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Assessment of Continuous Positive Airway Pressure Treatment in Obstructive Sleep Apnea Syndrome Using 24-Hour Urinary Catecholamines

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Summary

Background: Obstructive sleep apnea syndrome (OSAS) is related to diurnal sympathetic hyperactivity and increased blood pressure, both factors that are likely to lead to the development of cardiovascular disease.

Hypothesis: The study investigated whether 24-h urinary catecholamines would reflect the effect of obstructive sleep apnea on autonomic activity.

Methods: Standard polysomnography was performed in 17 patients with OSAS (age 53.7 ± 13.5 years, mean ± standard deviation). The number of apnea/hypopnea episodes per hour of sleep (apnea/hypopnea index [AHI]); number of oxygen desaturation episodes per hour (desaturation index [DSI]); arousals per hour (arousal index); lowest oxygen saturation (lowest SpO_2); and percentages of stages 1, 2, 3/4, and rapid eye movement sleep (% stage 1, −2, and −3/4, and % REM, respectively) were measured. Overnight continuous positive airway pressure (CPAP) titration was performed the night after the baseline sleep measurements had been taken. Twenty-four-hour urinary adrenaline and noradrenaline were also examined.

Results: During the CPAP treatment, both 24-h urinary adrenaline and noradrenaline were significantly lower compared with natural sleep. Continuous positive airway pressure significantly decreased the AHI, DSI, % stage 1, and arousal index and significantly increased the lowest SpO_2. There were no significant differences in % stage 2, % stage 3/4, and % REM between before and during CPAP treatment. Multiple analysis of covariance tests revealed that lowest SpO_2 was the most important factor for increasing 24-h urinary noradrenaline levels ($F = 4.75$, $p = 0.048$).

Conclusions: One night CPAP treatment could improve autonomic dysfunction. The assessment of 24-h urinary noradrenaline would provide important information for evaluating the effect of CPAP treatment.

Key words: catecholamine, adrenaline, noradrenaline, obstructive sleep apnea syndrome, autonomic activity, continuous positive airway pressure, lowest oxygen saturation

Introduction

Obstructive sleep apnea syndrome (OSAS) is characterized by repeated episodes of arousal from sleep and of hypoxemia associated with upper airway obstruction, resulting in stimulation of the sympathetic nervous system. These episodes have an immediate effect on the respiratory, circulatory, and central nervous systems.[1–9, 12] The high rate of morbidity and mortality in patients with severe OSAS is related to the coexistence of various cardiovascular diseases.[10–13] The levels of sympathetic activity and blood pressure were higher in patients with OSAS than in normal subjects.[14] We previously showed that hypertension in OSAS occurs both during sleep and when awake.[11] Hence, evaluating the effects of continuous positive airway pressure (CPAP) treatment on autonomic activities is clinically important in patients with OSAS.

The level of noradrenaline in blood varies up to twofold during changes in body position, exercise, stress, and pain.[15] However, the amount of noradrenaline in 24-h urine is more

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stable than that measured in blood and muscle. We speculated that noradrenaline in 24-h urine reflects an increase in sympathetic activity and blood pressure in OSAS both during sleep and when awake.

Accordingly, we investigated the usefulness of noradrenaline in 24-h urine for evaluating the effects of OSAS on autonomic activity and the efficacy of CPAP treatment.

Methods

Patients

Seventeen men with OSAS were enrolled in this study (mean ± standard deviation [SD] values: age, 53.7 ± 13.5 years; height, 168.1 ± 7.0 cm; weight, 76.2 ± 17.9 kg; body mass index, 26.7 ± 4.8 kg/cm^2); all provided appropriate informed consent. The study protocol was approved by the appropriate institutional review committee.

Polysomnography

Polysomnography (PSG) (Alice 3; Respironics, Inc., Murrysville, Penna., USA) was performed from midnight until the patients awoke spontaneously the next morning. The first-night record with natural sleep was considered the control, and the second-night record was used to assess the efficacy of CPAP (Tranquility; Respironics, Inc.). Attended CPAP titration was performed with manual titration on the second night after the baseline sleep, and level of CPAP pressure for each patient was set at the minimum pressure to abolish snoring, oxygen desaturation, obstructive respiratory events, or to determine the highest level tolerated. The electroencephalogram (C3-A2, C4-A1, O1-A2, and O2-A1 electrodes), right and left electro-oculogram, submental electromyograms, airflow (by oronasal thermistor), chest and abdominal movement (by piezo sensors), oxygen saturation (by pulse oximetry), and electrocardiograms (recorded with bipolar CM5) were recorded on PSG. Sleep stage was scored according to the criteria of Rechtschaffen and Kales[16] by visual monitoring.

The number of apnea/hypopnea episodes per hour of sleep (apnea/hypopnea index [AHI]); number of oxygen desaturation episodes per hour (desaturation index [DSI]), lowest oxygen saturation (lowest SpO_2), percentages of stages 1, 2, and 3/4, and rapid eye movement sleep (% stage 1, −2, and −3/4, and % REM, respectively); and the number of arousals per hour (arousal index) were examined. An apnea/hypopnea episode was defined as a cessation of airflow at the mouth and the nose lasting > 10s. The OSAS was defined as an AHI of ≥ 5 episodes/h.[17]

Twenty-Four-Hour Urinary Catecholamine

Sympathetic nervous system activity was estimated from noradrenaline in 24-h urine. The samples were collected into acidified containers containing 20 ml of 6 mol/l hydrochloric acid and stored at 4°C prior to analysis. Urinary noradrenaline was determined by high-performance liquid chromatography with fluorescent detection,[18] and concentrations were expressed as nanomoles per millimole of creatinine to adjust for the effects of urine volume and renal function.[19]

Statistical Analysis

Data are presented as mean ± SD and compared between the groups with the Wilcoxon signed rank sum test. A probability value of < 0.05 was considered to indicate statistically significant differences between the groups. The multiple analysis of covariance test was also performed.

Results

Apnea/hypopnea index, DSI, % stage 1, and arousal index were significantly lowered by the CPAP treatment (AHI, from 42.5 ± 25.9 to 9.3 ± 7.9/h; DSI, from 34.9 ± 26.4 to 5.5 ± 6.4/h; % stage 1, from 41.9 ± 24.7 to 26.3 ± 15.0%; arousal index, from 44.4 ± 17.8 to 19.1 ± 11.8 /h), and lowest SpO_2 was significantly increased (from 76.0 ± 12.0 to 86.9 ± 7.6%). There were no significant differences in % stage 2, % stage 3/4, and % REM between before CPAP and during CPAP treatment (Table I).

During CPAP treatment, 24-h urinary adrenaline and noradrenaline were both significantly lower compared with natural sleep (adrenaline, from 4.8 ± 2.0 to 3.1 ± 1.8 nmol/mmol creatinine [CRE]; noradrenaline, from 81.5 ± 47.8 to 47.0 ± 26.8 nmol/mmol CRE) (Fig. 1). A multiple analysis of covariance test revealed that lowest SpO_2 was the most important factor for increased noradrenaline in 24-h urine levels ($F = 4.75$, $p = 0.048$) (Table II).

Discussion

In patients with OSAS, AHI, DSI, % stage 1, and arousal index were significantly decreased, and lowest SpO_2 was sig-

TABLE I Polysomnographic findings

	Before	On CPAP	p Value
AHI (/h)	42.5 ± 25.9	9.3 ± 7.9	< 0.05
DSI (/h)	34.9 ± 26.4	5.5 ± 6.4	< 0.05
Lowest SpO_2 (%)	76.0 ± 11.9	86.9 ± 7.6	< 0.05
Stage 1 (%)	41.9 ± 24.7	26.3 ± 15.0	< 0.05
Stage 2 (%)	45.4 ± 25.8	50.7 ± 23.4	NS
Stage 3/4 (%)	0.7 ± 1.5	1.1 ± 2.9	NS
Stage REM	13.7 ± 7.3	21.3 ± 16.6	NS
Arousal index (/h)	44.4 ± 17.8	19.1 ± 11.8	< 0.05

All results given as mean ± standard deviation.
Abbreviations: AHI = the number of apnea/hypopnea episodes per hour, DSI = the number of oxygen desaturation episodes per hour, lowest SpO_2 = lowest oxygen saturation, arousal index = the number of arousals per hour, NS = not significant.

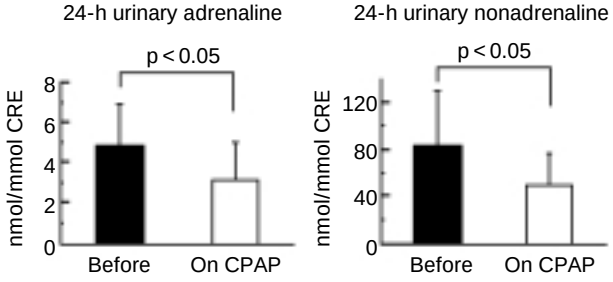

FIG. 1 Influence of continuous positive airway pressure (CPAP) treatment on 24-h urinary catecholamines. During CPAP treatment, 24-h urinary adrenaline and noradrenaline were both significantly lower compared with natural sleep (adrenaline, from 4.8 ± 2.0 to 3.1 ± 1.8 nmol/mmol CRE; noradrenaline, from 81.5 ± 47.8 to 47.0 ± 26.8 nmol/mmol CRE). CRE = creatinine.

nificantly increased with CPAP treatment. Noradrenaline in 24-h urine as an index of sympathetic nerve activity was lowered compared with the value before treatment. Twenty-four-hour urinary noradrenaline might thus provide a noninvasive index of autonomic function, yielding important information about the effect of CPAP.

Sympathetic nerve activity in muscle and blood pressure during sleep were higher in patients with OSAS than in normal control subjects,[14] which was consistent with our findings. Frequent episodes of hypoxia, respiratory acidosis, pleural pressure swings, arousal responses, and the resulting elevation in catecholamine secretion may contribute to an elevation in sympathetic nerve activity during both nighttime and daytime.[1, 2, 11, 12, 20–23] The nocturnal concentration of plasma noradrenaline in patients with OSAS was increased and correlated with the severity of overnight oxygen desaturation.[11, 23] Our finding suggests that hypoxemia and sleep fragmentation in patients with OSAS elevated sympathetic activity, leading to increased 24-h urinary noradrenaline.

The significant reduction in 24-h urinary noradrenaline by CPAP treatment indicates that increased sympathetic activity is caused by hypoxemia and sleep fragmentation in OSAS, which was improved by CPAP treatment. Waravdekar *et al.*[24] have demonstrated that muscle sympathetic nerve activity (MSNA), measured by peroneal microneurography, is elevated in patients with OSAS and that MSNA decreases after nasal CPAP treatment, which supports our findings. Minemura *et al.*[25] reported that patients who received CPAP showed a significant decrease in daytime and nighttime urinary noradrenaline levels, but that there were no correlations between PSG parameters and the reductions in catecholamine levels. Although the reason for the discrepancy between their results and the present findings is unclear, it is possible that the methods used to measure urinary noradrenaline levels contribute to the difference in the findings. The chronic effect of sleep apnea per se on the autonomic activity is not fully understood. A canine model of OSAS provided evidence that OSAS can lead to a persistent increase in blood pressure not only during both nighttime and daytime.[2] We previously showed that frequent

TABLE II Most important factor for increasing 24-h urinary noradrenaline levels

	F	p Value
AHI (/h)	0.60	NS
Lowest SpO_2 (%)	4.75	< 0.05
Arousal index (/h)	0.26	NS

Abbreviations as in Table I.

hypoxemia episodes with arousal result in an increase in nocturnal blood pressure.[9, 12, 13] Therefore, noradrenaline in 24-h urine is considered a useful indicator for evaluating the effect of CPAP treatment, including during follow-up.

While the noradrenaline in blood, muscle, and urine can be measured, the level in both blood and muscle requires invasive sampling and can easily fluctuate. Noradrenaline measured in blood is influenced by body position, exercise, stress, and pain.[15] In contrast, noradrenaline in 24-h urine is collected noninvasively and its level is more stable than that in blood and muscle. The urinary noradrenaline levels, by virtue of their integration throughout 24-h of monitoring, may be a more valid index of sympathetic activity[26] than plasma levels, which are greatly influenced by the condition of the subject in the few minutes prior to sampling.[27] On the other hand, the level of plasma noradrenaline represents a summation of all noradrenaline released throughout the body, but most prominently from the vasculature and the peripheral muscle beds,[28] whereas noradrenaline in 24-h urine reflects underlying pathophysiologic processes occurring during both sleep and when awake. The sympathetic activity increases both during sleep and when awake in OSAS,[1, 2, 11, 12, 20–23] and hence assessment of 24-h urinary noradrenaline could be a good tool for estimating autonomic dysfunction in OSAS.

Conclusion

We found that 24-h urinary noradrenaline reflecting sympathetic nerve activity was improved after 1 night CPAP treatment in patients with OSAS. The assessment of 24-h urinary noradrenaline represented important data for evaluating the effect of CPAP treatment on sympathetic activity.

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