



## Effect of Continuous Positive Airway Pressure on Nocturnal Urine Production in Patients With Obstructive Sleep Apnea Syndrome

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**Aim:** The aim of this study was to identify the clinical features of patients with obstructive sleep apnea syndrome (OSAS) and investigate the impact of continuous positive airway pressure (CPAP) treatment on nocturnal urine volume.

**Materials and Methods:** This study enrolled 53 patients with moderate-to-severe OSAS and an apnea-hypoxia index of >20/hr. Data were collected on serum brain natriuretic peptide (BNP) level, International Prostate Symptom Score-Quality of Life (IPSS-QOL) score, Overactive Bladder Symptom Score (OABSS), International Consultation on Incontinence Modular Questionnaire-Nocturia QOL (ICIQ-NQOL) score, Epworth Sleepiness Scale (ESS) score, and the frequency volume chart. Only patients who continued CPAP treatment for 3 months were included in the analysis.

**Results:** In total, 40 patients (33 men and 7 women) completed the study (75.5%). The mean age was 56.9 years. The night-time frequency to void was significantly decreased from 2.1 to 1.2 after CPAP treatment ( $P < 0.01$ ). The mean scores as assessed by ESS, IPSS-QOL, OABSS, and ICIQ-NQOL significantly improved after CPAP ( $P < 0.01$ ). The mean diastolic blood pressure significantly decreased after CPAP treatment. However, there was no significant change in the BNP level before and after CPAP treatment. In the frequency volume chart, hours of undisturbed sleep, total nocturnal voided volume, and nocturnal polyuria index significantly improved after CPAP treatment ( $P < 0.05$ ). However, 24-hr voided volume and mean voided volume during night-time did not change after CPAP treatment. **Conclusion:** CPAP treatment decreases night-time urinary frequency by reducing nocturnal urine production and improves QOL in patients with OSAS. *Neurourol. Urodynam.* 36:376–379, 2017. © 2015 Wiley Periodicals, Inc.

**Key words:** BMI; frequency volume chart; hypertension; nocturia

### INTRODUCTION

Nocturia is a common and bothersome problem, and its prevalence increases with age. Up to 60% of patients >70 years of age void  $\geq 2$  times per night.<sup>1</sup> The number of nocturia voids is associated with a detrimental effect on health-related quality of life (QOL). In elderly patients with  $\geq 2$  voids per night, the risk of falls and hip fracture increases remarkably.<sup>2–4</sup> In addition, in these populations, the risk of death increases even after adjusting for several possible contributing comorbidities and lifestyle factors.<sup>3,4</sup> In our recent study, 23.3% of younger patients (<49 years) visiting a general medical clinic showed nocturia; however, of them 80% did not visit a urological clinic.<sup>5</sup> Therefore, it is important to investigate the etiology of nocturia and treat it precisely and in a timely manner.

Multiple factors contribute to the occurrence of nocturia. Nocturnal polyuria is one of many causes of nocturia.<sup>6</sup> Obstructive sleep apnea syndrome (OSAS) is highly prevalent in older men and is believed to be one of the causes of nocturnal polyuria. In patients with OSAS, night-time frequency of more than once is reported to increase by 52–77%, depending on the severity of sleep-disordered breathing.<sup>7,8</sup> Nocturnal polyuria in patients with OSAS may be caused by an increasingly negative intrathoracic pressure because partial or complete obstruction of the airway stimulates venous return to the atrium, and atrial natriuretic peptide secretion is increased in response to right atrium distention.<sup>9–11</sup> In addition, OSA-induced hypoxemia results in increased pulmonary arterial resistance by alpha- and beta-adrenergic stimulation, and the latter causes increased

ANP production by the heart.<sup>12</sup> Continuous positive airway pressure (CPAP) treatment is one of the effective treatments for OSAS. CPAP treatment improves not only sleep disorder but also night-time frequency.<sup>13</sup> However, the underlying mechanisms by which CPAP treatment improves night-time frequency in patients with OSAS remains to be completely elucidated. The aim of this study was to identify the clinical features of patients with OSAS and investigate the impact of CPAP treatment on nocturnal urine volume.

### METHODS

#### Study Design

A prospective clinical study design was used for this investigation. The initial study sample consisted of patients with night-time frequency of  $\geq 1$ , who were referred to Nakamura Clinic and Yonabaru-Chuo Hospital in Okinawa,

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Japan, for polysomnography because of suspected OSAS between January 2013 and March 2015. After polysomnography, patients detected with no OSAS were excluded from the study. Only patients who continued CPAP treatment for 3 months were included in the analysis. This study was conducted in accordance with the Declaration of Helsinki and ethics guideline for clinical research and was approved by the institutional review board at the Ryukyu University (490). All patients gave written informed consent before participating in the study.

#### Participants

In total, 53 patients with moderate-to-severe OSAS and an apnea-hypoxia index (AHI) of  $>20/\text{hr}$  were enrolled in the study. Moderate OSAS was defined as  $15 \leq \text{AHI} < 30$ , while severe OSAS was defined as  $\text{AHI} \geq 30$ .<sup>14</sup> They agreed to undergo CPAP treatment and participate in this study. Subjects with urological diseases taking urological medication were excluded from the study. Similarly, patients who were treated with diuretics due to congestive heart failure or renal failure were also excluded from the study.

#### Study Protocol

All patients were screened by undertaking a clinical interview based on their medical history and current medication. Data were collected on age, sex, body mass index (BMI), and blood pressure. Concentrations of electrolytes in the nocturnal urine were determined. Biochemical profiles including hemoglobin A1c, estimated glomerular filtration rate (eGFR), and brain natriuretic peptide (BNP) level were examined. Nadir arterial oxygen saturation was also examined.

Before polysomnography, measurements were performed to evaluate the International Prostate Symptom Score-Quality of Life (IPSS-QOL) score, Overactive Bladder Symptom Score (OABSS), International Consultation on Incontinence Modular Questionnaire-Nocturia QOL (ICIQ-NQOL) score, and Epworth Sleepiness Scale (ESS) score to investigate the lower urinary tract symptoms and sleeping disorders. These questionnaires were translated into Japanese; the Japanese version was validated and its reliability confirmed.<sup>15-17</sup> The number of nocturnal voids was determined by question 7 in IPSS-QOL questionnaire ("In the last month or so, how many times did you typically get up to urinate, from the time you went to bed until the time you got up in the morning?"). OABSS urgency score (question 3 in questionnaire) of  $\geq 2$  and a total OABSS of  $\geq 3$  was defined as overactive bladder syndrome. During polysomnography, a frequency volume chart was determined.

OSAS was diagnosed on the basis of full-night polysomnography using a digital polysomnography system (ALICES Diagnostic Sleep System, Philips, Tokyo, Japan). Apnea was defined as a complete airflow cessation for at least 10 sec, and hypopnea was defined as  $\geq 50\%$  reduction in airflow for at least 10 sec, followed by  $\geq 3\%$  oxygen desaturation. AHI was calculated as the total number of apnea and hypopnea episodes per hour of sleep.

Change in these data was assessed 3 months after CPAP treatment, and the measurements were compared before and after CPAP treatment.

#### Statistical Analysis

Data were expressed as mean  $\pm$  SD and analyzed using commercial statistical software (JMP 9.0, Cary, NC). Changes of variables before and after CPAP treatment were evaluated by

the Wilcoxon signed rank test. A *P* value of  $<0.05$  was considered to be statistically significant.

## RESULTS

### Patient Characteristics

In total, 13 patients were excluded from the analysis, five because they did not show nocturia, six because they did not undergo CPAP treatment, and two because they quit CPAP treatment. Altogether, 40 patients (33 men and 7 women) completed the study (75.5%). The characteristics of the 40 eligible patients are listed in Table I. The mean patient age was  $56.9 \pm 14.1$  years, BMI  $28.4 \pm 4.2 \text{ kg/m}^2$ , AHI  $56.8 \pm 28.1/\text{h}$ , and ESS score  $8.3 \pm 5.1$ . Of the patients, 55% had hypertension; 40% had dyslipidemia, and 20% had diabetes mellitus. Concentrations of electrolytes in nocturnal urine was low ( $1.019 \pm 0.009$ ). Level of serum BNP level was high ( $27.6 \pm 56.3$ ).

### Effect of CPAP Treatment on BMI, Blood Pressure, ESS, and BNP

BMI had a tendency to decrease after CPAP treatment; however it was not significant. The mean diastolic blood pressure before CPAP treatment was 81.6 mmHg; however, after treatment it decreased to 77.5 mmHg ( $P < 0.05$ ). The mean ESS score before CPAP treatment was 8.3, whereas after treatment it decreased to 6.1 ( $P < 0.01$ ). However, serum BNP level remained unchanged after CPAP treatment (27.6 vs. 28.1) (Table II).

### Effect of CPAP Treatment on Lower Urinary Tract Symptoms and Parameters of the Frequency Volume Chart

The mean IPSS score before CPAP treatment was 7.6, and after treatment it decreased to 5.0 ( $P < 0.01$ ). The night-time frequency to void before CPAP treatment was 2.1 times; however, after CPAP treatment it decreased to 1.2 times ( $P < 0.01$ ). The mean QOL index before CPAP treatment was 3.4; however, after treatment it decreased to 1.9 ( $P < 0.01$ ). The mean OABSS before CPAP treatment was 4.2, which decreased

TABLE I. Patient Characteristics

Male:Female	33:7
Age, y	$56.9 \pm 14.1$
Diabetes mellitus, yes	n = 8 (20%)
Hypertension, yes	n = 22 (55%)
Dyslipidemia, yes	n = 16 (40%)
Cerebrovascular disease, yes	n = 3 (7.5%)
Ischemic heart disease, yes	n = 4 (10%)
Depression, yes	n = 3 (7.5%)
BMI ( $\text{kg/m}^2$ )	$28.4 \pm 4.2$
AHI (events/hr)	$56.8 \pm 28.1$
ESS	$8.3 \pm 5.1$
Blood pressure (mmHg)	
systolic	$140.0 \pm 20.1$
diastolic	$81.6 \pm 14.7$
Nadir pO <sub>2</sub> (mmHg)	$88.4 \pm 9.0$
Concentrations of electrolytes in nocturnal urine	$1.019 \pm 0.009$
eGFR ( $\text{ml/min}/1.73\text{m}^2$ )	$76.3 \pm 16.3$
HbA1c (%)	$5.9 \pm 0.8$
BNP (pg/ml)	$27.6 \pm 56.3$

BMI, body mass index; AHI, apnea-hypopnea index; ESS, Epworth Sleepiness Scale; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; BNP, brain natriuretic peptide.

to 2.0 after CPAP treatment ( $P < 0.01$ ). Urgency (as analyzed by question 3 in OABSS) before CPAP treatment was 1.2; it thereafter decreased to 0.6 ( $P < 0.05$ ). Before CPAP treatment, overactive bladder syndrome was detected in 11/39 patients (28.2%); however, after CPAP treatment, it was found to be decreased in 4/37 patients (10.8%). The mean ICIQ-NQOL score before CPAP treatment was 75.9%; after CPAP treatment, it improved to 89.6% ( $P < 0.01$ ). The mean impact on QOL before CPAP treatment was 2.3; after CPAP treatment it decreased to 1.3 ( $P < 0.05$ ).

Based on the frequency volume chart, the number of hours of undisturbed sleep was significantly prolonged from 193.6 min to 287.3 min after CPAP treatment. In addition, total nocturnal voided volume was significantly decreased from 723.3 ml to 453.6 ml after CPAP treatment ( $P < 0.01$ ). Nocturnal polyuria index was also significantly decreased from 37.0% to 28.6% after CPAP treatment ( $P < 0.05$ ). However, the 24-hr voided volume, mean voided volume during night-time, and 24-hr oral water intake did not change after CPAP treatment (Table II).

### DISCUSSION

Nocturia can cause overproduction of urine, reduced bladder capacity, or a combination of both.<sup>6</sup> OSAS may cause nocturia by overproducing urine during the night-time. One aim of the present study was to examine the impact of CPAP treatment on nocturnal urine production in patients with OSAS. In the present study, CPAP treatment decreased night-time urinary frequency and improved IPSS, QOL index, OABSS, and ICIQ-NQOL in patients with OSAS. Such improvement could only be ascribed to the reduction of nocturnal urine production because there was no improvement in other variables based on the frequency volume chart. There have been several studies about night-time frequency in patient with OSAS.<sup>18,19</sup> However, few studies have investigated the impact of CPAP treatment on nocturnal urine production and related QOL and biological findings.<sup>13</sup> In addition, the problem of treatment compliance is frequently encountered in patients with OSAS. Some studies have reported that 29–48.2% of patients with OSAS do not undergo CPAP treatment.<sup>20,21</sup> However, in the present study,

only 8/53 patients abandoned CPAP treatment (compliance ratio 84.9%). Therefore, the present study is unique, and all the parameters previously mentioned have been comprehensively analyzed with relatively high CPAP compliance rate.

In the present study, nocturnal urine production was decreased; this might have improved the night-time frequency, hours of undisturbed sleep, and ESS. The BNP level was high before CPAP treatment and remained unchanged after the decrease in nocturnal urine volume. One possible speculation to explain this discrepancy is that most of the participants in this study were relatively young and might not have an altered BNP level, which is a marker of heart pump failure. One reasonable explanation for the positive impact of CPAP treatment on nocturia is the normalization of atrial natriuretic peptide (ANP), although changes in serum ANP were not assessed in this study. Pressman et al.<sup>22</sup> reported that 79.4% of the awakenings during night were due to apnea, hypopnea, or other sleep disturbances. OSAS was associated with greater fractional urinary flows and lowered filtered sodium reabsorption.<sup>23</sup> Miyauchi et al.<sup>13</sup> also reported that nocturnal urine production and urine electrolytes (u-Na, u-Cl, and u-K) significantly decreased 1 month after CPAP treatment. Therefore, another explanation is that hypoxia by OSAS prevents reabsorption of sodium in the renal tubules, resulting in nocturnal polyuria during night-time, while CPAP treatment reverses it. In fact, in the present study, concentration of electrolytes in nocturnal urine was low, which may lead to the overproduction of urine. Further studies are necessary to clarify this point.

Nocturnal polyuria is unlikely to be the only component of OSAS-induced nocturia. Clinical studies showed that polysomnographically detected OSAS and oxygen desaturation correlate with cystometric changes in spike wave amplitude.<sup>24</sup> Witthaus et al.<sup>25</sup> reported that intermittent hypoxia (8 weeks) in rats induced cystometric changes, detrusor instability, and bladder noncompliance and increased spontaneous contractions accompanied by increase in tissue malondialdehyde and oxidation proteins. This suggests that it is possible to develop noninvasive urinary markers to diagnose bladder dysfunction. In the present study, the rate of overactive bladder syndrome decreased from 28.2% to 10.8% after CPAP treatment. However,

TABLE II. Changes in the QOLs and Biochemical Findings After CPAP Treatment Profile

	Before CPAP treatment (Mean $\pm$ SD)	After CPAP treatment for 3 months (Mean $\pm$ SD)	P-value
BMI (kg/m <sup>2</sup> )	28.4 $\pm$ 4.2	28.2 $\pm$ 4.0	0.113
Blood pressure (mmHg)			
Systolic	140.0 $\pm$ 20.1	135.3 $\pm$ 16.6	0.091
Diastolic	81.6 $\pm$ 14.7	77.5 $\pm$ 9.2	0.03
BNP (pg/ml)	27.6 $\pm$ 56.3	28.1 $\pm$ 51.8	0.603
ESS	8.3 $\pm$ 5.1	6.1 $\pm$ 3.8	0.005
IPSS total	7.6 $\pm$ 5.5	5.0 $\pm$ 4.3	0.005
Q7 night time frequency (times)	2.1 $\pm$ 1.2	1.2 $\pm$ 1.1	0.001
QOL index	3.4 $\pm$ 1.5	1.9 $\pm$ 1.5	0.000
OABSS total	4.2 $\pm$ 2.6	2.0 $\pm$ 1.6	0.000
Q3 urgency	1.2 $\pm$ 1.6	0.6 $\pm$ 1.1	0.013
ICIQ-NQOL (%)	75.9 $\pm$ 18.5	89.6 $\pm$ 12.5	0.000
Impact on QOL	2.3 $\pm$ 2.4	1.3 $\pm$ 2.3	0.028
Hours of disturbed sleep (min)	193.6 $\pm$ 132.1	287.3 $\pm$ 136.4	0.001
Total nocturnal voided volume (ml)	723.3 $\pm$ 498.4	453.6 $\pm$ 251.4	0.007
24 hr-voided volume (ml)	2119.7 $\pm$ 1621.9	1729.6 $\pm$ 877.3	0.062
Nocturnal polyuria index (%)	37.0 $\pm$ 16.2	28.6 $\pm$ 14.7	0.011
Mean voided volume during night time (ml)	316.9 $\pm$ 164.5	289.4 $\pm$ 154.1	0.31
Water intake per day (ml)	1604.3 $\pm$ 720.4	1600.4 $\pm$ 629.7	0.779

BMI, body mass index; BNP, brain natriuretic peptide; ESS, epworth sleepiness scale; IPSS, International Prostate Symptom Score; OABSS, overactive bladder symptom score; ICIQ-NQOL, International Consultation on Incontinence Modular Questionnaire-Nocturia QOL.

mean voiding volume during night-time did not change significantly after CPAP treatment (316 ml vs. 289 ml). It is possible that CPAP treatment for 3 months might not be sufficient to restore oxidative changes. Taken together, OSAS may be a consequence of recurring hypoxia/reoxygenation and oxidative damage to tissues (i.e., renal tubules and bladder), resulting in nocturia.

In this study, we found that patients with OSAS were concomitant with 55% of hypertension, and CPAP treatment decreased diastolic blood pressure. Hypertension is associated with a significant increase in the risk of nocturia.<sup>5</sup> Because nocturnal polyuria is characterized by natriuresis,<sup>26</sup> it has been suggested that nocturnal polyuria and essential hypertension are manifestations of the same pathological process. Hypertension may be related to nocturia because of its effect on cardiovascular (edema and congestive heart failure with atrial stretch and release of atrial natriuretic peptide) or renal (effects on GFR and tubular transport) physiologies.<sup>27</sup> Previous studies showed that CPAP treatment improves not only the symptom of OSAS but also the rate of comorbid disorders, cardiovascular morbidity, and mortality.<sup>20,28–30</sup> However, BMI did not change significantly after CPAP treatment in the relatively short period (3 months) of the present study. Further research investigating the relationship between nocturia, blood pressure, sodium and water homeostasis, and factors influencing endogenous pressor secretion are required. Overall, CPAP treatment may cause a reduction in the blood pressure that may in turn improve nocturnal urine volume.

A limitation of this study is its small sample size and low number of females, despite males being more at risk of OSAS.<sup>31</sup> Secondly, the frequency volume chart was measured before and after CPAP treatment on a single night. Thirdly, the questionnaires were self-reported, and lastly, we cannot completely rule out the possibility that the increased prevalence of pathological nocturia is attributed to another reason. However, the results reported in this study relied on a numerical factor before and after CPAP treatment based on BNP and QOL evaluations. Despite this limitation, we believe that the outcomes of the present study are of significance for future studies on nocturia.

### CONCLUSION

We found that CPAP treatment decreased nighttime urinary frequency by reducing nocturnal urine volume and improved QOL in patients with OSAS. Diastolic blood pressure was also decreased after CPAP treatment. However, BNP level did not change with the decrease in nocturnal urine volume. An improvement in natriuresis associated with hypertension and hypoxia in the kidney might be the main effect of CPAP treatment in patients with OSAS.

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