Effect of continuous positive airway pressure therapy on hypothalamic-pituitary-adrenal axis function and 24-h blood pressure profile in obese men with obstructive sleep apnea syndrome

Gláucia Carneiro,1 Sônia Maria Togeiro,2 Lilian F. Hayashi,1 Fernando Flexa Ribeiro-Filho,1 Artur Beltrame Ribeiro,3 Sérgio Tufik,2 and Maria Teresa Zanella1

1Department of Medicine, Division of Endocrinology; 2Department of Psychobiology, Sleep Disorders Center, Universidade Federal de São Paulo; and 3Hospital do Rim e Hipertensão, Fundação Oswaldo Ramos, São Paulo, Brazil

Submitted 15 December 2007; accepted in final form 30 May 2008


Obstructive sleep apnea syndrome (OSAS) is receiving increased attention because it seems to be associated with a variety of long-term consequences, such as high rates of morbidity and mortality, mostly due to cardiovascular disease (23). Although obesity is the main risk factor for OSAS (39), it has been demonstrated that OSAS may increase the risk for hypertension, myocardial infarction, congestive heart failure, and stroke independently of obesity. Continuous positive airway pressure (CPAP) therapy is the treatment of choice for patients with moderate-to-severe OSAS, since it is highly effective in improving nocturnal hypoxia and sleep fragmentation, enhancing the quality of life and reducing many cardiovascular complications related to OSAS. However, the lack of acceptance and inadequate adherence to CPAP therapy remain the major causes of sleep apnea treatment failure (10, 20, 21, 31, 32).

The mechanisms proposed to explain the increased cardiovascular disease in obstructive sleep apnea are under assessment. It is speculated that recurrent episodes of upper airway constriction, progressive hypoxemia, and sleep fragmentation may result in neural and metabolic changes, including activation of peripheral sympathetic activity, inflammatory pathways, and hypothalamic-pituitary-adrenal (HPA) axis, impairment of insulin sensitivity, and generation of reactive oxygen species, which could predispose to vascular damage (16, 26, 27, 34).

Sympathetic nervous system has been well demonstrated to be activated in sleep apnea patients by investigating muscle sympathetic nerve activity, heart rate variability, blood, and urinary catecholamine levels (2). In contrast, there are a limited number of studies that assess the effects of obstructive sleep apnea on cortisol secretion (9, 12, 13, 18, 35). Some studies show an elevation of cortisol levels (13, 18, 35) in patients with OSAS, whereas others do not (9, 12).

The aim of the present study was to evaluate HPA axis, 24-h heart rate, and blood pressure values in severely obese patients with and without OSAS and to assess whether OSAS treatment with nasal CPAP influenced responses.

MATERIALS AND METHODS

Twenty-nine obese men who were on the waiting list for bariatric surgery were consecutively recruited from the Obesity Outpatient Clinic and Sleep Disorders Center of the Federal University of Sao Paulo. These patients, aged from 18 to 65 yr and with body mass index between 35 and 60 kg/m2, submitted to polysomnography recordings and were classified according to their apnea-hypopnea index (AHI) in two different groups: AHI <5 events/h, obese controls (n = 13); or AHI ≥10 events/h, OSAS patients (n = 16).

Exclusion criteria included history of smoking, sleep apnea treatment, cardiovascular disease, malignant tumors, thyroid disorders, or severe depression, subjects with diabetes mellitus, chronic renal, or hepatic failure, and use of medication that could potentially affect sympathetic nervous system or steroid hormone secretion (alcohol, psychotropics, steroids, sympathomimetics, β-blockers) and hepatic enzyme inducers such as carbamazepine, phenytoin, phenobarbitone.

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
and rifampicin, which reduce plasma dexamethasone concentrations (17). Anti hypertensive medications remained unchanged during the study period.

A questionnaire included demographic data, sleep symptoms, medical history, and medications in use. Physical examinations and anthropometric measurements, including weight (in kg) and height (in m), were recorded. Body mass index was calculated as the weight divided by the height squared.

Polysomnograms were recorded by the Sleep Analyzer Computer (Alice 3 Diagnostics system), including one for OSAS diagnosis and another for positive airway pressure titration. An experienced sleep physician scored all sleep stages (28), arousals, and respiratory events according to American Sleep Disorders Association criteria (1, 1a).

In healthy individuals, glucocorticoid synthesis and secretion follow a circadian rhythm, with the highest levels in the morning and the nadir at around midnight. Overnight administration of dexamethasone (DEX), a potent exogenous glucocorticoid, suppresses the nocturnal surge in ACTH production and cortisol levels when measured the next morning (22). Dexamethasone test is the most commonly used method to evaluate the sensitivity of the HPA axis to negative feedback. However, the conventional dose of 1 mg completely suppresses cortisol secretion in normal people. For this reason, low-dose DEX test (<1 mg) has been used by some authors to induce a more modest suppression, enabling the detection of subtle differences in feedback sensitivity of glucocorticoid on the HPA axis (7, 15, 19, 25, 29, 33).

The assessment of the HPA axis function in this study included low-dose (0.25 mg) DEX suppression test and the circadian rhythm of cortisol secretion. Salivary cortisol measurement reflects the free fraction of cortisol in plasma. Advantages are the easy and noninvasive collection procedure and its stability at room temperature for 7 days (5, 36, 37). The subjects were given three Salivettes (Sarstedt, Rommelsdorf, Germany), which consist of small cotton swabs inside centrifugation tubes used to collect saliva, and a half-tablet of 0.5 mg DEX (Decadron, Aché, Brazil). Salivary sample was obtained in the morning (8:00 AM) and at bedtime, ~11:00 PM, for all patients just before the administration of DEX. The next morning, more salivary and blood samples were collected at 8:00 AM to measure cortisol and DEX concentrations by RIA to confirm the ingestion of the drug. To analyze the results, we used an index of percentage of salivary cortisol suppression (%cortisol suppression) calculated as the difference between the post-DEX cortisol levels and baseline cortisol levels at 8:00 AM divided by baseline cortisol levels at 8:00 AM.

Twenty-four-hour ambulatory blood pressure monitoring was recorded with a SpaceLabs model 90202 ambulatory blood pressure monitor (Redmond, WA). An appropriately sized cuff was applied. Blood pressure was registered every 15 min during daytime (awake) and every 20 min during nighttime (asleep) on the basis of the patient’s reports on their activities during day and night. The percentage of fall in systolic blood pressure at night was calculated by dividing the difference between mean daytime and mean nighttime systolic blood pressures by the mean daytime systolic blood pressure (24). Blood pressure was considered to be controlled in those patients with 24-h mean blood pressure values <135/85 mmHg (6).

Six patients with mild or moderate OSAS immediately underwent bariatic surgery, and 10 patients with severe OSAS (AHI of >30 events/h of sleep) were advised to follow nasal CPAP (nCPAP) therapy before bariatric surgery (mean nCPAP pressure of 11.2 ± 0.7 cm of H2O) to avoid surgery complications related to sleep apnea. One man who failed to use the device was excluded from the study before the followup analysis. Therefore, after 3 mo of nCPAP therapy, nine patients with severe OSAS were reassessed and all measurements were repeated. The average nightly use of nCPAP was measured with a run time course that ran when the patient was breathing through the machine and not just when the machine was switched on.

This study was approved by the Univesidade Federal de Sao Paulo Ethics Committee, and written informed consent was obtained from all participants.

Normally distributed variables are expressed as means ± SE or percentiles when appropriate. Continuous variable comparisons between OSAS and control obese groups were performed using unpaired Student’s t-test. Analysis of covariance tests were used to adjust comparisons for body mass index. To assess differences between categorical variables, we used chi-square statistics. The results before and after nCPAP therapy were compared using paired t-test. Correlations between variables were assessed by Pearson coefficient. A P value of <0.05 was considered statistically significant. Data analysis was performed using SPSS for Windows version 13.0.

RESULTS

As shown in Table 1, no differences between groups for age, body mass index, and prevalence of hypertension were observed. In OSAS men, the mean 24-h heart rate was higher (P = 0.022) and the percentage fall in blood pressure during sleep time lower compared with obese men controls (P = 0.027). Mean 24-h systolic and diastolic blood pressure values were similar in the two groups.

Although basal salivary cortisol values at 8:00 AM (P = 0.715) and at bedtime (P = 0.388) were not different between groups, a smaller cortisol suppression post-DEX (%cortisol suppression) was evident in OSAS patients compared with obese controls (P = 0.012) (Fig. 1). As a consequence, salivary cortisol post-DEX was significantly higher in OSAS patients than in obese control (P = 0.038). Comparisons between groups were adjusted for body mass index (Table 1).

All patients had detectable circulating plasma DEX level, indicating that all participants had ingested the DEX tablets (Table 1). DEX levels did not differ between OSAS patients and obese controls (84.5 ± 9.3 vs. 101 ± 10.5, P = 0.241), and in the total group, DEX levels did not correlate to plasma cortisol levels post-DEX (r = −0.219, P = 0.328).

Three months of nCPAP therapy was associated with a significant reduction in salivary cortisol after DEX (P = 0.009) and heart rate (P = 0.036) compared with baseline. Also, a greater cortisol suppression (%cortisol suppression) post-DEX was observed.

Table 1. Clinical and laboratory characteristics of obese men with and without sleep apnea

<table>
<thead>
<tr>
<th>OSAS</th>
<th>No (n = 13)</th>
<th>Yes (n = 16)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHL events/h</td>
<td>3.2 ± 0.5</td>
<td>65.7 ± 9.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age, yr</td>
<td>38.8 ± 3.3</td>
<td>40.1 ± 2.8</td>
<td>0.378</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>42.8 ± 1.3</td>
<td>46.9 ± 2.0</td>
<td>0.116</td>
</tr>
<tr>
<td>24-h SBP, mmHg</td>
<td>127.6 ± 2.3</td>
<td>131.3 ± 3.3</td>
<td>0.492</td>
</tr>
<tr>
<td>24-h DBP, mmHg</td>
<td>76.1 ± 1.9</td>
<td>79.6 ± 2.3</td>
<td>0.349</td>
</tr>
<tr>
<td>24-h Heart rate, beats/min</td>
<td>76.3 ± 2.8</td>
<td>89.3 ± 3.4</td>
<td>0.022</td>
</tr>
<tr>
<td>%ΔBP, %</td>
<td>11.5 ± 1.8</td>
<td>5.5 ± 1.2</td>
<td>0.027</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>7 (53.8)</td>
<td>11 (68.8)</td>
<td>0.466</td>
</tr>
<tr>
<td>Salivary cortisol, ng/dl</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>483.9 ± 77.5</td>
<td>442.2 ± 57.5</td>
<td>0.715</td>
</tr>
<tr>
<td>11:00 PM</td>
<td>177.8 ± 53.5</td>
<td>233.5 ± 56.3</td>
<td>0.388</td>
</tr>
<tr>
<td>Post-DEX</td>
<td>233.2 ± 65.6</td>
<td>445.4 ± 61.6</td>
<td>0.038</td>
</tr>
<tr>
<td>%ΔCortisol suppression</td>
<td>−48.8 ± 10.5</td>
<td>−16.6 ± 6.1</td>
<td>0.012</td>
</tr>
<tr>
<td>DEX, ng/dl</td>
<td>101 ± 10.5</td>
<td>84.5 ± 9.3</td>
<td>0.241</td>
</tr>
<tr>
<td>Excess cortisol mg/dl</td>
<td>3.6 ± 1.0</td>
<td>6.9 ± 1.0</td>
<td>0.059</td>
</tr>
</tbody>
</table>

Data are expressed as means ± SE or n (%). OSAS, obstructive sleep apnea syndrome; AHI, apnea-hypopnea index; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; ΔBP, %fall in systolic blood pressure at night; %cortisol suppression, cortisol post-dexamethasone (DEX) minus cortisol basal at 8:00 AM/cortisol basal at 8:00 AM. *Significance after adjustment for BMI.
was evident in apneic patients following the use of nCPAP ($P = 0.001$). This was similar to the levels of obese controls (Fig. 1). Average body mass index ($P = 0.913$) did not change, and no differences in sleep blood pressure fall and blood pressure values were observed after nCPAP therapy (Table 2).

**Table 2. Characteristics of men with sleep apnea before and after 3 mo of nCPAP therapy**

<table>
<thead>
<tr>
<th></th>
<th>CPAP ($n = 9$)</th>
<th>Change from Baseline</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHI, events/h</td>
<td>Pre: 92 ± 7.6</td>
<td>Post: 21.1 ± 9.7</td>
<td>-70.8 ± 5.3</td>
</tr>
<tr>
<td>BMI, kg/m$^2$</td>
<td>44.3 ± 2.4</td>
<td>44.4 ± 2.5</td>
<td>0.07 ± 0.7</td>
</tr>
<tr>
<td>24-h SBP, mmHg</td>
<td>131.5 ± 3.7</td>
<td>125.7 ± 1.9</td>
<td>-5.7 ± 3.9</td>
</tr>
<tr>
<td>24-h DBP, mmHg</td>
<td>77.3 ± 2.5</td>
<td>76.0 ± 2.7</td>
<td>-1.3 ± 2.9</td>
</tr>
<tr>
<td>24-h Heart rate, beats/min</td>
<td>82.1 ± 3.8</td>
<td>74.3 ± 3.5</td>
<td>-7.7 ± 3.08</td>
</tr>
<tr>
<td>ΔBP, %</td>
<td>6.2 ± 1.9</td>
<td>7.3 ± 1.5</td>
<td>1.2 ± 2.1</td>
</tr>
<tr>
<td>Salivary cortisol, ng/dl</td>
<td>Basal: 501.1 ± 89.0</td>
<td>Post-DEX: 521.2 ± 58.6</td>
<td>20.1 ± 89</td>
</tr>
<tr>
<td></td>
<td>%Cortisol suppression: -21.8 ± 8.5</td>
<td>-69.4 ± 6.2</td>
<td>47.5 ± 8.6</td>
</tr>
</tbody>
</table>

Data are expressed as means ± SE. CPAP, continuous positive airway pressure; nCPAP, nasal CPAP.

Six patients (67%) took antihypertensive drugs, and blood pressure was controlled at entry.

Improvement of AHI in response to nCPAP was positively correlated with the improvement of cortisol suppression after oral DEX ($r = 0.799, P = 0.010$) and negatively correlated with cortisol suppression before nCPAP ($r = -0.883, P = 0.002$) (Fig. 2).

**DISCUSSION**

In the present study, we demonstrated a blunted response of cortisol suppression after dexamethasone and a higher 24-h heart rate in obese men with obstructive sleep apnea syndrome compared with obese male controls. These findings may reflect activation of sympathetic nervous and stress system in apneic patients, which could be due to nocturnal hypoxia and sleep fragmentation, with several awakening and arousal episodes. In addition, we showed a significant reduction in heart rate and a marked improvement in dexamethasone-induced salivary cortisol suppression in patients with OSAS after 3 mo of nCPAP therapy. The reduction of apnea-hypopnea index after nCPAP therapy was positively correlated with cortisol suppression in response to low-dose oral dexamethasone.

Stress-related disorders such as depression, anorexia, alcoholism, excessive exercising, malnutrition, and premenstrual tension syndrome may be associated with increased corticotropin-releasing hormone activity and ACTH secretion, resulting in chronic exposure to circulating cortisol levels and loss of...
the normal negative feedback of the HPA axis by glucocorticoids (8). In accordance with this hypothesis, it was expected that OSAS would be associated with an activation of HPA axis in response to stress caused by recurrent intermittent hypoxia, sleep fragmentation, and frequent cerebral arousals during apneic events. However, only a few studies have assessed the relationship between sleep apnea and HPA axis, and the results are still controversial (9, 12, 13, 18, 35). In the majority of these studies, the HPA axis was assessed by a single morning plasma cortisol measurement, which might not reflect the episodic nature of cortisol secretion and its appropriate elevations during the hypoxemia stress (8). Two recent studies (9, 35) have evaluated the 24-h circadian secretory pattern of cortisol in obese patients with and without sleep apnea. In agreement with our results, both studies have demonstrated that salivary and plasma cortisol secretion was circadian in OSAS patients and obese controls. However, Dadou et al. (9) failed to find any significant differences for overnight cortisol secretion between obese patients with or without sleep apnea syndrome. Our results match those who have demonstrated that sleep apnea in obese men is associated with increased cortisol level during the nighttime period (11 PM to 7 AM) compared with obese controls, which is recovered after the use of nCPAP for 3 mo (35). Hence, we hypothesize that obstructive sleep apnea should be recognized by clinician and corrected before further clinical investigations of endocrine causes of hypercortisolism.

Long-term mild activation of HPA axis has been shown to alter important functions in patients with some evidence of hypercortisolism, i.e., adrenal incidentalomas, depression, or alcoholism, increasing the risk for chronic conditions such weight gain, lethargy, weakness, loss of libido, diabetes mellitus, hypertension, and osteoporosis (22). Thus, further prospective studies should explore these clinical manifestations in patients with OSAS and increased cortisol levels.

A positive and well-established relationship between sleep apnea and the prevalence and severity of hypertension has been reported (4, 14, 26, 38). Nevertheless, we did not find any differences in 24-h blood pressure values between patients with or without sleep apnea. Blood pressure fall during sleep, however, was smaller in OSAS patients than in obese controls. The reasons for these discrepancies might be the fact that, in our study, more than one-half of patients were on hypertensive medication, although none received β-blocker therapy.

Therapy with nCPAP is the most effective treatment for sleep apnea, preventing recurrent occlusion of the upper airway during sleep (32). However, the effects of nCPAP on blood pressure have shown conflicting results (1b, 3, 21). We did not find significant changes in blood pressure levels and blood pressure fall during sleep after nCPAP therapy in severe obese patients with OSAS. Because our patients were under antihypertensive therapy and blood pressure levels were controlled at baseline, this may be the reason for negative results. Consistent with our findings, Campos-Rodriguez et al. (3) reported that 24 mo of therapeutic nCPAP reduced 24-h ambulatory blood pressure measurements only in a subgroup of patients with incompletely controlled hypertension at baseline. They suggest that, in a group of controlled hypertensive patients, nCPAP therapy failed to reduce blood pressure.

Some limitations of the current study include the small sample size and lack of a post-nCPAP treatment control group. However, at the time of the study, sham-CPAP machines capable of use in a double-blinded setting were not available. Moreover, ethical approval to leave patients with severe symptomatic OSAS untreated before bariatric surgery was not forthcoming from university ethics committee.

In conclusion, our findings demonstrate that obstructive sleep apnea syndrome is associated with increased 24-h heart rate, decreased percentage of fall in systolic blood pressure at night, and lower cortisol suppression after low-dose dexamethasone, suggesting that there is an activation of sympathetic nervous system and HPA axis. Our results also show the beneficial effects of nCPAP on 24-h heart rate and salivary cortisol levels after a low-dose dexamethasone test, which may contribute to reducing cardiovascular and metabolic complications related to OSAS.

ACKNOWLEDGMENTS

We thank Eveli Truksinas for skilful technical assistance in the followup assessment of nCPAP therapy.

GRANTS

This work was supported by grants from Associação Fundo de Incentivo à Psicofarmacologia, Hospital do Rim e Hipertensão-Fundação Oswaldo Ramos, Coordenação de Aperfeiçoamento de Pessoal de nível Superior, and Fundação de Amparo à Pesquisa do Estado de São Paulo-Centros de Pesquisa, Inovação e Difusão.

REFERENCES


9. Dadou F, Darmon P, Achar V, Boullu-Ciocca S, Philip-joel F, Alesis MC, Rey M, Grino M, Dutour A. Effect of sleep apnea syndrome...