Catecholamines and Blood Pressure in Obstructive Sleep Apnea Syndrome*

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To evaluate the release of catecholamines and their relationship with systemic blood pressure (BP) in normotensive patients with obstructive sleep apnea syndrome (OSAS), diurnal and nocturnal urinary norepinephrine (NE) and epinephrine (E) excretion in 12 normal subjects and in 10 OSAS patients were compared; in addition, nocturnal NE and E excretion were measured in the patients while receiving short-term CPAP. Blood pressure was continuously monitored in the patients during both nights of urine collection. In normal subjects, both NE and E excretion decreased from day to night. In the patients without CPAP, only NE excretion decreased at night, and BP increased from wakefulness to sleep; both NE and E excretion were higher in patients than in normal subjects. With CPAP, which prevented apneas, only E excretion decreased with respect to the previous night, while BP no longer increased during sleep. The extent of nocturnal E decrease with CPAP was not correlated to BP variations. These results suggest that in normotensive OSAS subjects, sympathetic nervous system activity, based on NE excretion, is continuously increased and is not affected by short-term CPAP treatment. Conversely, adrenal activity, based on E excretion, is also increased, but it tends to be normalized by short-term CPAP. No clear relationship could be found between sympatho-adrenal behavior and BP during sleep.
(Chest 1993; 103:722-27)

AHI = apnea-hypopnea index; BMI = body mass index; BP = blood pressure; CPAP = continuous positive airway pressure; E = epinephrine; NE = norepinephrine; OSAS = obstructive sleep apnea syndrome; Pd = diastolic blood pressure; Ps = systolic blood pressure; SaO_2 = oxyhemoglobin saturation.

Obstructive sleep apnea syndrome (OSAS) profoundly affects systemic blood pressure (BP). During sleep, BP decreases in the early portion of apneas, slowly increases in the late apneic portions, and undergoes a sudden and marked increase at the resumption of ventilation.[1-3] Besides showing these BP oscillations during sleep, many patients with OSAS are hypertensive during wakefulness.[4]

Although the pathogenesis of BP oscillations during apneas is not fully understood, catecholamines are suspected to play some role. Furthermore, an increased norepinephrine (NE) release could contribute to sustain high diurnal BP in OSAS patients.[5] Several studies have been published about the behavior of NE and epinephrine (E) secretion in OSAS, as well as about the effects of treatment on their release.[5-12] Nevertheless, some points may need further clarification. Since apneas recur only during sleep, thus mainly at night, they could be expected to alter the circadian rhythm of catecholamine release. However, most studies explored catecholamine release in OSAS only in the nocturnal hours.[7-12] In addition, the same studies did not compare the results obtained in OSAS patients with those of a control sample. Only one study distinguished between diurnal and nocturnal excretion, and compared results between OSAS subjects and controls:[5] however, it examined only hypertensive OSAS patients and hypertensive control subjects. To our knowledge, no study has been performed to compare the circadian excretion of catecholamines in OSAS patients normotensive during wakefulness and in normotensive non-OSAS subjects.

Since catecholamines may be involved in the pathogenesis of both diurnal and nocturnal hypertension, we chose to study the circadian excretion of NE and E in OSAS patients who were normotensive during wakefulness. These results were compared with those obtained in normal subjects and were related to the behavior of nocturnal BP in the patients, both during control conditions and during the application of nasal continuous positive airway pressure (CPAP).

Methods

Ten patients, nine male and one female, affected by OSAS were studied: their characteristics are shown in Table 1. Nine subjects were normotensive, and one was mildly hypertensive during wakefulness (140/95 mm Hg), but was not receiving antihypertensive treatment. Patients were requested to collect urine samples separately from 6 AM to 10 PM (day) and from 10 PM to 6 AM (night). Twelve normal normotensive subjects (BP 118 ± 5.2/72 ± 3 mm Hg) (mean ± SE), 10 male and 2 female, aged 43.8 ± 3.9 years, who were not habitual snorers, with a BMI of 23.1 ± 0.7 kg/m² were requested to collect urine samples during 1 day in the same intervals.

Urine specimens for each sample were collected in polyethylene containers, acidified with HCl 6M as preservative, and stored at −30°C before analysis.

In the same night when they were collecting urine specimens,

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This work was supported by the Italian National Research Council (CNR) Targeted Project "Prevention and Control of Disease Factors," Subproject "Control of Cardiovascular Disease."
Manuscript received March 27; revision accepted July 7.
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Table 1—*Characteristics of the Patients*

Characteristic	Mean ± SE
Age, yr	48.5 ± 3.6
BMI, kg/m²	40.9 ± 2
Systolic BP, mm Hg	129 ± 3.7
Diastolic BP, mm Hg	77 ± 3.3
PaO_2, mm Hg	74.7 ± 2.7
$PaCO_2$, mm Hg	44.3 ± 1.4
FEV_1/FVC, %	76.6 ± 1.6

patients were subjected to polysomnography, lasting from 10 PM to 6 AM. In addition to the commonly monitored signals, BP was continuously monitored (Finapres 2300 TM Ohmeda) and SaO_2 was monitored by an ear oximeter (Biox 3700 Ohmeda). One night later, between 10 PM and 6 AM, patients were subjected to one more polysomnographic study during which nasal CPAP was applied and regulated at the proper level in order to prevent apneas.[13] At the same time, patients were requested to repeat the nocturnal collection of urine specimens.

All the urine samples were purified with alumina; after the addition of 3,4 dihydroxybenzilamine (internal standard) and tris-EDTA buffer at a pH of 8.6, they were agitated for 10 min and centrifugated; the supernatant was discarded. Alumina was washed with water and eluted with acetic acid 0.25M. The eluate was filtered and injected in a system (Beckman HPLC) (the analytical column was a Beckman C-18 RP). An electrochemical detector (ESA) (consisting of a series of three electrodes working in the oxidation-reduction mode) was used. The intra-assay coefficient of variability was <5 percent for NE and <6 percent for E. The results were expressed in terms of microgram per gram of creatinine.

Differences in excretion in NE and, respectively, E, between day and night as well as between untreated patients and control subjects were assessed, after two-way analysis of variance, by pairwise comparisons with the Newman-Keuls test. Differences in nocturnal excretion of NE and, respectively, E in patients without and during CPAP application were tested by two-tailed Student's *t* test. The variation in E excretion in each patient between the nights without treatment and with CPAP application was evaluated in terms of percentage of change (E during CPAP * 100/E without CPAP).

On each sleep study, apnea-hypopnea index (AHI) (No. of apneas and hypopneas per hour of sleep time) mean lowest SaO_2 (mean of all the lowest values of SaO_2 recoded at the end of apneas) and mean SaO_2 in the whole recording period were calculated.

Nocturnal BP was analyzed, separately for systolic (Ps) and diastolic (Pd) values, as well as for wakefulness and sleep. For the night without CPAP, Ps and Pd values during wakefulness were obtained by sampling and averaging values relevant to one cardiac cycle each minute, while BP appeared stable; as regards sleep, one of every three apneas was selected: lowest Ps and Pd values during these apneas, as well as highest Ps and Pd following them, were measured and separately averaged for each patient. Statistical analysis of variations in Ps and, respectively, Pd among mean wakefulness values, mean lowest apneic values, and mean highest postapneic values were performed using a one-way analysis of variance and pairwise comparisons using the Newman-Keuls test. For the night with CPAP, both wakefulness and sleep BP levels were calculated sampling Ps and Pd values recorded during one cardiac cycle each minute and averaging them; when residual apneas were present during sleep, the mean value between highest and lowest Ps and Pd was taken into account. The differences between mean Ps and respectively Pd values during wakefulness and sleep were assessed with two-tailed Student's *t* test for paired data.

Values of $p<0.05$ were considered significant.

Results

Characteristics of sleep structure and respiration during sleep in the patients are shown in Table 2. The AHI decreased in all patients with CPAP application, although in some of them it remained higher than normal, due to more time required to set CPAP at the proper level: in any case, residual apneas and hypopneas were shorter and associated with a smaller SaO_2 fall than during the study without CPAP.

Table 2—*Characteristics of Sleep and Respiration in the Patients**

CPAP		TST, min	REM, %TST	AHI No./h	Mean Lowest SaO_2, %	Mean SaO_2, %
Without	Mean	346	18	75	79	87.4
	SE	17	3	5	2	1.7
With	Mean	347	25	10	86	92.4
	SE	19	2	2	1	0.4

*TST = total sleep time; REM = rapid eye movement; AHI = apnea-hypopnea index; CPAP = continuous positive airway pressure.

Mean BP levels during wakefulness and sleep, both without and with CPAP, are shown in Figure 1. Blood pressure increased at the end of apneas much more than it decreased during the events, suggesting that the overall effect of apneas was to increase the mean BP level during sleep. The BP variations were more

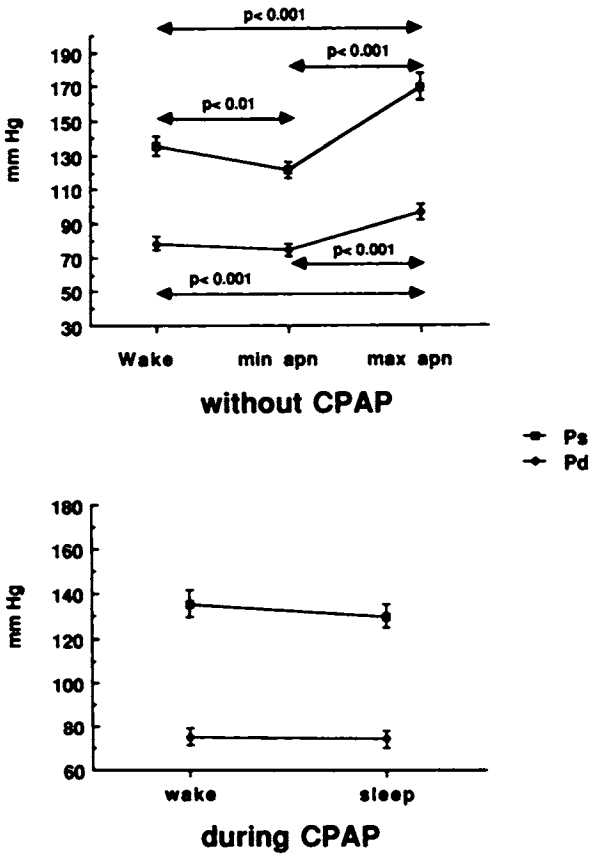

FIGURE 1. Systolic BP (Ps) and diastolic BP (Pd) (mean ± SE) in the ten patients during wakefulness and sleep. *Upper panel:* night without continuous positive airway pressure (CPAP). The sleep values recorded in the early portion of apneas (min apn) and soon after apneas (max apn) are shown. *Lower panel:* night during CPAP.

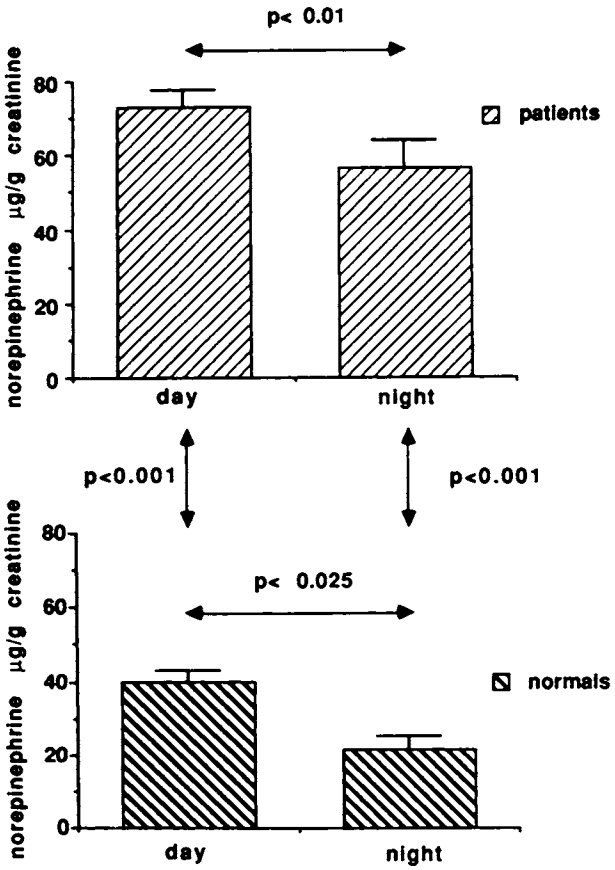

FIGURE 2. Norepinephrine (NE) (mean ± SE) excreted with urine specimens. *Upper panel:* patients; *lower panel:* control subjects. *Left columns:* diurnal hours; *right columns:* nocturnal hours.

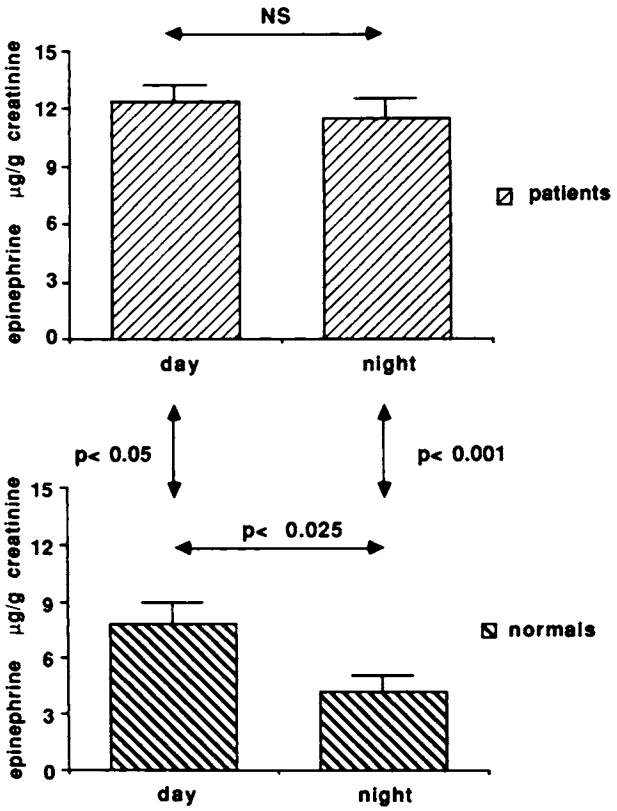

FIGURE 3. Epinephrine (E) (mean ± SE) excreted with urine specimens. *Upper panel:* patients; *lower panel:* control subjects. *Left columns:* diurnal hours; *right columns:* nocturnal hours.

marked for systolic than for diastolic values. CPAP was not associated with significant variations in BP during sleep with respect to wakefulness; therefore, CPAP prevented nocturnal BP increase.

The 24-h NE excretion levels in both patients and control subjects are shown in Figure 2. Nocturnal NE excretion decreased similarly in the patients (by 17.9 ± 4 µg/g of creatinine, $p<0.01$, nocturnal vs diurnal values) and in control subjects (by 18.1 ± 2.5 µg/g of creatinine, $p<0.025$). However, both the diurnal and the nocturnal NE excretions were much higher in the patients than in the control subjects ($p<0.001$).

The 24-h E elimination levels are shown in Figure 3. No significant nocturnal reduction in E elimination was found in the patients (−0.81 ± 0.9 µg/g of creatinine) while in the control subjects E decreased significantly at night (−3.6 µg/g of creatinine, $p<0.025$). The difference in E elimination between patients and control subjects was significant ($p<0.05$), but small in the diurnal sample, while it was highly significant in the nocturnal sample ($p<0.001$).

Nocturnal CPAP administration in the patients was associated with an unmodified NE elimination, and with a significant reduction in E excretion ($p<0.002$) (Fig 4).

The only patient with mild diurnal hypertension showed NE and E elimination levels that were in the average of the range showed by all the patients.

Since CPAP decreased nocturnal E excretion and normalized BP oscillations, we wondered whether the percentage of change in E could be related to BP oscillations during apneas without CPAP; we could not show any significant correlation between these variables. Similarly, the variation in E excretion did not correlate with the decrease in the number of apneas or the increase in mean SaO_2 during CPAP application (Table 3).

DISCUSSION

The results of this study show that in normotensive OSAS subjects, NE and E excretion is higher than in normal subjects both during the day and at night; however, while for NE the difference between OSAS patients and normal subjects is similar in the diurnal and nocturnal hours, for E the difference is more evident in the nocturnal hours. In fact, NE decreases at night with respect to the day similarly, in absolute terms, in patients and in normal subjects, while E decreases only in normal subjects. CPAP, which can prevent the increase in both Ps and Pd that occurs with apneas, results in a decrease in nocturnal E, but not in NE.

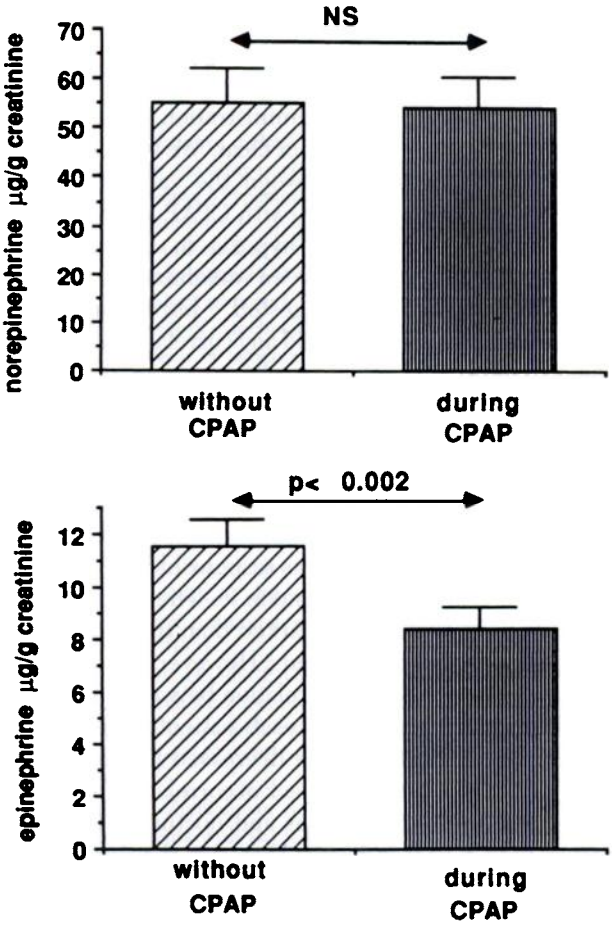

FIGURE 4. Nocturnal excretion of norepinephrine (NE) *(upper panel)* and epinephrine (E) *(lower panel)* (mean ± SE) in the patients. *Left columns:* without continuous positive airway pressure (CPAP); *right columns:* during CPAP.

Both NE and E can rapidly affect BP, but their effects and their origin differ.[14] Norepinephrine induces a generalized vasoconstriction and an increase in both systolic and diastolic BP. It is both a hormone secreted by the adrenal medulla and the postganglionic sympathetic nervous system mediator: NE released at the synaptic level reaches to some extent the bloodstream, so that plasma NE is believed to reflect sympathetic nervous system activity. Epinephrine increases cardiac output and systolic BP. It is only released in the bloodstream by the adrenal medulla. Since both NE and E are excreted with urine, either after metabolization or unmodified, it is possible to derive indications on sympathetic nervous system and adrenal medulla activity by measuring urinary catecholamine excretion. We chose to perform urinary rather than plasma measurements of catecholamines since we believe that urinary measurements may reflect more closely the average level of catecholamine release during prolonged periods. This may account for some differences between our results and others based on plasma measurements.[8,11] Although catecholamines are mostly excreted in urine as their metabolites, the small urinary quantities of unmodified NE and E are believed to closely reflect the total release of catecholamines.[15]

Table 3—*Correlation Coefficients of Percentage of Epinephrine Variation Between the Two Nights With Polysomnographic Data**

E variation (%)—mean apneic Ps increase, mm Hg	−0.117
E variation (%)—apnea number reduction, %	0.173
E variation (%)—variation in mean SaO_2, %	0.383

*E = epinephrine, Ps = systolic blood pressure.

Before discussing the main results of this study, the composition of our control sample deserves some comment. Normal subjects were selected with age similar to our patients, since it has been demonstrated that NE release increases with age.[16,17] As regards gender, although no difference has been reported between male and female subjects,[18] we were able to find a sample where, like in our patients, men were much more numerous than women. We were not able to match control subjects and patients also for weight. The effect of body weight on sympathetic activity is controversial; some authors reported a positive,[19,20] some authors reported a negative,[21] and others reported no correlation[22,23] between the level of obesity and the sympathetic nervous system activity. However, since OSAS is common in obese subjects, it would be hypothesized that the reported increase in sympathetic activity in obese subjects, when present, was related at least in part to undiagnosed OSAS. In fact, in the only study in which obese subjects with and without OSAS were compared,[5] the OSAS subjects showed a higher NE excretion, suggesting a possible additive effect of obesity and OSAS on catecholamine release.

The results concerning NE show that an elevation of this hormone in OSAS in both nocturnal and diurnal hours, already pointed out in hypertensive subjects,[6] can also be found in normotensive subjects. Clark et al,[6] in an early study, had also shown an elevated 24-h elimination of catecholamines in OSAS; however, they did not report data relevant to each catecholamine or separately evaluate diurnal and nocturnal elimination of catecholamines. In another study, Ehlenz et al[7] showed that OSAS subjects with a history of severe hypertension have higher nocturnal NE levels than other OSAS patients, but they did not measure daytime NE levels; in addition, nocturnal NE did not correlate with BP levels during sleep.

The persistent elevation of NE levels in OSAS suggests that sympathetic activity in this syndrome is constantly elevated. A similar conclusion was also reached by Hedner et al:[24] these authors used a microneurographic technique and found that peroneal nerve activity during wakefulness is higher in OSAS

patients than in normal subjects. However, the mechanisms accounting for the continuously increased sympathetic activity in OSAS are still unexplained.

As regards nocturnal BP behavior, our data do not support the hypothesis of a role of NE and of the sympathetic nervous system in influencing it. In fact, NE tended to decrease at night, similarly in OSAS patients and control subjects; conversely, BP during sleep in OSAS subjects increased, while it has been shown that in normal subjects it decreases.[25-27] In addition, nasal CPAP prevented nocturnal BP elevation but left NE elimination unchanged. These results suggest that apnea recurrence is not associated with an immediate modification of the mean level of sympathetic nervous system activity. It is still possible, however, that sympathetic activity during apneas undergoes marked oscillations, consisting of increasing activity alternated to marked activity falls, without change in the mean level of NE reaching the bloodstream with respect to undisturbed sleep. Actually, Hedner et al[24] have demonstrated a similar oscillation in the rate of discharge of the peroneal nerve in the sleep apneic cycles.

Our result, showing no effect of one-night CPAP administration on NE, is in agreement with data reported by Krieger et al.[9] Conversely, Baruzzi et al[12] found that one-night CPAP decreased NE elimination. Although in our study some apneas and hypopneas were still observed during CPAP application, the large improvement with CPAP (mean decrease in AHI, 87 percent) makes it unlikely that residual apneas and hypopneas could be the cause of the unmodified nocturnal NE excretion. On the other hand, the effect of a more prolonged treatment was also reported: after 7 days of CPAP treatment, Jennum et al[10] did not find any decrease in NE, while Fletcher et al[5] found a decrease only in some patients after tracheostomy. A limitation of our study design could be that we did not study the effects of CPAP application on control subjects. It cannot be excluded that CPAP application, by causing discomfort, influences catecholamine release. However, CPAP is tolerated worse by normal subjects than by patients with severe OSAS, as in ours. Therefore, finding an increased catecholamine excretion in normal subjects after CPAP administration would not necessarily imply that a similar effect occurs in OSAS patients.

As regards E, we found that unlike control subjects, the patients did not show any decrease in E excretion in the nocturnal with respect to the diurnal hours; therefore, although E excretion was higher in the patients than in the control subjects in the diurnal hours, this difference was much more marked in the nocturnal hours. Similarly, in hypertensive OSAS subjects,[5] a difference in E excretion with respect to control subjects was found only in the nocturnal hours. This finding suggests that apneas have an immediate influence on E release. This hypothesis is also supported by our finding of a decrease in nocturnal E elimination during CPAP administration. How apneas may influence E release is not clear. We were not able to find any correlation between the variations in E excretion and in mean SaO_2 with CPAP, which would have suggested a role of hypoxia in increasing E release. A relationship between wakefulness state and increase in E has been suggested,[28] but is controversial.[17] Again, we could not find any correlation between the variation in E release and in number of apneas with CPAP, which would have suggested a role of arousals and sleep fragmentation in increasing E release. Since CPAP reduced E excretion while preventing BP increase, we wondered if these results could be related. It could be hypothesized that E increase at night in OSAS was responsible for periodic increases in cardiac output and in Ps. The Ps variations during apneas were more marked than those of Pd, as had been previously observed.[3] However, we were not able to find a significant correlation between mean BP oscillation during apneas in each patient (which were prevented by CPAP) and the decreased E elimination with CPAP; in addition, the lack of correlation between decreased number of apneas and nocturnal E elimination with CPAP indicates that also the number of BP oscillations is not correlated with E release. Actually, the effects of OSAS treatment on E reported so far are conflicting. Tracheostomy, in one study,[6] and CPAP, in two studies,[9,12] did not affect nocturnal E elimination; conversely, Jennum et al[10] found a reduction in plasma E after CPAP. Our results cannot completely rule out a role of E in BP oscillations in obstructive apneas. In fact, each subject could have a different pressure response to similar levels of the hormone; in addition, the variable contribution given to BP oscillations by many different pathogenetic factors could mask a possible effect of E.

In conclusion, our data suggest that OSAS is associated with a steadily increased sympathetic tone in 24 h, even when patients are normotensive during wakefulness; E is mainly increased at night, likely as an immediate consequence of apneas. A cause-effect relationship between BP swings in apneas and catecholamines could not be demonstrated.

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