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ORIGINAL ARTICLE

Pituitary-gonadal function in men with obstructive sleep apnea.

The effect of continuous positive airways pressure treatment

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Abstract

OBJECTIVES: Decreased libido and a decline in morning serum testosterone levels were reported in men with obstructive sleep apnea (OSA). Our study aimed to evaluate the pituitary-gonadal axis in middle age men with OSA before and after treatment with nasal continuous positive airway pressure (CPAP).

MATERIAL AND METHODS: Measurement of the nocturnal serum luteinizing hormone (LH) and testosterone levels and sleep recordings before and after nine months of CPAP treatment in five men with OSA aged 49.5±5.2 years. Patients were evaluated during nocturnal sleep at base line and during CPAP treatment.

Serum LH and testosterone levels were determined at 20 minutes interval between 1900h and 0700h with concomitant determination of sleep quality, respiration and oxygen saturation.

RESULTS: At base line, patients had higher RDI and PaO2<90%, lower mean and integrated (AUC) values of LH and testosterone. During CPAP treatment, RDI and PaO2<90% were normal. Mean and AUC values of testosterone and LH increased.

CONCLUSIONS: OSA in men is associated with dysfunction of the pituitary-gonadal axis. The central suppression of nocturnal testosterone in these patients is partially corrected during chronic CPAP treatment.

Abbreviations

1. OSA	Obstructive sleep apnea
2. CPAP	nasal continuous positive airway pressure
3. RDI	Respiratory disturbance index
4. PaO2< 90%	oxygen saturation below 90%
5. LH	Luteinizing hormone
6. AUC	Area under the curve
7. REM sleep	Rapid eye movement sleep
8. CV	coefficients of variation

Introduction

Sleep apnea syndrome is mostly associated with cardiovascular co-morbidity [1–3]. Less is known about the impact of the nocturnal apneic events on the reproductive system. The sleep-related rise in testosterone, which in young adults is linked with the first REM sleep episode [4], and is dependent on the integrity of the sleep process [5], was shown to be affected in sleep apnea [6]. Decreased morning testosterone concentrations were found in male patients with OSA [7], and middle-aged men with sleep apnea were shown to secrete less LH and testosterone throughout sleep compared with healthy age matched controls of similar body weight [8]. The present study was undertaken to investigate the effects of nasal continuous positive airway pressure (CPAP) treatment on LH and testosterone secretion in sleep apnea.

Methods

Diagnostic procedure of OSA

Patients evaluated for OSA first completed a comprehensive questionnaire on their sleep and medical history. Diagnostic sleep recordings included: Electrooculography, electromyography, electroencephalography, respiration, and oxygen saturation. Respiration was recorded using nasal and oral thermistor and a thoracic strain gauge. The oxygen saturation level was determined by a finger pulse oximeter. We determined the percentage of time spent asleep with oxygen saturation below 90% (PaO2 <90%). Apneas and hypopneas were counted, and the respiratory disturbance index (RDI) was calculated by dividing their total number by hours of sleep. Apnea was defined as a cessation of airflow through the mouth and nose for more than 10 sec. Hypopnea was defined as a decrease in the amplitude of the respiratory signal of at least 50% for a minimum of 10 sec, followed by either a decrease in oxygen saturation of 4% or signs of physiological arousal. A diagnosis of OSA was based on a combination of characteristic symptoms (loud and disturbing snoring, excessive daytime sleepiness, morning fatigue) and a finding of RDI greater than 10 [2, 9–10].

Subjects

Five men (age 49.5±5.2 yr) diagnosed as having severe obstructive sleep apnea (RDI, 52.6 ± 17.4; PaO2 <90%, 7.1 ± 8.8%) participated in the study. Subjects underwent whole night conventional sleep recording because of suspected sleep apnea before the present study. The Helsinki Committee of the Afula Medical Center (Afula, Israel) approved the study. All participants gave their informed consent before the start of the study.

Study protocol

Subjects were admitted to the Sleep Research Center at 1600 h. At 1700 h, an IV catheter was inserted into an antecubital vein and was kept patent with a slow infusion of 0.9% NaCl. Blood samples (3 ml) were collected every 20 min from 1900–0700 h. From 2200–0700 h, lights were off, and subjects retired to sleep. Conventional sleep recordings were obtained from 2200–0700 h, in single bed, air-conditioned, sound-attenuated rooms. A second night of sleep recordings was performed on all men with OSA to determine the optimum air pressure to use with the CPAP device. This was done by gradually increasing the CPAP pressure until apneas disappeared. If apneas returned because of changes in either body position or sleep stages, the attending technician modified pressure level accordingly. A second experimental night was performed after at least nine months of CPAP treatment for the determination of post treatment nocturnal serum hormone levels and sleep recordings.

Analysis of sleep stages

Electrodes were attached for the following electrophysiological recordings: 2 electroencephalograms (levels C3-A2 and C4-A1), 2 electrooculograms, and 1 electromyogram of the mentalis. Sleep stages were scored in 30sec epochs according to conventional criteria [11].

CPAP Device

Patients with OSA were fitted with a commercially available CPAP device (Respironics, Murrysville, Pa). The level of pressure required to achieve a normal respiration was established during an all-night sleep recordings. Pressure ranged from 4 to 10 cm H_2O (mean level=6.4±1.4 cm H_20). The mean daily use of the CPAP device as determined by the built in meters was 5.2 ± 2.4 hours per day.

Hormone measurements

Blood was centrifuged, immediately separated, and stored at –20 C until assayed. Serum LH and testosterone levels were determined by immunoradiometric technique (Biodata Diagnostics, Rome, Italy). The LH intraassay coefficients of variation (CV) were 2.1% and 3.2% for low (2.2–3.3 IU/liter) and high (27– 41 IU/liter) concentrations, respectively. The interassay CVs were 3.7% and 0.8%, respectively. The sensitivity of the assay was 0.15 IU/liter. The testosterone intraassay CV were 6.0% and 3.0% for low (2.2– 4.0 nmol/liter) and high (29.4 –62.0 nmol/liter) concentrations, respectively. The interassay CVs were 1.9% and 1.6%, respectively. The sensitivity of the assay was 0.15 nmol/liter.

Statistical analysis

Mean and integrated [area under the curve (AUC)] serum LH and testosterone levels from 1900–0700h were determined in the two experimental periods. The onset of the testosterone rise was defined as the time of the first occurrence of at least three consecutive samples exceeding the mean levels obtained between

1900 and 2200h by more than one SD. The data of the OSA patients before and after CPAP treatment were compared by the signed rank test. Significant LH and testosterone secretory pulses were identified using the pulse detection program ULTRA [12]. The general principle of this algorithm is the elimination of all peaks for which either the increment (difference between the peak and the preceding trough) or the decrement (difference between the peak and the next trough) does not exceed a certain threshold related to measurement error. The standard deviation of the error associated with each calculated secretory rate was calculated following the theory of error propagation, assuming normally distributed errors on plasma levels. For each significant pulse, the amplitude was defined as the difference between the level at the peak and the level at the preceding trough. We determined the number and interpulse interval of LH and testosterone pulses, the absolute increment of the pulse and the half-life, using a threshold of 2 CVs.

Results

All subjects completed the experimental paradigm. CPAP treatment significantly reduced RDI ($p< 0.003$) and PaO2<90% ($p< 0.02$) and improved sleep quality (Tables 1–2). CPAP treatment did not affect the occurrence of the first REM sleep episode. It was observed at 24:04±0:51h in comparison to 23:24±0:47h after CPAP (difference not significant). REM latency however, was significantly shorter after treatment (0:53±0:25h vs. 2:11±0:35h; $p<0.003$). All participants showed a well-defined nocturnal testosterone rise. Before treatment, testosterone onset was observed at 01:00h and after CPAP at 24:00h. The mean and AUC values of both LH and testosterone before treatment were lower than the values after treatment (table 3, figures 1–2) with a significant increase in mean testosterone levels during CPAP treatment ($p< 0.04$). The first REM sleep period antedated the testosterone onset by 54 minutes at base line and by 76 minutes during CPAP treatment. Analysis of LH and testosterone pulse characteristics (table 4) revealed that before treatment patients had similar LH pulse frequency but of longer duration and lower increment than after CPAP treatment. There was no difference in testosterone pulse characteristics before and after treatment, except for relative increment data.

Discussion

In the present study, we demonstrated that in men with sleep apnea amelioration of the nocturnal hypoxia and apneic events during CPAP treatment, were associated with a

Table 1. Clinical characteristics of the study population [Values are given as mean ± SD]

Parameter	OSA	CPAP
Age [Years]	49.5±5.2	49.8±5.6
BMI [Kg/m^2]	31.7±4.7	31.6±4.7
RDI [Events/hour]	56.0±22.4	6.5±6.5
SaO2<90% [% time]	10.9±0.5	0.7±0.5

Table 2. Sleep characteristics in OSA patients before and after CPAP treatment [data are given as mean ± SD]

Parameter	OSA	CPAP	P value
Sleep duration [Hours: minutes]	6:24±0:58	6:34±1:12	NS
Sleep efficiency [%]	78.2±10.1	76.2±7.8	NS
Stage 1[%]	3.7±3.0	1.1±1.2	0.04
Stage 2[%]	54.1±11.0	35.8±8.8	0.03
Stage 3-4[%]	5.7±7.2	20.1±10.0	0.01
Stage REM [%]	17.9±7.1	21.6±6.7	NS
First REM episode [Clock hour]	24:04±0:51	23:24±0:47	NS

NS: not significant

Table 3. Pituitary-gonadal hormones status in OSA patients before and after CPAP treatment [data are given as Mean±SD].

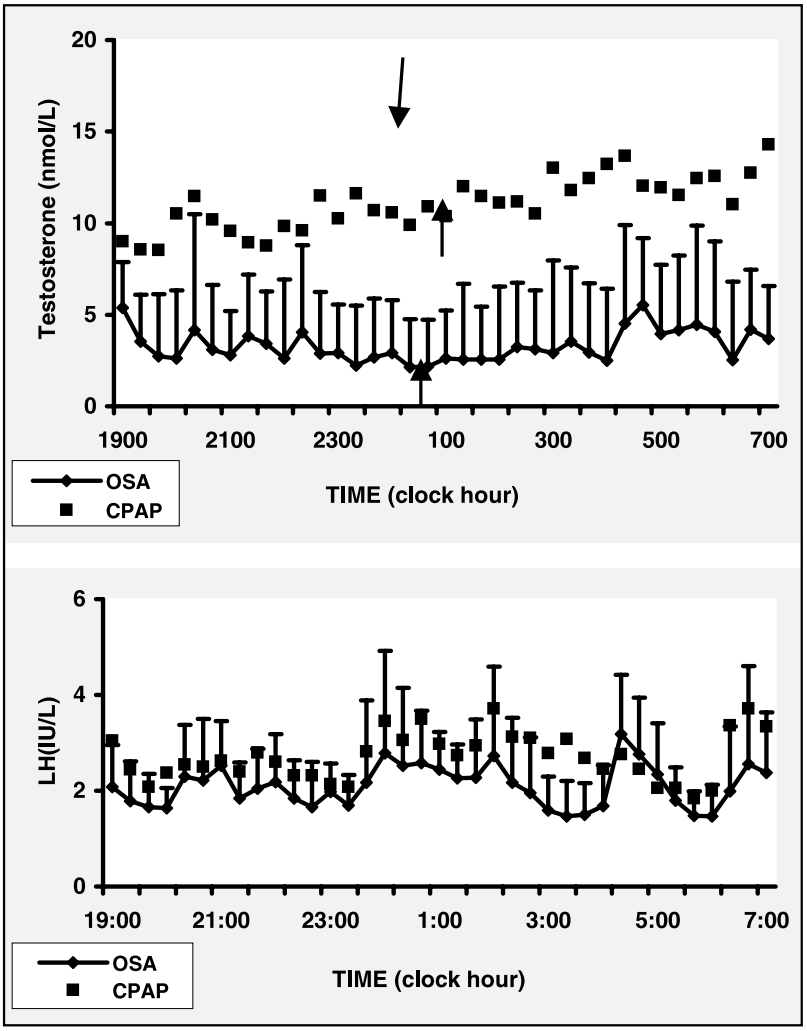
Parameter	OSA	CPAP	P value
LH			
Mean [IU/L]	2.1±0.8	2.6±0.2	NS
AUC [IU/Lxh]	22.7±7.3	30.0±3.1	0.06
Testosterone			
Onset [Clock hour]	1:30±01:00	1:15±24:40	NS
Onset level [nmol/L]	1.9±8.3	2.9±10.3	NS
Morning (07:00 h) level [nmol/L]	2.5±11.1	3.0±13.7	NS
Mean [nmol/L]	2.9±6.7	2.6±11.3	0.04
AUC [nmol/Lxh]	19.0±99.6	31.0±125.1	0.06

NS: not significant

Table 4. Characteristics of pulsatile LH and testosterone secretion in OSA patients [data are given as Mean±SD].

Parameter	OSA	CPAP	P value
LH			
Number of pulses [/12 hours]	4.0±0.6	4.3±0.5	NS
Duration [Minutes]	153.0±15.9	117.0±16.9	0.04
Increment [IU/L]	0.8±0.4	1.2±0.4	0.03
Half life [Minutes]	130.0±17.9	79.8±5.3	0.01
Testosterone			
Number of pulses [/12 hours]	4.0±1.8	4.0±1.8	NS
Duration [Minutes]	153.8±58.0	153.8±56.8	NS
Relative Increment	0.8±0.3	0.16±0.3	0.02
Half life [Minutes]	130.0±110.4	120.0±107.5	NS

NS: not significant



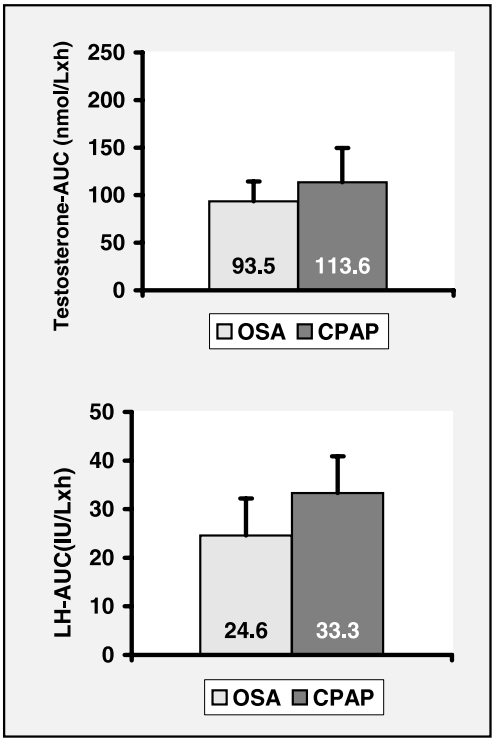


Figure 1. Effect of sleep apnea on nocturnal pulsatile LH and testosterone secretion. Treatment with CPAP was associated with increase in hormone levels throughout the night. An arrow indicates first REM sleep episode.

Figure 2. Integrated nocturnal [area under the curve] LH and testosterone secretion in men with OSA before and during CPAP treatment.

significant change in sleep architecture but only with a mild increase in LH-testosterone secretory characteristics. The mean testosterone levels were statistically significantly higher in comparison with base line values. Significant changes were observed with LH pulse characteristics but not with testosterone pulses. During CPAP treatment, LH-testosterone levels were still lower than the values observed in control men of similar ages [8].

Several factors may account for the reduced LH-testosterone secretion observed in our study. These include residual hypoxia and sleep fragmentation, duration of CPAP treatment, obesity, advanced age, and the number of subjects studied. The relative importance of hypoxia and sleep fragmentation in the genesis of gonadal dysfunction is not fully elucidated [8]. In normal young adults, sleep deprivation was associated with suppression of gonadal steroids [13, 14]. When OSA patients with severe oxygen desaturation were compared with patients with less severe desaturation, a significant correlation was found between peak testosterone level and total desaturation time, suggesting that hypoxia affected the testosterone circadian rhythm [15]. Similar findings were demonstrated in a study comparing testosterone levels with minimum SaO2. Neither testosterone nor LH concentrations correlated with apnea index [7]. Decreased basal LH and FSH levels were observed in men with sleep apnea with a blunted FSH response to GnRH stimulation [16]. Reduced serum progesterone and estradiol levels were demonstrated in women with RDI>10 [17].

In OSA men, CPAP treatment for1–4 nights were associated with normalization of leptin and growth hormone levels [18, 19] but not with a change in cortisol, glucagon and insulin concentrations [20]. Total testosterone levels reverted to normal after three months of treatment with CPAP [6], whereas treatment with CPAP for seven months was not associated with a change in the reduced LH levels [21].

Obesity is common in OSA and is associated with increased severity of sleep apnea as indicated by the RDI [22, 23]. In massively obese men, hypogonadal testosterone levels significantly increased to normal values after weight reduction [24, 25]. Obesity is associated with higher estradiol and decreased total testosterone levels [26]. Estradiol is likely to be higher in OSA men where obesity is common. Since estradiol is a potent inhibitor of gonadotropin secretion, higher levels in OSA male patients may explain the reduced pituitary stimulation of testosterone secretion observed in our study. In moderate and severe obese men, serum LH, total and free testosterone levels significantly increased after weight loss. A functional decrease of LH pulse amplitude and mean LH levels were suggested to explain the decreased androgen levels in these men [24]. Others have demonstrated that the altered sex

hormone milieu characteristic of extreme obesity was associated with a significantly shorter half-life of LH compared with lean control men. Thus, modifying the intensity and duration of LH signal delivered to the gonad [26]. The lack of weight reduction in our patients during CPAP treatment may imply that obesity is a major contributing factor to the reduced pituitary-gonadal function observed in OSA patients.

The decline in serum testosterone levels with advanced age is considered to result from pituitary and testicular defects [27]. Low testicular volume was described in elderly men with a decrease in inhibinB /FSH and testosterone/LH ratios, suggesting a combined Leydig cell and Sertoli cell dysfunction [28]. On the other hand, low basal LH levels and blunted LH response to GnRH stimulation were observed in healthy elderly men, suggesting hypothalamic-pituitary dysfunction [29]. Recently, we have demonstrated that in middle age men, less pulsatile testosterone and more LH are secreted at night than in young men with disruption of the association between testosterone rhythm and REM sleep. The decline in nocturnal testosterone secretion appears to involve a combination of testicular and pituitary hypogonadism [30].

In conclusion, chronic CPAP therapy improved respiratory function and sleep quality but only partially increased pituitary-gonadal function. Changes in LH but not testosterone pulse characteristics suggest that decreased androgen secretion may be associated with impaired function of the gonadostat. In addition to hypoxia and sleep fragmentation, obesity and advanced age may participate in the genesis of reduced testosterone secretion in sleep apnea.

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