Sleep Apnea and Hypertension*

The Role of Peripheral Chemoreceptors and the Sympathetic System

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Study objectives: **To examine the central inspiratory drive response to hypoxia in patients with obstructive sleep apnea (OSA), according to their circadian BP profile, and in healthy control subjects. Another objective was to evaluate the relationships among sleep architecture, hypoxic sensitivity, urinary catecholamine excretion, and BP in OSA patients.**

Patients and interventions: **Polysomnography, 24-h ambulatory BP recording, and urinary excretion of catecholamines were simultaneously examined in 24 consecutive OSA patients and 11 healthy subjects. OSA patients were categorized as being normotensive (type 1), having BP elevation only during sleep (type 2), and as being hypertensive with elevated BP at all times (type 3). The response of mouth occlusion pressure at 0.1 s after onset ($P_{0.1}$) to progressive isocapnic hypoxic stimulation was measured.**

Results: **There was a significant difference in the $P_{0.1}$ response to hypoxia among control subjects ([mean $\pm$ SD] 0.353 ± 0.129 cm H_2O/%) and type 1 (0.228 ± 0.062 cm H_2O/%), type 2 (0.345 ± 0.106 cm H_2O/%), and type 3 (0.508 ± 0.118 cm H_2O/%) OSA patients. In OSA patients, chemosensitivity was related to the apnea-hypopnea index and to the nocturnal excretion of epinephrine. Significant relationships between the nocturnal excretion of epinephrine and BP were noted. On multiple linear regression analysis, the $P_{0.1}$ response to hypoxia was the only variable significantly related to diurnal ($r^2 = 0.364$; $p = 0.005$) and nocturnal mean BP ($r^2 = 0.461$; $p = 0.002$).**

Conclusion: **The findings of the present study suggest a possible mediating role of the peripheral chemosensitivity in the association between sleep apnea and hypertension.**

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Key words: BP; carotid body; catecholamines; chemosensitivity; sleep apnea

Abbreviations: AHI = apnea-hypopnea index; DBP = diastolic BP; HPLC = high-performance liquid chromatography; MBP = mean BP; OSA = obstructive sleep apnea; $P_{0.1}$ = mouth occlusion pressure at 0.1 s after the onset of inspiration; $P_{0.1}/SaO_2$ = $P_{0.1}$ response to progressive isocapnic hypoxic stimulation; $PETCO_2$ = end-tidal carbon dioxide pressure; Raw = airway resistance; SaO_2 = arterial oxygen saturation; SBP = systolic BP; WASO = wakefulness after sleep onset

O bstructive sleep apnea (OSA) is characterized by the occurrence of episodes of complete or partial upper airway obstruction during sleep. Prevalence surveys estimate that 2% of women and 4% of men of middle age are affected by this syndrome.[1] OSA has been recognized increasingly as an impor-

tant medical condition producing severe morbidity and appreciable mortality.[2] The most relevant long-term consequences of OSA arise from its cardiovascular morbidity, which may be explained by the effects on systemic BP caused by obstructive apneas.[3] The strong association between OSA and systemic hypertension is well recognized.[4,5] Forty to 60% of patients with OSA have arterial hypertension.[6] Although this association is complicated by confounding factors, such as obesity, age, and sex, previous studies have identified OSA as an independent predictor for sustained hypertension.[4,7]

Several reports have described transient increases in systemic BP during sleep apneic episodes.[5,8] Acute BP elevations during apnea are explained by

chemoreflex mechanisms and their interactions with baroreflexes and the pulmonary afferents.[8] Hypoxia and hypercapnia act synergistically to increase sympathetic discharge to the muscles of the vascular beds.[8] Increased negative intrathoracic pressure, causing increased venous return, and arousal also contribute to the rise in BP at the end of an episode of apnea.[5] In fact, arousal is the dominant cause of postapnea BP elevation.[8]

The cyclical increases in BP during the night in OSA patients, which are caused by the episodes of apnea, modify the circadian variation of BP. On the basis of circadian BP profiles, the following three BP patterns have been identified in OSA patients: normotensive subjects with physiologic nocturnal drop in BP; subjects with nocturnal hypertension; and hypertensive patients with elevated BP throughout a 24-h period.[9]

The mechanism that translates nocturnal recurrent BP increases into sustained, daytime systemic hypertension is still controversial. However, it has been proposed that an altered chemotransduction could play a pathogenic role.[10] Hedner et al[11] reported that OSA patients develop an exaggerated BP response to progressive hypoxia during wakefulness, whereas such a response is absent in control subjects. Thus, it can be hypothesized that recurrent obstructive apneas may reset the chemoreceptor output to a higher level, causing a chronic increase in sympathetic tone and initiating hypertension.[10]

The purpose of the present study was to examine the central inspiratory drive response to hypoxia in the three types of OSA patients, according to their circadian BP profile, and in healthy control subjects. Furthermore, we investigated the relationships among sleep architecture, hypoxic sensitivity, urinary catecholamine excretion, and BP in OSA patients.

Materials and Methods

Subjects

Twenty-four consecutive OSA patients and 11 healthy subjects were selected to be studied. Patients were excluded from the study for the following reasons: unwillingness or inability to perform the testing procedure; obstructive or restrictive lung disease demonstrated on pulmonary function testing; known valvular heart disease; current drug or mechanical treatment for sleep apnea; known neuromuscular disease; abnormal thyroid function; morbid obesity (body weight > 150% of ideal); recent (< 3 months) myocardial infarction or cerebrovascular accident; BP > 180/110 mm Hg; and secondary hypertension.

Control subjects were judged healthy by history, findings from physical examination, and the results of ECG, basal spirometry, and chest fluoroscopy.

Antihypertensive treatment (with diuretics, β-blocking agents, angiotensin-converting enzyme inhibitors, or calcium channel blockers) was discontinued 1 week before the examination.

Subjects were asked not to eat for 4 h before the study period, and they also were asked to refrain from using coffee, tea, and alcohol for ≥ 12 h and tobacco for ≥ 2 h before each study.

The study was approved by the institutional ethics committee at the hospital. All subjects gave their written informed consent prior to enrollment.

BP Monitoring

BP was measured at 30-min intervals over a 24-h period with an ambulatory BP monitoring instrument (Micro AM; Kontron Instruments; Watford, UK). During daytime monitoring BP, subjects were instructed to avoid strenuous exercise. According to the classification proposed by Noda et al,[9] OSA patients were divided into the following three groups: type 1 OSA were those patients normal BP (systolic BP [SBP], < 140 mm Hg; and diastolic BP [DBP], < 90 mm Hg) throughout a 24-h period and with a nocturnal fall in BP; type 2 OSA were patients with progressive BP elevation from the onset of sleep to early morning; and type 3 OSA patients were hypertensive with elevated BP (SBP, ≥ 140 mm Hg; and/or DBP, ≥ 90 mm Hg) at all times during 24-h monitoring and were without nocturnal dipping in BP values.

Catecholamines in Urine

Subjects were requested to collect separate urine samples from 7:00 AM to 11:00 PM (day) and from 11:00 PM to 7:00 AM (night). Urine specimens for each sample were collected in polyethylene containers, were acidified with 6 mol/L HCl as a preservative, and were stored at − 40°C before analysis.

A 5-mL aliquot of a urine sample was filtered; 3,4-dihydroxybenzylamine (internal standard) and 0.1% ethylenediamine-tetraacetic acid were added to the filtrate, were adjusted to pH 6.5, and subsequently were placed on a × 70 cation exchange column (Biore; Bio-Rad; Munich, Germany). After the sample entered completely into the resin, the column was washed with distilled water and the catecholamines were eluted with 10 mL 0.65 mol/L boric acid. After this procedure, 20 μL of the effluent was injected into a high-performance liquid chromatography (HPLC) system composed of an HPLC pump (model 510; Waters; Milford, MA), a 20-μL injection valve (Rheodyne; Cotati, CA), a chromatographic column (HR-80, RP-C18; ESA; Chelmsford, MA), a coulometric detector (Coulochem II; ESA), a high-sensitivity analytical cell (model 5011; ESA), and a conditioning cell (model 5021; ESA). Concentrations of detected compounds were calculated on a personal computer using integration software (712 HPLC system controller, version 1.2; Gilson; Madison, WI) that measures the heights of the peaks and relates them to external standards.

Intra-assay coefficients of variation were 3% for norepinephrine, 3% for epinephrine, and 1.5% for dopamine. Interassay coefficients of variation were 9% for norepinephrine, 10.5% for epinephrine, and 6.4% for dopamine. The results were expressed in terms of micrograms per gram of creatinine.

Polysomnography

During the same night when urine specimens were collected, healthy subjects and OSA patients were subjected to polysomnography from 11:00 PM to 7:00 AM, EEG (electrode placements C3-A2 and C4-A1), electro-oculogram, chin electromyogram, electromyograms of the tibialis anterior of both legs, and ECG were continuously recorded. Respiration was monitored using oronasal thermistors and thoracoabdominal strain gauges. Simultaneously, arterial oxygen saturation (SaO_2) was monitored with a pulse oximeter (Pulsox DP-8; Minolta; Ramsey, NJ).

Sleep was analyzed using the standard criteria[12] for epochs of 20 s, and the following sleep variables were calculated: total sleep time; wakefulness after sleep onset (WASO); and sleep efficiency, defined as the ratio of total sleep time to sleep episode duration. Obstructive apnea was defined as the cessation of airflow for at least 10 s in the presence of continued respiratory efforts. Hypopnea was defined as a decrease of $\geq 50\%$ in oronasal airflow lasting > 10 s, or a fall in oronasal airflow with an oxygen desaturation $\geq 3\%$ of the preceding baseline level. The apnea-hypopnea index (AHI) was established as the number of apneas and hypopneas per hour of sleep. OSA was defined as an AHI > 10 and a percentage of obstructive apneas $> 70\%$ in combination with daytime hypersomnolence. As indexes of nocturnal oxygen saturation, the mean SaO_2 throughout the night and the mean lowest nocturnal SaO_2 (mean of the minimal SaO_2 after each apnea) were computed.

Lung Function Study

Immediately after awakening, pulmonary function tests were performed, as previously described,[13] with subjects seated and always in the same order to allow enough rest between each maneuver. All procedures were performed by the same technician, who was blinded to the results.

Arterial blood gas values were measured with subjects in a seated position while they breathed room air. Spirometry was performed by means of a pneumotachograph, and static lung volumes were measured with a constant-volume body plethysmograph (MasterLab Body; Erich Jaeger GmbH; Würzburg, Germany), according to European Respiratory Society standardization.[14] Maximal static inspiratory expiratory pressures were measured using a differential pressure transducer (M-163; Sibelmed; Barcelona, Spain). Patients, comfortably seated and wearing a nose clip, performed maximal respiratory efforts either at residual volume or at total lung capacity against an obstructed mouthpiece with a small leak (internal diameter, 0.7 mm) to minimize oral pressure artifacts. The maneuvers were repeated until three measurements that were sustained for at least 3 s with $< 5\%$ variability were recorded. The highest value obtained was used for analysis.

Mouth occlusion pressure at 0.1 s after the onset of inspiration ($P_{0.1}$) was measured by the method of Whitelaw et al,[15] and mouth pressure was recorded with a differential pressure transducer (Model DWD; Erich Jaeger Gmbh). Approximately every 15 s, the inspiratory line was occluded without the subject's knowledge for < 0.5 s by means of a pneumatic inflatable balloon (series 9327; Hans-Rudolph; Kansas City, MO). The mean of at least five measurements was determined. The values for dead space and resistance of the system up to a flow of 100 mL were 173 mL and 0.1 kPa/L/s, respectively.

The $P_{0.1}$ response to progressive isocapnic hypoxia was determined using the rebreathing method of Rebuck and Campbell.[16] SaO_2 was measured continuously with a finger-pulse oximeter (Pulsox-7; Minolta). In the seated position with nose clips applied, subjects breathed room air through a mouthpiece via a three-way valve while expired gas was continuously sampled at the mouthpiece using a rapidly responding infrared CO_2 analyzer (model RE-3000; Fukuda Sangyo; Chiba, Japan). The gas analyzer was calibrated with gases previously analyzed by the Scholander technique. After a stable end-tidal CO_2 concentration was achieved, subjects rebreathed through a 7-L bag containing the initial gas mixture of 21% O_2 and 7% CO_2 in nitrogen. The end-tidal CO_2 concentration was held constant (± 1 mm Hg) at the resting end-tidal pressure ($PETCO_2$) using a variable CO_2 absorber bypass containing a soda lime CO_2 absorbent layer and

a variable fan. Approximately every 15 s without the subject's knowledge, mouth occlusion pressure was recorded as indicated previously. $P_{0.1}$, SaO_2, and $PETCO_2$ were recorded continuously on a multichannel chart recorder (Hellige-218088; Erich Jaeger GmBh). Mouth occlusion pressure was measured manually from each tracing. $P_{0.1}$ was plotted against SaO_2 on linear coordinates, and the slope was calculated by least squares linear regression. The trial of hypoxic response was terminated when the subjects reached 80% of SaO_2.

Statistical Analysis

The differences between the means of variables in study group were analyzed using one-way analysis of variance. *Post hoc* analysis was performed using the Bonferroni adjustment for multiple comparisons. Correlations between polysomnographic findings, 24-h BP monitoring, catecholamine levels, and peripheral chemosensitivity were determined by linear regression analysis. In order to determine which independent variables were correlated with SBP, DBP, and mean BP (MBP), both for the sleep and the waking periods, stepwise multiple linear regression analysis was performed.[17] Independent variables entered into the regression included AHI, WASO, mean lowest SaO_2 throughout the night, $P_{0.1}$ response to hypoxia, and nocturnal excretion of epinephrine. Stepwise criteria were a probability of fixed factor (F) to enter ≤ 0.05 and a probability of fixed factor (F) to remove ≥ 0.10. These analysis were performed using computer software (Statistical Package for the Social Sciences for Windows, version 8.0; SPSS; Chicago, IL) In all cases, p values < 0.05 were considered to be significant. Data are expressed as mean $\pm$ SD.

RESULTS

Subject Characteristics

According to the 24-h arterial BP patterns, 10 patients were classified as having type 1 OSA, 8 patients as having type 2 OSA, and 6 patients as having type 3 OSA. Anthropometric and sleep characteristics of the three OSA patient groups and control subjects are given in Table 1. As would be expected, the AHI was higher in the OSA patients than in the control subjects. Sleep-onset latency was shorter in the three OSA groups than in the control subjects. The duration of WASO was longer in the three OSA groups than in the control group. Furthermore, type 2 and type 3 OSA patients had more WASO than did type 1 OSA patients. The efficiency of sleep was lower in the three OSA groups than in the control subjects. There were no significant differences in age, body mass index, mean nocturnal SaO_2, or mean low nocturnal SaO_2 among the four groups.

Pulmonary Function and Breathing Control

Arterial blood gas levels, lung volumes, airway resistance (Raw), and maximal static respiratory pressures for each group are shown in Table 2. No differences were observed in any of the above variables among the groups.

Table 1—Anthropometric, Sleep, and Urinary Excretion of Catecholamines Data*

Characteristics	Control Subjects (n = 11)	OSA Patients Type 1 (n = 10)	OSA Patients Type 2 (n = 8)	OSA Patients Type 3 (n = 6)
Age, yr	56.1 ± 12.9	52.9 ± 6.9	53.3 ± 9.2	53.6 ± 8.4
Sex, No.				
Male	9	9	7	6
Female	2	1	1	0
Body mass index, kg/m^2	31.2 ± 3.2	29.8 ± 3.5	30.4 ± 3.7	33.1 ± 4.3
Smokers, %	36	40	13	17
Total sleep time, min	373 ± 42	312 ± 104	318 ± 26	315 ± 29
Sleep efficiency, %	85 ± 8	76 ± 7†	69 ± 4†‡	69 ± 5†
Sleep onset latency, min	33 ± 12	14 ± 13†	9 ± 12†	2 ± 2†
WASO, min	32 ± 36	89 ± 44†	134 ± 23†‡	141 ± 17†‡
AHI, h	2.4 ± 1.7	37.5 ± 27.9†	39.2 ± 18.2†	45.7 ± 26.7†
Mean nocturnal SaO_2, %	96 ± 1	95 ± 2	92 ± 6	92 ± 2
Mean low nocturnal SaO_2, %	90 ± 2	81 ± 7	78 ± 7§	78 ± 11§
Diurnal norepinephrine, μg/g	62.1 ± 41.5	65.4 ± 67.8	81.6 ± 78.0	50.7 ± 14.0
Diurnal epinephrine, μg/g	9.2 ± 11.3	8.5 ± 9.4	8.2 ± 4.1	8.2 ± 4.9
Diurnal dopamine, μg/g	299 ± 91	326 ± 273	331 ± 233	220 ± 36
Nocturnal norepinephrine, μg/g	28.7 ± 10.8	40.9 ± 25.3	50.1 ± 44.6	43.5 ± 25.5
Nocturnal epinephrine, μg/g	1.1 ± 1.2	2.6 ± 1.6§	3.5 ± 1.3§	3.8 ± 1.4§
Nocturnal dopamine, μg/g	238 ± 62	306 ± 149	318 ± 177	248 ± 53

*Values are given as mean ± SD unless otherwise indicated.
†p < 0.01 for the comparison with the control group.
‡p < 0.05 for the comparison with type 1 OSA patients.
§p < 0.05 for the comparison with the control group.

OSA patients had a central inspiratory drive ($P_{0.1}$) greater than that of control subjects (Table 2). Moreover, resting $P_{0.1}$ was significantly higher in type 2 and type 3 OSA patients than in type 1 OSA patients (Fig 1).

Table 2 shows the $P_{0.1}$ response to hypoxia in OSA patients and in control subjects. The $P_{0.01}$ response to progressive isocapnic hypoxic stimulation ($P_{0.1}/SaO_2$) in type 1 OSA patients was lower than that in control subjects. Type 2 OSA patients had a $P_{0.1}/$

Table 2—Lung Function Data for the Control Subjects and OSA Patients*

Characteristics	Control Subjects	OSA Patients Type 1	OSA Patients Type 2	OSA Patients Type 3
PaO_2, mm Hg	72.8 ± 8.9	73.4 ± 12.9	73.4 ± 10.0	72.3 ± 8.9
$PaCO_2$, mm Hg	39.0 ± 3.2	38.6 ± 3.3	38.3 ± 4.4	41.6 ± 5.3
FVC, L	3.29 ± 1.01	3.78 ± 0.78	3.53 ± 1.04	4.13 ± 0.96
FEV_1, L	2.52 ± 0.86	2.98 ± 0.60	2.70 ± 1.04	3.37 ± 1.15
FRC, L	3.22 ± 0.84	2.79 ± 0.63	3.52 ± 1.09	3.41 ± 0.72
TLC, L	5.75 ± 1.29	6.11 ± 1.16	6.54 ± 1.20	6.96 ± 0.51
RV, L	2.40 ± 1.05	2.24 ± 0.68	2.81 ± 0.89	2.78 ± 0.74
Raw, cm H_2O/s/L	5.265 ± 2.541	4.541 ± 1.776	4.061 ± 1.653	5.224 ± 3.633
PImax, cm H_2O	102 ± 22	114 ± 33	100 ± 31	105 ± 31
PEmax, cm H_2O	126 ± 37	147 ± 31	171 ± 53	144 ± 45
$P_{0.1}$, cm H_2O	1.43 ± 0.20	1.94 ± 0.20†	2.35 ± 0.41‡§	2.65 ± 0.92‡§
$PETCO_2$ rebreathing, mm Hg	33.5 ± 3.2	33.1 ± 3.3	32.8 ± 4.4	33.7 ± 2.0
$P_{0.1}/SaO_2$, cm H_2O/%	0.353 ± 0.129	0.228 ± 0.062†	0.345 ± 0.106§	0.508 ± 0.118‡‖¶

*Values are given as mean ± SD. FRC = functional residual capacity; TLC = total lung capacity; RV = residual volume; PImax = maximal inspiratory pressure; PEmax = maximal expiratory pressure.
†p < 0.05 for the comparison with the control group.
‡p < 0.01 for the comparison with the control group.
§p < 0.05 for the comparison with type 1 OSA patients.
‖p < 0.01 for the comparison with type 1 OSA patients.
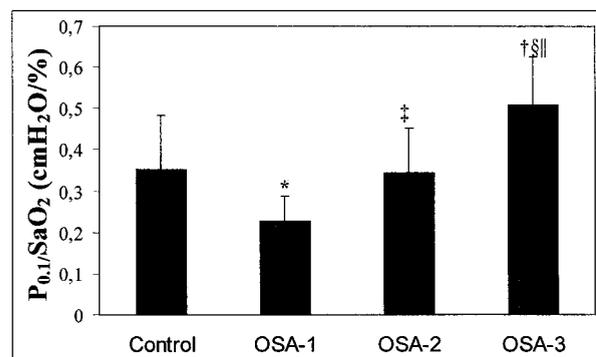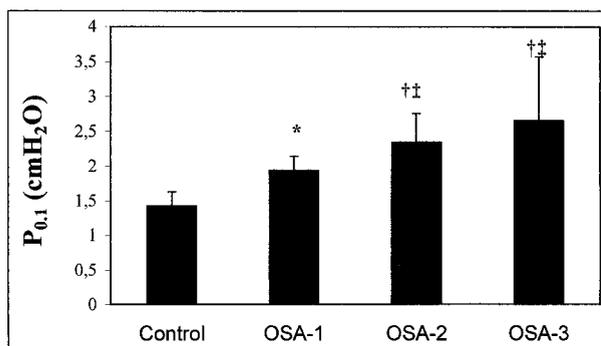¶p < 0.05 for the comparison with type 2 OSA patients.

FIGURE 2. The relationship between WASO and $P_{0.1}/SaO_2$ ratio in the OSA patients; see Figure 1 legend for definition.

FIGURE 1. $P_{0.1}$ (*top*) and $P_{0.1}$ response to hypoxia (*bottom*) for each type of OSA patients and for control subjects. * = p < 0.05 for the comparison with control group; † = p < 0.01 for the comparison with control group; ‡ = p < 0.05 for the comparison with type 1 OSA patients; § = p < 0.01 for the comparison with type 1 OSA patients; ‖ = p < 0.05 for the comparison with type 2 OSA patients; $cmH_2O/\%$ represents changes in $P_{0.1}$ (cm H_2O) induced by each precent change in SaO_2.

SaO_2 ratio that was higher than that in type 1 OSA patients and was similar to that control subjects. Type 3 OSA patients had a $P_{0.1}/SaO_2$ ratio that was higher than that in type 1 and type 2 OSA patients and control subjects (Fig 1). There were no significant differences in the average PETCO₂ levels used during rebreathing among the four groups.

Relationship Between Sleep Characteristics and Hypoxic Response

In OSA patients, the $P_{0.1}/SaO_2$ ratio correlated significantly with the AHI ($r = 0.457$; $p = 0.02$), sleep onset latency ($r = -0.480$; $p = 0.02$), and WASO ($r = 0.483$; $p = 0.01$). In contrast, none of the nocturnal oxygen saturation measurements, mean nocturnal SaO_2 ($r = -0.164$; $p = 0.56$) and mean low nocturnal SaO_2 ($r = -0.441$; $p = 0.07$), correlated significantly with the hypoxic response. On stepwise multiple linear regression analysis, the only significant correlation found was a positive one between WASO and $P_{0.1}$ response to hypoxia (multiple $r^2 = 0.634$; $p = 0.003$; Fig 2).
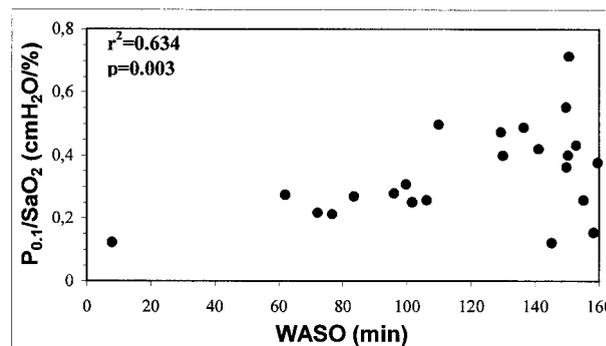
Relationship Between Hypoxic Response and Catecholamines

The nocturnal urinary excretion of epinephrine was higher in the OSA patients than in the control group (Table 1). No differences were observed in any of the other catecholamine urinary fractions among the groups.

In OSA patients, the $P_{0.1}/SaO_2$ ratio was related to nocturnal epinephrine urinary excretion ($r = 0.427$; $p = 0.04$). No significant relationship was found for the waking period ($r = 0.133$; $p = 0.53$). No significant correlations were found between the $P_{0.1}$ response to hypoxia and the diurnal or nocturnal urinary levels of norepinephrine or dopamine.

Relationship Between Catecholamines and BP

The relationship between nocturnal epinephrine excretion and BP values are depicted as a graph in Figure 3, which presents the scatter diagrams for SBP and DBP values, and for nocturnal excretion of epinephrine for the sleep and waking periods. Although the correlations for the sleep and waking BP measurements were of approximately similar orders of magnitude, all the correlations were higher for the sleep period.

Diurnal epinephrine excretion as well as diurnal and nocturnal levels of norepinephrine and dopamine in urine did not correlate with BP values.

Factors Contributing to BP

On stepwise multiple linear regression analysis, the only variable significantly correlated to BP values was the $P_{0.1}$ response to hypoxia. During the waking period, the $P_{0.1}/SaO_2$ ratio correlated to SBP (multiple $r^2 = 0.393$; $p = 0.003$), DBP ($r^2 = 0.326$; $p = 0.009$), and MBP ($r^2 = 0.364$; $p = 0.005$). Indeed, the $P_{0.1}/SaO_2$ ratio correlated to SBP values during sleep (multiple $r^2 = 0.338$; $p = 0.001$), to
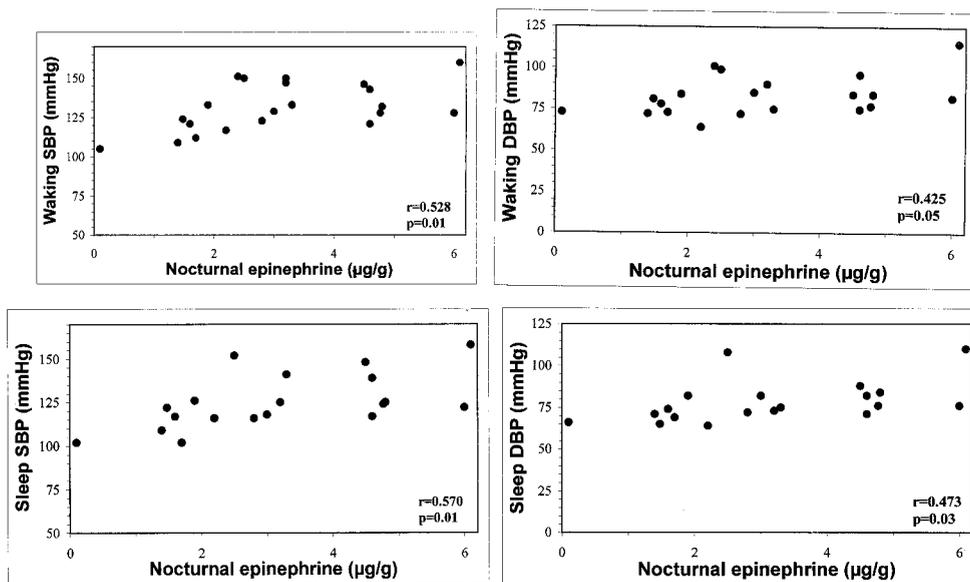
FIGURE 3. Correlation between nocturnal epinephrine urinary excretion and BP in OSA patients.

DBP values ($r^2 = 0.339$; p = 0.011), and to MBP values ($r^2 = 0.461$; p = 0.002). Figure 4 shows the relationship between the $P_{0.1}/Sao_2$ ratio and BP values.

DISCUSSION

The main results of our study comparing three type of OSA patients and control subjects are the following[1]: OSA sensitivity to hypoxia differs accord-ing to the patient's circadian variation in BP; type 1 OSA patients have a lower sensitivity to hypoxia than type 2 OSA patients and control subjects; type 1 and type 2 OSA patients have a lower chemosensitivity than type 3 OSA patients[2]; the sensitivity of OSA patients to hypoxia is related to sleep fragmentation but is not associated with nocturnal hypoxemia; and the nocturnal urinary epinephrine concentration is related to hypoxic responsiveness.

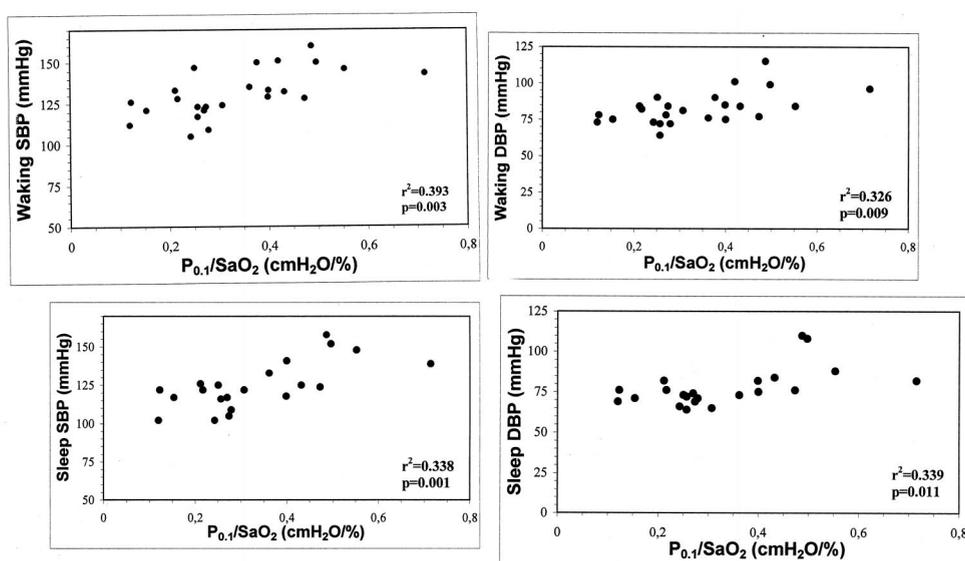The decreased hypoxic response observed in normotensive (type 1) OSA patients has been

FIGURE 4. Relationship between $P_{0.1}/Sao_2$ ratio and BP in OSA patients; see Figure 1 legend for definition.

previously reported. Generally, it is accepted that OSA patients have a reduced sensitivity to hypoxia. Krieger et al[18] described a group of OSA patients with impaired hypoxic ventilatory responses. Recently, it has been suggested that the decreased $P_{0.1}$ response to hypoxia in patients with OSA may be due to an abnormality in dopaminergic mechanisms in peripheral chemoreceptors.[19]

The mechanism of the altered hypoxia responsiveness in this group of OSA patients is not well established.[20] However, it seems probable that the diminished hypoxic response represents a specific adaptation to the repeated hypoxia induced during apneas.[21] It is known that a reduction in ventilatory response to hypoxia occurs during both short-term and long-term hypoxic exposure.[22] Although only very limited data exist on ventilatory changes during repeated episodes of hypoxia,[21] the reduced hypoxic $P_{0.1}$ response of normotensive OSA patients could represent an adaptive response to the hypoxic environment. Previous studies indicated that adaptation to sustained hypoxia may result from changes in either carotid chemoreceptors or central hypoxic sensitivity. The latter may be due either to altered central processing of afferent carotid-body stimuli or to a change in direct CNS sensitivity to hypoxia.[22]

The most striking finding in the present study is the higher $P_{0.1}$ response to hypoxia in type 2 and type 3 OSA patients than that in type 1 OSA patients (Table 2). Animal experiments have suggested that increasing peripheral chemosensitivity may lead to BP elevations.[23] Enlargement of the carotid body is commonly found in cases of primary hypertension.[5] Moreover, an augmented ventilatory response to hypoxia has been shown in young subjects with mild hypertension.[24]

The evidence suggesting an abnormal chemoreceptor function in hypertensive OSA patients comes from different studies. It has been reported that OSA patients, either normotensive or hypertensive, develop a hypertensive response to hypoxia during wakefulness. However, the pressure response to hypoxia did not correlate with daytime BP.[11] Alternatively, Tafil-Klawe et al[25] reported that OSA patients have a lower reactivity in their carotid chemoreceptors than control subjects, which possibly is related to their increased upper Raw, although hypertensive OSA patients have a higher peripheral chemosensitivity than normotensive OSA patients. In this way, another study shows that ventilatory responses to hypoxia were higher in hypertensive patients than in normotensive OSA patients.[26]

The present report demonstrates that hypertensive OSA patients have a greater peripheral chemosensitivity than normotensive OSA patients. Moreover, in our OSA patients, the $P_{0.1}$ response to hypoxia was the only independent factor related to BP. The relationship between $P_{0.1}$ response to hypoxia and the waking and sleep BP values described in our patients (Fig 4) is further evidence that the systemic hypertension of OSA patients is in part mediated by peripheral chemoreceptors.

The sequence of events leading to an increase in peripheral chemoreceptor sensitivity in hypertensive OSA patients is unresolved, but it has been proposed that in these patients the carotid chemoreceptor output may reset to a higher level as a result of recurrent episodic hypoxia.[11] Nevertheless, results from our study do not support this hypothesis. In our OSA patients, the degree of the nocturnal SaO_2 does not seem to contribute to the $P_{0.1}$ response to hypoxia. Results from several studies suggest that hypoxia is not the only cause of OSA-induced systemic hypertension.[27] Ringler et al[28] demonstrated that postapneic arterial pressure elevations are similar in patients with apneas that are recorded while they are receiving oxygen supplementation and in those patients with apneas that are recorded without the patient receiving oxygen supplementation.

On the other hand, some evidence suggests a hypertensive role of the arousal reaction. It has been described that acoustic arousals in OSA patients who are sleeping without apnea or hypoxemia who are receiving nasal continuous positive airway pressure are sufficient to reproduce the increases in BP that followed apnea in the same patients.[28] BP increases related to the magnitude of arousals and inspiratory efforts also have been described in patients with upper Raw syndrome and in nonapneic snorer subjects.[29,30] Indeed, in our patients, multiple linear regression analysis shows that the $P_{0.1}$ response to hypoxia is only significantly related to WASO, a sleep fragmentation index (Fig 2). Therefore, repetitive abrupt arousals from sleep could be more important contributors to the increase of the peripheral chemoreceptor output than hypoxia. Measurements of cortical or autonomic arousal might better reflect sleep fragmentation, but it is known that nocturnal BP monitoring increases the number of arousals.[31]

It has been reported that the termination of obstructive apnea and the arousal are mediated by the excitation of the reticular formation through inputs from medullar respiratory neurons that are stimulated by afferent mechanoreceptor impulses arising from the respiratory muscles during inspiratory efforts against the occluded airway.[32] In this sense, it could be hypothesized that repeated increases in nocturnal sympathetic activity, which are linked to arousals, may contribute to the increase in peripheral chemosensitivity. Alternatively, the activation of reticular formation also could lead to a higher central transduction of chemoreceptor activity.

Several studies have shown that an increase in sympathetic tone in the peripheral vasculature is most likely a significant contributor to the BP increase in OSA patients. In these patients, elevated sympathetic nerve traffic and circulating levels of catecholamines have been demonstrated not only during sleep and apneic events, but also during resting waking periods.[8] A biochemical assessment of sympathetic activity has been widely used, but the information obtained by such techniques is controversial. Some authors[33,34] reported that norepinephrine levels are increased in subjects with apnea but failed to relate norepinephrine and BP. In contrast, we found a relationship between nocturnal epinephrine levels and values for waking and sleep BP (Fig 3). The role of epinephrine was previously emphasized by Marrone et al.[35] They demonstrated that both norepinephrine and epinephrine were elevated in subjects with OSA, but while norepinephrine levels decreased at night, urinary epinephrine levels remained elevated. Only epinephrine excretion decreased on the subsequent night, with the elimination of apnea by nasal continuous positive airway pressure.

The etiology of sympathetic nervous system activation in sleep apnea is unknown. Our results suggest a relationship between peripheral chemosensitivity and nocturnal epinephrine levels. There is some evidence supporting a role for carotid bodies in catecholamine secretion. In rats, it has been demonstrated that peripheral chemoreceptor stimulation releases catecholamines from the adrenal medulla.[36] Moreover, it is well established that catecholamines are synthesized by glomus cells, stored in secretory granules, and released during carotid body stimulation.[37,38] There is a strong temporal relationship between changes in chemoreceptor nerve activity and changes in catecholamine secretion.[37,38]

In conclusion, the findings of the present study suggest a possible mediating role of peripheral chemosensitivity in the association between sleep apnea and hypertension.

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