Continuous Positive Airway Pressure Treatment Improves Baroreflex Control of Heart Rate during Sleep in Severe Obstructive Sleep Apnea Syndrome

Maria R. Bonsignore, Gianfranco Parati, Giuseppe Insalaco, Oreste Marrone, Paolo Castiglioni, Salvatore Romano, Marco Di Rienzo, Giuseppe Mancia, Giovanni Bonsignore

Istituto di Fisiopatologia Respiratoria, Italian National Research Council, Palermo; Clinica Medica 1, Milano-Bicocca University, Istituto Auxologico Italiano; Centro di Bioingegneria, Fondazione Don Carlo Gnocchi ONLUS, Milano and Politecnico di Milano, Milan; and Clinica Medica, Milano University, Ospedale San Gerardo, Monza, Italy

The role of the arterial baroreflex in the cardiovascular changes associated with the obstructive sleep apnea syndrome (OSAS), and the effect of nasal continuous positive airway pressure (CPAP) treatment on baroreflex function during sleep are unknown. Baroreflex control of heart rate was studied in 29 normotensive patients with OSAS under no treatment, in 11 age-matched control subjects, and in 10 patients at CPAP withdrawal after 5.5 ± 3.7 (range 3–14) months of treatment. Baroreflex control of heart rate was assessed by "sequence method" analysis of continuous blood pressure recordings (Finapres) obtained during nocturnal polysomnography. In untreated OSAS, baroreflex sensitivity (BRS) was low during wakefulness and non–rapid eye movement (REM) stage 2 sleep compared with control subjects, and correlated inversely with mean lowest Sa_{O_2} and the blood pressure increase after apneas. After CPAP treatment, the apnea-hypopnea index was lower, and mean lowest Sa_{O_2} higher than before treatment. After CPAP, patients were more bradycardic, blood pressure and its standard deviation decreased as Sa_{O_2} improved in non-REM stage 2 sleep, and BRS increased (nocturnal wakefulness: +59%; non-REM stage 2 sleep: +68% over pretreatment values). Our data suggest that baroreflex dysfunction in OSAS may be at least partly accounted for by nocturnal intermittent hypoxemia, and can be reversed by long-term CPAP treatment.

Keywords: sleep-disordered breathing; hypertension; autonomic nervous system

Marked cardiovascular fluctuations, secondary to hypoxia-induced sympathetic activation (1), arousal (2), and mechanical effects of airway obstruction (3) occur during sleep in obstructive sleep apnea syndrome (OSAS). However, the cardiovascular effects of OSAS extend beyond night-time: OSAS is associated with diurnal sympathetic hyperactivity (1) and increased blood pressure responsiveness to hypoxia (4, 5), both factors likely contributing to the pathogenesis of sustained systemic hypertension and a high risk for cardiovascular disease (6).

The role of the arterial baroreflex in OSAS-induced cardiovascular alterations during sleep and wakefulness is not completely defined. The arterial baroreflex normally buffers acute changes in blood pressure by feedback modulation of sympathetic activity and vascular resistance. During daytime, both decreased (7) and normal (8, 9) baroreflex control of heart rate (HR) were found in untreated patients with OSAS.

Therefore, decreased baroreflex efficiency in OSAS could potentiate sympathetic hyperactivity and apnea-associated peripheral vasoconstriction (10). Assessing baroreflex control of HR in OSAS might be clinically relevant, since a low baroreflex sensitivity (BRS) is an unfavorable prognostic indicator and a marker of autonomic dysfunction in diseases such as diabetes (11), chronic heart failure (12), and coronary artery disease (13).

Baroreflex activity cannot be directly assessed by nerve recording in humans, partly accounting for the limited knowledge on the effects of OSAS on baroreflex. However, because baroreflex activation/deactivation is associated with changes in the vagal discharge to the heart, baroreflex function can be explored by analyzing HR responses to pharmacologically-induced changes in blood pressure. During sleep, injection of vasoactive substances frequently causes arousal (14), a problem that may be overcome by a technique based on detection of baroreflex sequences (i.e., spontaneous changes in ECG R-R interval associated with blood pressure fluctuations), similar to the effects evoked by bolus injection of vasoactive drugs (15). Spontaneous BRS can be assessed as the sequence slope, as in the traditional method. Disappearance of spontaneous sequences after carotid denervation (16) strongly supports their baroreflex origin. Clinically, the sequence technique was shown to yield results similar to those obtained by the bolus injection method (17), and was employed to study circadian BRS changes in normotensive and hypertensive subjects (18, 19). In nonapneic, nondesaturating snorers, spontaneous BRS decreased during non–rapid eye movement (REM) sleep (20), suggesting that sleep-disordered breathing can impair baroreflex function. No studies have analyzed spontaneous BRS during sleep in untreated OSAS.

The effects of continuous positive airway pressure (CPAP) treatment on OSAS-induced autonomic dysfunction and cardiovascular alterations are still controversial. Acute CPAP application normalizes OSAS-induced high cardiovascular variability during sleep (21), but norepinephrine excretion remained high after a single CPAP night (22). After long-term CPAP, sympathetic hyperactivity during wakefulness decreased (23, 24) and autonomic stress tests improved (25–27) in patients with good compliance to treatment. Blood pressure during the daytime was reported to decrease (27–30) or remain unchanged (24). No studies have examined baroreflex control of HR and cardiovascular variables during sleep in OSAS after long-term CPAP.

In this study, we analyzed spontaneous baroreflex control of HR during sleep by the sequence technique in untreated patients with OSAS normotensive during wakefulness, and in healthy control subjects of similar age. Changes in baroreflex control of HR during sleep were assessed in 10 patients on the first night of CPAP withdrawal after prolonged CPAP treatment. This protocol was chosen to study CPAP-treated pa-

tients in conditions as similar as possible to those of the control study (31).

METHODS

Subjects

A total of 29 men, normotensive during wakefulness and with newly diagnosed OSAS, and 11 normal men of similar age were studied. Inclusion criteria were: (1) repeated office blood pressure measurements of greater than 140/90 mm Hg; (2) no clinical or laboratory evidence of chronic heart failure, hypertension, or other diseases causing autonomic dysfunction; and (3) no treatment with cardiovascular drugs. No subject reported habitual alcohol intake of more than 30 g/day or drug use. Caffeine intake was 2–4 cups/day in all subjects. A total of 5 control subjects and 15 patients with OSAS were current smokers (all control subjects and 4 patients with OSAS smoked 7 cigarettes or fewer per day, 7 patients with OSAS smoked 20 cigarettes or fewer per day, and 4 patients with OSAS smoked more than 20 cigarettes per day). Subjects were asked to refrain from caffeine and alcohol consumption and smoking on the day of the study.

The effects of CPAP treatment were analyzed in 10 of the 29 patients after at least 3 months of treatment. Body mass index (BMI) and office blood pressure were measured at entry and follow-up. No change in drinking or smoking habits was reported at follow-up. Mean nightly use of CPAP was calculated as the difference in ventilator hourly counts from beginning of treatment to post-CPAP study divided by the number of days of treatment. Polysomnography was obtained in the first night of CPAP withdrawal.

All subjects gave informed consent to the study, the protocol of which was approved by the ethics committee of one of the hospitals involved.

Measurements

Full nocturnal polysomnography (Somnostar 2000, SensorMedics Corporation, Yorba Linda, CA) was obtained in all subjects and conditions; recordings at CPAP withdrawal were obtained by the same equipment used at baseline. Arterial blood pressure was noninvasively monitored beat-by-beat (Finapres 2300, Ohmeda, Englewood, CO). Finger cuff inflation was stopped for 5 minutes every 40 minutes to prevent discomfort, and the hand to which the Finapres unit was applied was held in a constant position. The Finapres was held in autocalibration mode (automatic quality check).

Data Analysis

Sleep was scored in 30-second epochs according to standard rules (32). Only epochs recorded during nocturnal wakefulness, non-REM stage 2, and REM sleep were considered, due to the physiologic instability of non-REM stage 1 sleep and lack of slow-wave sleep in severe OSAS. Epochs without blood pressure recordings (periodic interruption, Finapres calibration, or blood pressure artifacts) were also excluded. Apnea was defined as an interruption of airflow lasting at least 10 seconds; it was scored as obstructive or central according to persistence or absence of thoracoabdominal movements, respectively. Mixed apneas started as central and subsequently developed obstructive features. Hypopnea was defined as airflow decreased by at least 50%, associated with decrease in Sa_{O_2} of 4% or more. All patients with OSAS showed predominantly obstructive events. The apnea–hypopnea index (AHI), mean Sa_{O_2} during wakefulness, and mean lowest Sa_{O_2} in non-REM stage 2 and REM sleep were calculated.

Short-term cardiovascular variability during nocturnal wakefulness, non-REM stage 2, and REM sleep was estimated in each subject by analyzing all 2-minute segments of the recording showing unchanged polysomnographic stage (32) and blood pressure signal for 85% or more of segment duration (to avoid inclusion of segments with periodic interruptions of Finapres recording). All sleep segments analyzed in patients with OSAS showed recurrence of obstructive apneas. Mean systolic (SBP) and diastolic (DBP) blood pressure and pulse interval (PI) over 2 minutes were calculated, and their standard deviations (SD) taken as estimates of variability. Mean highest and lowest blood-pressure values were calculated in non-REM sleep stage 2 apneas in each patient.

The baroreflex was studied by the sequence method (15, 18). Briefly, sequences of four or more consecutive beats where both PI and SBP progressively increased (+PI/+SBP) or decreased (−PI/−SBP) were identified. BRS was calculated as the slope of each sequence (milliseconds/mm Hg). In each subject, mean BRS and number of sequences/hour were calculated in each stage.

Statistical Analysis

Data were averaged for each group and polysomnographic stage and means ± SD were calculated. Student's t test was used to test for differences between control and OSAS groups (unpaired) and between untreated and treated OSAS groups (paired). The effects of group and sleep stages were analyzed by two-way analysis of variance with Bonferroni correction. The relationships between cardiovascular variables and BRS versus age, BMI, AHI, and mean lowest Sa_{O_2} were analyzed by simple linear regression. Results were statistically significant at $p < 0.05$.

RESULTS

Untreated OSAS and Control Subjects

Table 1 (left columns) reports anthropometric, daytime blood pressure and sleep data for control subjects and untreated patients with OSAS. Age was similar in both groups, but patients with OSAS showed a greater BMI and higher office blood

TABLE 1. CHARACTERISTICS OF THE SAMPLES

	Controls (n = 11)	Untreated OSAS (n = 29)	p*	OSAS before CPAP (n = 10)	OSAS at CPAP withdrawal	p†
Age, yr	40.0 ± 7.5	45.2 ± 8.5	NS	46.6 ± 8.9		
BMI, kg/m²	24.1 ± 9.5	35.2 ± 5.7	< 0.0001	34.7 ± 3.8	33.7 ± 4.0	NS
Office systolic BP, mm Hg	118.2 ± 13.3	131.4 ± 10.2	< 0.005	133.5 ± 8.8	133.5 ± 13.8	NS
Office diastolic BP, mm Hg	74.1 ± 7.0	85.2 ± 6.6	< 0.0001	84.5 ± 6.4	81.5 ± 9.7	NS
AHI	2 ± 1	77 ± 22	—	82 ± 14	63 ± 26	< 0.05
BP recording time, min	303 ± 86	298 ± 75	NS	260 ± 65	293 ± 68	NS
Nocturnal wakefulness, %‡	19.9 ± 7.5	15.4 ± 8.1	NS	16.9 ± 10.5	21.7 ± 15.7	NS
REM stage 2 sleep, %‡	52.7 ± 7.2	64.3 ± 10.6	< 0.005	64.8 ± 13.7	61.1 ± 17.6	NS
Slow wave sleep, %‡	6.1 ± 6.9	3.1 ± 6.0	NS	1.2 ± 2.2	1.5 ± 2.8	NS
REM sleep, % (n = 26)‡	12.1 ± 3.1	8.1 ± 4.1	< 0.01	8.2 ± 4.9	6.8 ± 3.8	NS
Sa_{O_2}-wakefulness, %	97.3 ± 0.8	95.6 ± 1.5	< 0.001	95.5 ± 1.3	95.7 ± 1.1	NS
Mean lowest Sa_{O_2} NREM, %	96.6 ± 1.0	81.2 ± 7.1	< 0.0001	85.5 ± 4.7	89.6 ± 2.6	< 0.01
Mean lowest Sa_{O_2} REM, %	96.2 ± 0.9	67.7 ± 12.7	< 0.0001	62.3 ± 16.2	68.9 ± 17.4	NS

Definition of abbreviations: AHI = apnea-hypopnea index; BMI = body mass index; BP = blood pressure; CPAP = continuous positive airway pressure; NREM = non–rapid eye movement; OSAS = obstructive sleep apnea syndrome; REM = rapid eye movement.

* Unpaired t test (normal subjects versus untreated OSAS).

† Paired t test (pre- versus post-CPAP).

‡ % refers to BP recording time (< 100%, data for non-REM stage 1 sleep not reported, *see text*).

pressure values, albeit in the normal range. OSAS was severe in our sample, as indicated by the AHI and Sa_{O_2} values recorded during sleep. Over an average 5-hour recording of blood pressure, REM sleep was identified in all control subjects and in 26 untreated patients with OSAS, its overall duration being slightly greater in the former than in the latter group. The percentage of non-REM stage 3–4 sleep was low in both groups. In patients with OSAS the supine position accounted for $71.4 \pm 21.4\%$ of total recording.

The mean number of 2-minute segments analyzed to assess cardiovascular variability was similar in control subjects (97 ± 34) and untreated patients with OSAS (94 ± 34), the highest percentage of segments being obtained in non-REM stage 2 sleep ($67 \pm 10\%$ in control subjects, $77 \pm 10\%$ in OSAS, p < 0.01). Mean SBP, DBP, and PI over 2-minute periods did not change significantly from supine wakefulness to sleep (Table 2). Both nocturnal SBP and DBP were markedly and significantly greater in patients with OSAS than in control subjects, whereas PI was markedly and significantly lower in patients with OSAS. Mean HR values in OSAS and control subjects, respectively, were: 76.8 ± 12.2 and 63.2 ± 7.1 beats per minute (bpm) during wakefulness; 70.3 ± 10.8 and 60.3 ± 7.0 bpm in non-REM stage 2; 68.3 ± 9.0 and 61.0 ± 6.8 bpm in REM sleep; (p < 0.01). Patients with OSAS showed much greater variabilities of SBP, DBP and PI, i.e., larger SD over 2-minute intervals during sleep than control subjects. During interapneic hypertensive peaks in non-REM stage 2 sleep, SBP increased from 123 ± 14 to 165 ± 18 mm Hg, and DBP increased from 61 ± 8 to 91 ± 10 mm Hg. Blood pressure increase after apneas did not correlate with age or AHI. In non-REM stage 2 sleep, mean lowest Sa_{O_2} correlated with SD of SBP ($r = -0.46$, p < 0.05) and mean PI ($r = 0.55$, p < 0.005). In REM sleep, mean lowest Sa_{O_2} correlated with mean SBP and DBP ($r = -0.46$, p < 0.05 for both), but not with SD of SBP, SD of DBP, mean PI, or SD of PI.

A large number of $+PI/+SBP$ and $-PI/-SBP$ sequences was recorded during polysomnography (i.e., 100 sequences or more per type per subject) in both control subjects and patients with OSAS. The number of sequences did not differ between OSAS and control subjects in any sleep stage (Figure 1, *upper panels*). BRS was significantly lower in patients with OSAS than in control subjects during wakefulness and sleep (Figure 1, *lower panels*). No significant difference in BRS was found between current smokers and nonsmokers in either group.

Spontaneous BRS in patients with OSAS, either during wakefulness or sleep, did not correlate with age, BMI, or AHI. There was, however, a significant correlation between mean lowest Sa_{O_2} and BRS (Figure 2) in non-REM sleep (i.e., the lower Sa_{O_2}, the lower BRS). The same correlation was not significant in REM sleep (Figure 2). Mean BRS in non-REM sleep was lowest in the patients showing marked SBP increase after apneas ($r = -0.45$, p = 0.01).

Effects of CPAP Treatment

The patients studied after CPAP treatment (Table 1, *right columns*) showed anthropometric characteristics, blood pressure during wakefulness, and OSAS severity in the untreated state similar to those of the entire OSAS group. Mean BMI did not differ between pre- and posttreatment studies. The mean CPAP level prescribed was 11.6 ± 2.5 cm H_2O. Average CPAP nightly use was 5.1 ± 1.6 hours, and mean treatment duration was 5.5 ± 3.7 months (range 3–14 months).

At CPAP withdrawal, AHI was lower compared with no treatment. Mean apnea duration was 27.9 ± 9.1 seconds under no treatment, and 26.1 ± 11.5 seconds at CPAP withdrawal (NS). Mean lowest Sa_{O_2} in non-REM stage 2 was higher at CPAP withdrawal than under no treatment (Table 1), with a similar trend in REM sleep (paired REM sleep data available in seven patients). Sleep structure (Table 1) did not differ between pre- and post-CPAP studies. The percentage of non-REM stage 3–4 sleep was low in both studies. Time spent supine did not differ between studies ($67.6 \pm 23.3\%$ versus $76.8 \pm 19.1\%$ of total recording). Similarly, sleep efficiency (total sleep time/time in bed) was $81 \pm 11\%$ pretreatment, and $78 \pm 14\%$ posttreatment (NS).

CPAP treatment did not affect blood pressure significantly, either during daytime (Table 1) or at night (Table 3). The number of 2-minute segments analyzed was similar in pre- (88 ± 33) and post-CPAP (97 ± 27) polysomnographies. Table 3 illustrates the main changes in SBP, DBP, and PI observed at CPAP withdrawal, as compared with no treatment conditions: (*1*) the trend to increased SD of SBP and DBP from wakefulness to sleep was blunted; (*2*) the SD of SBP and DBP in non-REM stage 2 sleep decreased; and (*3*) patients were more bradycardic (i.e., mean PI was higher) in nocturnal wakefulness and non-REM stage 2 sleep. Mean HR before and after treatment, respectively, was: 80.9 ± 12.9 bpm and 68.8 ± 9.7 bpm during wakefulness; 73.2 ± 12.9 and 65.7 ± 9.0 bpm in non-REM stage 2; 66.6 ± 5.6 and 65.3 ± 9.0 bpm in REM

TABLE 2. SHORT-TERM VARIABILITY AND UNPAIRED *t* TESTS OF SYSTOLIC BLOOD PRESSURE, DIASTOLIC BLOOD PRESSURE, AND PULSE INTERVAL DURING NOCTURNAL WAKEFULNESS AND SLEEP IN NORMAL SUBJECTS AND PATIENTS WITH OBSTRUCTIVE SLEEP APNEA SYNDROME
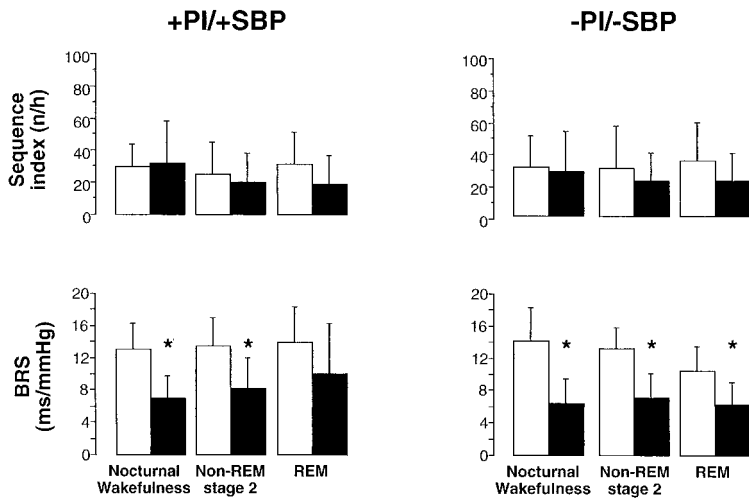
Sleep Stage	Mean SBP (*mm Hg*)			SD of SBP (*mm Hg*)			Mean DBP (*mm Hg*)		
	Normal Subjects	Patients w/ OSAS	p	Normal Subjects	Patients w/ OSAS	p	Normal Subjects	Patients w/ OSAS	p
Nocturnal wakefulness	117.1 ± 19.6	134.6 ± 15.0	0.005	7.4 ± 2.0	$11.1 \pm 3.7^*$	< 0.005	67.4 ± 13.3	77.3 ± 9.5	< 0.01
Non-REM 2	110.1 ± 16.9	134.5 ± 15.5	0.0001	6.0 ± 0.8	15.6 ± 4.3	< 0.0001	62.3 ± 11.3	73.7 ± 8.4	< 0.001
REM	122.3 ± 19.3	143.5 ± 21.4	< 0.01	7.6 ± 1.6	15.6 ± 4.1	< 0.0001	66.9 ± 13	78.0 ± 9.4	< 0.01

Sleep Stage	SD of DBP (*mm Hg*)			Mean PI (*ms*)			SD of PI (*ms*)		
Nocturnal wakefulness	4.2 ± 1.3	$6.2 \pm 1.9^*$	< 0.005	961 ± 113	$798 \pm 113^\dagger$	< 0.0005	73 ± 20	$58 \pm 21^*$	< 0.05
Non-REM 2	3.2 ± 0.7	8.7 ± 2.0	< 0.0001	$1,007 \pm 120$	871 ± 119	< 0.005	58 ± 12	90 ± 28	< 0.001
REM	4.3 ± 1.0	9.4 ± 2.5	< 0.0001	995 ± 107	892 ± 108	0.01	74 ± 26	114 ± 51	< 0.05

Definition of abbreviations: DBP = diastolic blood pressure; OSAS = obstructive sleep apnea; PI = pulse interval; REM = rapid eye movement; SBP = systolic blood pressure.
* Wakefulness data different from non-REM stage 2 and REM sleep data (p < 0.0005).
† Wakefulness data significantly different from REM sleep data (p < 0.005).
Unpaired *t* test applied to test for differences between groups; ANOVA applied to test for differences among sleep stages in each group.

Figure 1. Spontaneous baroreflex control of HR during sleep in normal subjects (*open bars*) and untreated patients with OSAS (*filled bars*). +PI/+SBP and −PI/−SBP refer to hypertension/bradycardia and hypotension/tachycardia sequences, respectively (for details, *see* text and [16]). *Upper panels*: mean number of sequences per hour recorded in each polysomnographic stage; *lower panels*: mean sequence slope (BRS). *Asterisks* indicate significant differences between control and OSAS groups (p < 0.0005).

sleep (p < 0.01). After treatment, nocturnal HR in OSAS was close to the values found in control subjects. Mean SBP and DBP, and SD of SBP in non-REM stage 2 sleep, decreased in those patients showing an increased mean lowest Sa_{O_2} after treatment ($r = -0.91$, -0.86, and -0.85, respectively, p < 0.002 for all regressions, Figure 3); SD of DBP showed a similar trend (p = 0.05, Figure 3). The improvement in mean lowest Sa_{O_2} after treatment mostly occurred in young patients (ΔSa_{O_2} between studies versus age: $r = -0.79$, p < 0.01). Accordingly, age was positively associated with post-treatment changes in mean SBP during non-REM sleep ($r = 0.77$, p < 0.01). Conversely, no significant correlation was found between improved mean lowest Sa_{O_2} and changes in mean PI or its SD in any sleep stage (data not shown).

After CPAP treatment, mean BRS increased compared with pretreatment during nocturnal wakefulness and non-REM stage 2 sleep, but not in REM sleep (Figure 4). Mean BRS increased from 5.0 ± 1.7 to 8.0 ± 2.9 milliseconds/mm Hg during nocturnal wakefulness (+59%, p < 0.01), and from 5.6 ± 1.5 to 9.3 ± 3.6 milliseconds/mm Hg in non-REM stage 2 sleep (+68%, p = 0.005). Corresponding values in REM sleep were 6.9 ± 2.9 and 7.2 ± 2.8 milliseconds/mm Hg (NS). The number of sequences per hour was similar before and after treatment, the only exception being a small decrease in +PI/+SBP sequences during wakefulness after CPAP (Figure 4).
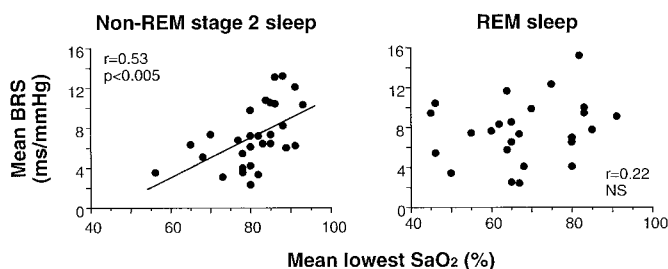
Figure 5 shows the change in mean BRS from pre- to post-treatment condition in the individual patients. The change in BRS after CPAP (ΔBRS) did not correlate with age, treatment duration, mean nightly use of CPAP, or the BRS value recorded under no treatment. No significant relationship was found between ΔBRS after treatment and changes in AHI or

apnea duration. BRS for −PI/−SBP sequences increased after treatment as mean lowest Sa_{O_2} in non-REM stage 2 sleep increased ($r = 0.66$, p = 0.01). Apnea-induced hypertensive peaks were significantly lower after CPAP (p < 0.05 by paired *t* test), but their change after treatment did not correlate with ΔBRS.

DISCUSSION

Our study indicates that baroreflex control of HR during sleep: (*1*) was impaired in severe untreated OSAS, and (*2*) improved significantly after CPAP treatment. Spontaneous BRS was much lower in patients with OSAS compared with normal subjects, and was lowest in the patients with the highest apnea-induced hypertensive peaks, supporting the hypothesis that baroreflex dysfunction may contribute to OSAS-induced cardiovascular changes. Significant relationships were found in non-REM sleep between mean lowest Sa_{O_2} and BRS under no treatment, and between improved nocturnal Sa_{O_2} after CPAP and changes in BRS, mean SBP and DBP, and SBP variability, suggesting a role of hypoxemia in OSAS-induced baroreflex dysfunction. However, because intrathoracic pressure swings during apneas may also decrease after prolonged CPAP treatment (33), the possibility that changes in the mechanical effects of OSAS might contribute to the observed improvement in baroreflex function cannot be excluded. Whatever the mechanism, the increased BRS after treatment supports the concept that long-term CPAP improves cardiovascular control in OSAS.

Before discussing the results, some methodologic issues should be addressed. The sequence technique has been validated in experimental animals (16) and humans (17), and employed in different clinical conditions including sleep (18–20). Although we cannot exclude the possibility that baroreflex-like sequences might occur in our experimental conditions independent of baroreflex intervention, previous observations suggested a nonrandom distribution of sequences in the apneic cycle (34). Moreover, preliminary evaluation of our data by spectral analysis of PI and SBP signals at different frequencies (i.e., the α coefficient) yielded superimposable results to those obtained with the sequence technique. Finally, we analyzed only baroreflex control of HR, since no method is available to investigate spontaneous baroreflex control of peripheral resistance and blood pressure. During wakefulness, baroreflex-dependent modulation of muscle sympathetic activity was found to be lower in patients with OSAS compared with con-

Figure 2. Relationship between BRS and mean lowest Sa_{O_2} in non-REM stage 2 sleep (*left*) and REM sleep (*right*) in the OSAS group. Each point represents a patient.

TABLE 3. SHORT-TERM VARIABILITY OF SYSTOLIC BLOOD PRESSURE, DIASTOLIC BLOOD PRESSURE, AND PULSE INTERVAL DURING NOCTURNAL WAKEFULNESS AND SLEEP IN 10 PATIENTS WITH OBSTRUCTIVE SLEEP APNEA SYNDROME STUDIED UNDER NO TREATMENT CONDITIONS AND AFTER LONG-TERM CPAP TREATMENT

	Mean SBP (*mm Hg*)			SD of SBP (*mm Hg*)			Mean DBP (*mm Hg*)		
	No treatment	Long-term CPAP	p	No treatment	Long-term CPAP	p	No treatment	Long-term CPAP	p
Nocturnal									
wakefulness	135.6 ± 12.5	131.9 ± 11.7	NS	11.5 ± 5.0	9.5 ± 3.6	NS	77.0 ± 12.9	73.1 ± 7.0	NS
Non-REM 2	133.6 ± 11.0	127.0 ± 15.0	NS	15.7 ± 4.0	11.0 ± 2.5	< 0.05	71.4 ± 8.2	70.9 ± 6.3	NS
REM, n = 7	141.3 ± 16.4	139.0 ± 24.2	NS	14.1 ± 3.7	10.2 ± 4.1	NS	76.0 ± 5.1	74.8 ± 14.5	NS

	SD of DBP (*mm Hg*)			Mean PI (*ms*)			SD of PI (*ms*)		
Nocturnal									
wakefulness	6.4 ± 2.6	5.4 ± 1.7	NS	776 ± 100*	886 ± 117	< 0.0005	46 ± 9*	65 ± 29	NS
Non-REM 2	8.6 ± 1.8	6.4 ± 1.7	< 0.05	839 ± 125	934 ± 140	< 0.005	75 ± 17	79 ± 32	NS
REM, n = 7	8.7 ± 2.3	6.0 ± 2.8	NS	907 ± 76	932 ± 110	NS	101 ± 48	86 ± 53	NS

Definition of abbreviations: CPAP = continuous positive airway pressure; DBP = diastolic blood pressure; PI = pulse interval; REM = rapid eye movement; SBP = systolic blood pressure.

* Wakefulness significantly different from REM sleep ($p < 0.01$) from ANOVA applied to each group to test for differences among sleep stages.

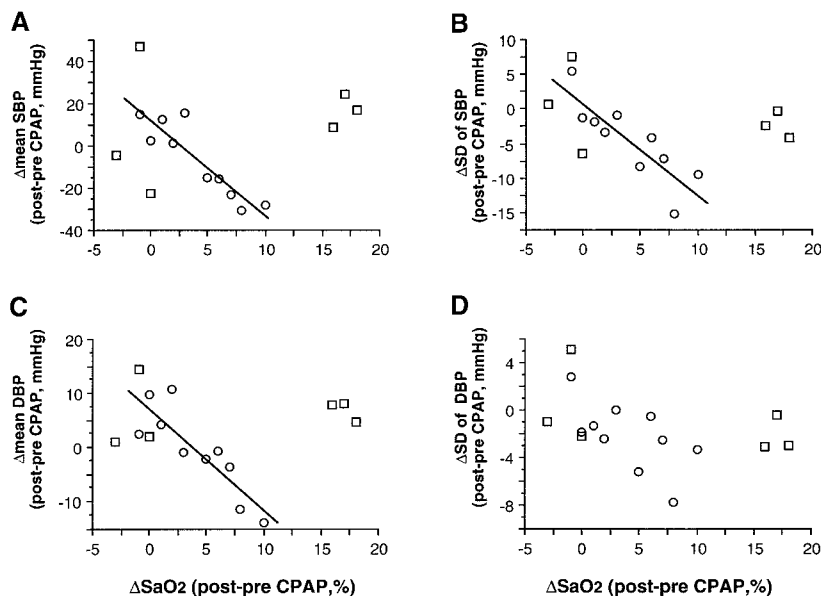Paired *t* test applied to test for differences between conditions.

trol subjects (9). On the other hand, the sequence technique shows a major advantage for sleep studies, since it requires no active intervention on the part of the subject. Injection of vasoactive substances caused arousal (14) with increases in blood pressure and HR (2), suggesting that bolus injections may heavily interfere with baroreflex assessment during sleep. Moreover, a vasoactive drug may evoke different responses according to the timing of injection in the apneic cycle, possibly resulting in artifacts and increased variability of results.

In untreated patients with severe OSAS, spontaneous baroreflex control of HR during wakefulness and sleep was low compared with age-matched normal subjects, but patients with OSAS were obese and control subjects were not. Baroreflex control of HR was reported to be lower in obese than nonobese awake humans and improved after weight reduction (35); it also improved after a low-calorie diet in patients with OSAS, but the respective roles of weight reduction and reduced OSAS severity associated with weight loss were not assessed (36). On the other hand, obesity was associated with sympathetic hyperactivity during wakefulness only in patients with sleep-disordered breathing, suggesting a major role of OSAS in the autonomic disturbances associated with obesity (37). Although our study does not allow us to draw any con-
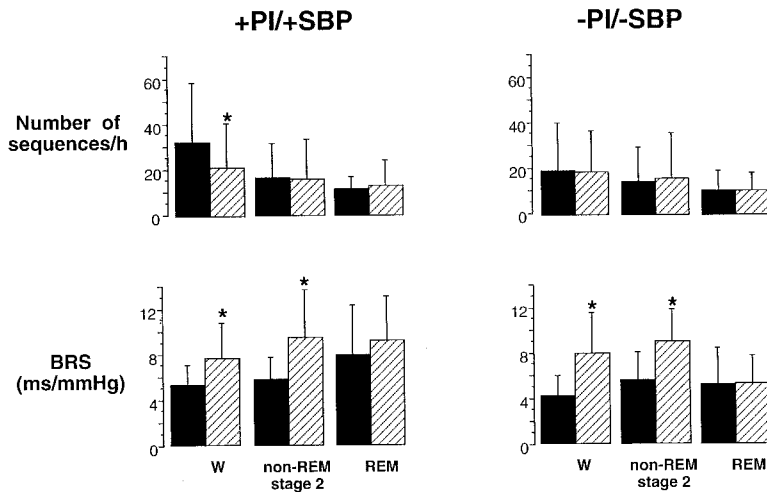
clusions on the relationship between obesity and BRS, our data support the hypothesis that OSAS affects baroreflex control of HR. Indeed, BRS in untreated OSAS did not correlate with BMI, but correlated with mean lowest Sa_{O_2} during sleep (i.e., a marker of OSAS severity). Finally, baroreflex control of HR improved considerably after CPAP treatment, whereas BMI did not change during follow-up.

Subjects were asked to avoid drinking and smoking on the days of the study. Some control subjects and OSAS patients were current smokers, but BRS did not differ between smokers and nonsmokers in either group. In addition, the effects of smoking on BRS were previously found to be short-lived (38), and smaller at night compared with daytime (39). Ethanol administration acutely depressed baroreflex sensitivity in humans (40), but none of our subjects could be classified as a moderate or heavy drinker before or after treatment.

In severe untreated OSAS, apnea-induced hypoxemia in non-REM sleep correlated significantly with BRS. According to experimental studies on baroreceptor–chemoreceptor interactions, marked stimulation of either receptor type was associated with attenuated responses to stimulation of the other receptor (41–43). In humans, baroreflex control of HR decreased as hypoxia, acutely induced by simulated high alti-

Figure 3. Changes in mean lowest Sa_{O_2} and blood pressure during sleep at CPAP withdrawal. *Circles*: non-REM stage 2 sleep; *squares*: REM sleep; *regression lines* refer to non-REM sleep points. Improvement in Sa_{O_2} during non-REM stage 2 sleep correlated with decreased mean SBP (*A*); variability of SBP (*B*), i.e., the standard deviation of SBP, over 2-minute periods of stable sleep also decreased as Sa_{O_2} improved (*upper right panel*); and DBP (*C*). A similar trend ($p = 0.05$) was observed for SD of DBP (*D*). In REM sleep, no relationship was significant.

Figure 4. Effect of long-term CPAP on baroreflex control of HR during sleep. *Black bars:* untreated OSAS; *hatched bars:* first night of CPAP withdrawal after treatment. +PI/+SBP and −PI/−SBP: same as in Figure 1. Statistical significance (*asterisks*) refers to paired comparisons between pre and posttreatment studies. Paired data in REM sleep were available in six subjects for +PI/+SBP sequences, and in five for −PI/−SBP sequences.

tude, progressed (44). During acclimatization to high altitude, normal subjects showed an enhanced blood pressure response to hypoxia during wakefulness (45), with a similar trend for the pressor response to periodic breathing during sleep (46), suggesting that chronic hypoxia is likely associated with increased chemoreceptor sensitivity, and thus possibly baroreflex impairment.
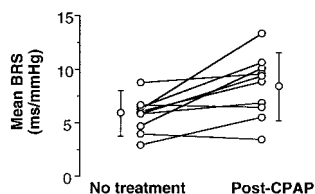
BRS improved after CPAP treatment, but hypoxemia during sleep was less severe at CPAP withdrawal. Therefore, results of the present study will not allow a determination of whether the observed increase in BRS was secondary to decreased severity of desaturation during sleep or an overall improvement in autonomic function after prolonged treatment. We favor the second hypothesis, because BRS did not show major changes in patients with OSAS during CPAP application (47). There is evidence that regular CPAP treatment in OSAS decreases sympathetic hyperactivity (23, 24), as well as tonic activation of peripheral chemoreceptors (5) and hyperresponsiveness to hypoxia (4, 5). CPAP treatment improved OSAS-induced autonomic dysfunction (24–27), and HR during sleep was lower at CPAP withdrawal, observations that are in line with similar findings during wakefulness (26). Thus, we favor the explanation that the improvement in BRS after long-term CPAP seems mostly secondary to chronic rather than acute effects of treatment.

The change in BRS did not correlate with compliance to, or duration of, CPAP treatment. Moreover, the link between nocturnal hypoxemia and BRS was weaker after CPAP compared with untreated OSAS. A large number of patients may be needed to show significant relationships between variables. Alternatively, other factors, such as the duration of disease before patients sought medical care, may affect BRS recovery. In the present study, the greatest improvements in nocturnal hypoxemia and cardiovascular variables were observed in relatively young patients. Because the risk of systemic hypertension is higher in younger patients with OSAS compared with

older patients (48, 49), our results suggest that it may be young patients who benefit most from CPAP.

We did not measure intrathoracic pressure, leaving the important question of the role of OSAS-induced mechanical changes on baroreflex control of HR unanswered. Airway obstruction alters the balance of afferent activity from aortic (intrathoracic) and carotid (extrathoracic) baroreceptors in experimental animals (50). Indirect data by pulse transit time suggest respiratory efforts as a likely explanation for the blunted decline in nocturnal blood pressure seen in apneic patients (3). Spontaneous BRS reflects the integrated response to multiple inputs to cardiovascular control mechanisms, yielding no direct information on the relative roles of mechanical and chemical changes induced by airway obstruction during sleep. However, a direct role of intrathoracic pressure swings on BRS is supported by the finding that spontaneous BRS progressively decreased with increasing snoring frequency in nonapneic, nondesaturating snorers during non-REM sleep (20). The data obtained at CPAP withdrawal do not provide any additional insight into the relative role of apnea-induced mechanical and chemical changes on BRS. Indeed, after prolonged CPAP treatment, esophageal pressure swings were significantly reduced compared with pretreatment studies (33). On the other hand, studying patients on CPAP is not ideal, since CPAP treatment could affect cardiovascular regulation independent of its effects on upper airways. Indeed, decreased venous return and peripheral vasoconstriction were documented in healthy awake subjects during positive-pressure ventilation (51).

No significant change in office daytime blood pressure was detected after CPAP treatment, possibly because we studied normotensive subjects. Hypertensive patients with OSAS were excluded due to the known association of high blood pressure with decreased baroreflex function (18). Whether CPAP positively affects baroreflex control of HR in hypertensive OSAS remains to be determined. In the present study, beat-by-beat analysis of blood pressure clearly indicated that both average values and blood pressure variability during sleep fell significantly after treatment. Intermittent 24-hour blood pressure monitoring showed decreased blood pressure after CPAP treatment in those patients with frequent significant desaturation episodes while untreated, but the change in blood pressure was small (29, 30). Therefore, continuous blood pressure recording seems necessary in OSAS to detect changes in nocturnal blood pressure after treatment (52).

Figure 5. Mean BRS over the entire recording before and after CPAP treatment in individual patients (n = 10).

This study was not randomized or placebo-controlled. Preliminary data by the Oxford group showed no improvement in BRS during wakefulness after sham CPAP, but daytime BRS significantly increased after 4 weeks of effective CPAP treatment (53), ruling out a placebo effect on BRS. Finally, we did not measure left ventricular ejection fraction, but no patient showed clinical symptoms or signs of heart failure, making it unlikely that our findings might be accounted for by changes in cardiac function.

Some consistent differences in BRS were observed between non-REM stage 2 and REM sleep: (*1*) in untreated OSAS, BRS and mean lowest Sa$_{O_2}$ correlated in non-REM stage 2 but not in REM sleep; and (*2*) after CPAP treatment, BRS increased during wakefulness and non-REM sleep, but not in REM sleep. Because REM sleep is normally characterized by increased sympathetic nervous activity compared with non-REM sleep (54), the lack of change in BRS after treatment during REM sleep could reflect the physiologic autonomic imbalance of this sleep phase. The ventilatory response to hypoxia is reduced during REM sleep (55), suggesting decreased chemosensitivity and/or state-dependent effects on the central integration of baroreflex input.

In conclusion, CPAP treatment significantly improved the depressed spontaneous baroreflex control of HR found in patients with severe OSAS during sleep. The relationship between nocturnal BRS and OSAS-induced hypertensive peaks supports a link between baroreflex dysfunction, chronic intermittent hypoxia, and sympathetic hyperactivity in OSAS, a result that is similar to data obtained during wakefulness (7). The clinical efficacy of CPAP therapy in decreasing arterial blood pressure or cardiovascular risk in OSAS is still debated (24, 28–30). Since arterial baroreflex dysfunction is a marker of high cardiovascular risk in patients with coronary artery disease (13) or heart failure (12), we speculate that it may also indicate an increased cardiovascular risk in patients with OSAS. This study clearly indicates that OSAS-induced baroreflex dysfunction is partly reversible, but long-term prospective observations in larger patient samples are needed to test whether baroreflex control of HR may be used as a clinical risk marker in OSAS.

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