom}] = 2.06; p < 0.05\)). None of the three independent variables predicted MDBP.

### Table 1—Patient Sample Characteristics*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Normal</th>
<th>Hypertensive</th>
<th>Apneic</th>
<th>Apneic Hypertensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>24</td>
<td>11</td>
<td>17</td>
<td>15</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>18</td>
<td>6</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>Female</td>
<td>6</td>
<td>5</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Age, yr†</td>
<td>43.9 (5.7)</td>
<td>45.8 (4.6)</td>
<td>51.2 (5.8)</td>
<td>50.3 (7.6)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>27.3 (3.5)</td>
<td>27.7 (4.1)</td>
<td>28.5 (3.7)</td>
<td>29.2 (2.4)</td>
</tr>
<tr>
<td>Screening BP, mm Hg‡</td>
<td>122/75</td>
<td>150/97</td>
<td>126/81</td>
<td>151/94</td>
</tr>
<tr>
<td>RDI†</td>
<td>6.1 (5.7)</td>
<td>6.5 (7.2)</td>
<td>51.0 (32.2)</td>
<td>74.2 (51.5)</td>
</tr>
<tr>
<td>TST, min</td>
<td>271 (73)</td>
<td>292 (75)</td>
<td>268 (64)</td>
<td>251 (71)</td>
</tr>
<tr>
<td>Sleep efficiency, %</td>
<td>75.7 (12.9)</td>
<td>78.5 (9.2)</td>
<td>73.1 (14.6)</td>
<td>71.3 (14.5)</td>
</tr>
<tr>
<td>CAI</td>
<td>2.0 (1.4)</td>
<td>2.9 (2.9)</td>
<td>2.8 (3.8)</td>
<td>2.9 (2.2)</td>
</tr>
<tr>
<td>MAI‡</td>
<td>13.0 (7.3)</td>
<td>11.8 (9.0)</td>
<td>32.7 (20.0)</td>
<td>56.7 (37.7)</td>
</tr>
<tr>
<td>BNE, ng/mL†</td>
<td>0.374 (0.148)</td>
<td>0.358 (0.184)</td>
<td>0.431 (0.185)</td>
<td>0.525 (0.159)</td>
</tr>
<tr>
<td>24-h urine NE, ng†</td>
<td>27.0 (11.4)</td>
<td>24.2 (10.2)</td>
<td>34.6 (14.1)</td>
<td>35.1 (6.9)</td>
</tr>
</tbody>
</table>

*Values expressed as mean (SD) unless otherwise noted. Sleep efficiency = (TST/total time in bed) \(\times 100\).
†Apneics significantly higher (\(p < 0.05\)).
‡Hypertensives significantly higher (\(p < 0.05\)).
§Significant apnea \(x\) hypertension interaction (\(p < 0.05\)).

### Table 2—Pearson Correlations Between MAI and SNS Activity Variable After Bonferroni Correction*

<table>
<thead>
<tr>
<th>Variables</th>
<th>(r)</th>
<th>(p) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine NE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daytime urine NE</td>
<td>0.39</td>
<td>0.002†</td>
</tr>
<tr>
<td>Nighttime urine NE</td>
<td>0.14</td>
<td>0.311</td>
</tr>
<tr>
<td>24-h urine NE</td>
<td>0.37</td>
<td>0.008</td>
</tr>
<tr>
<td>Plasma NE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BNE</td>
<td>0.41</td>
<td>0.001†</td>
</tr>
<tr>
<td>Stage 2 sleep NE</td>
<td>0.32</td>
<td>0.022</td>
</tr>
<tr>
<td>BP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daytime SBP</td>
<td>0.34</td>
<td>0.005</td>
</tr>
<tr>
<td>Daytime DBP</td>
<td>0.38</td>
<td>0.001†</td>
</tr>
<tr>
<td>Stage 2 sleep SBP</td>
<td>0.12</td>
<td>0.380</td>
</tr>
<tr>
<td>Stage 2 sleep DBP</td>
<td>0.22</td>
<td>0.097</td>
</tr>
<tr>
<td>REM sleep SBP</td>
<td>0.53</td>
<td>&lt; 0.001†</td>
</tr>
<tr>
<td>REM sleep DBP</td>
<td>0.34</td>
<td>0.015</td>
</tr>
</tbody>
</table>

*DBP = diastolic BP.
†Based on Bonferroni’s correction, a significant \(p\) value was determined to be \(\leq 0.0023\).
sympathetic tone. To investigate if arousals significantly contribute to SNS activity, efforts were made to control for potential confounding factors, apneic subjects were slightly older than nonapneic subjects ($p < 0.05$). However, age was probably not a factor, because it did not correlate with those measurements of SNS activity correlated with MAI.

Both hypertension and OSA were associated with higher MAI. Sleep apnea was the stronger of the two factors. This is probably related to the strong association of MAI to RDI noted in this study. However, it is unclear why hypertension was associated with a higher MAI, since hypertension did not influence RDI in our sample population (Table 1). CAIs were similar in all groups, suggesting that CAs are not associated with RDI. Both urinary and plasma NE levels were higher in sleep apneic subjects, which supports the reported higher SNS activity in OSA.

Both TST and sleep efficiency were low for all groups, suggesting significantly disturbed sleep. While these findings are not unusual for sleep apneic patients (50% of our subjects), normal subjects usually have higher values. We are not sure why the sleep duration was limited in our sample population. The question of whether or not sleep quality affects NE levels is controversial. Some have reported that sleep efficiency is associated with urine NE levels, however, others have reported that sleep deprivation had no influence in urinary catecholamine levels nor awakenings that influenced plasma catecholamines. We have previously evaluated the relative importance of some of the most common markers of sleep quality in alterations of the SNS. TST, sleep efficiency, slow wave sleep, and wake after sleep onset were unrelated to 24-h urine NE levels.

Subjects with OSA often suffer from hundreds of brief arousals each night, probably because arousals play an important part in opening the airway at the end of an apnea. However not all arousals are associated with a respiratory event. The literature also suggests that sleep apneic subjects have higher than normal tonic SNS activity even while awake. The most logical stimuli to increase SNS activity in OSA include the respiratory disturbances during sleep and oxyhemoglobin desaturation. Therefore, it was interesting to note that movement arousals were correlated with some measurements of daytime SNS activity, namely, BNE, daytime urine NE, and MDBP. Movement arousals were also correlated with REM sleep SBP (Table 2).

MAI and RDI were highly correlated in this sample. We wondered if the observed correlation between movement arousals and daytime SNS measurements were a function of the respiratory disturbance or nighttime episodic desaturation, rather than the effect of the arousals themselves. MAI, RDI, and SpO$_2$ together accounted for a modest but significant percent of the variances for BNE, daytime urine NE, and REM SBP. However, only MAI independently predicted BNE when all independent variables were entered simultaneously in the multiple regression equation (Table 3).

It is difficult to determine what component of a movement arousal (EEG or EMG activity) most influences sympathetic functioning. However, our findings suggest that increases in EMG activity during an arousal best correlate with SNS activity during wakefulness.

In conclusion, in a heterogeneous population, arousals that include increases in EMG activity correlate with daytime plasma NE levels. These
findings suggest that movement arousals influence daytime sympathetic tone independently of RDI and nighttime saturation.

**References**