The Impact of Obstructive Sleep Apnea Syndrome on Nocturnal Urine Production in Older Men with Nocturia

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INTRODUCTION

Nocturia, defined by the International Continence Society as having to wake up one or more times to void, is the most prevalent of lower urinary tract symptoms[1] and occurs with increasing frequency with advancing age.[2] Nocturia is particularly bothersome for patients and their partners because of sleep disturbance.[3] Sleep fragmentation and chronic sleep loss attributed to nocturia have a negative impact on quality of life (QOL), and are associated with increased morbidity and mortality.[4] It is very important to investigate the etiology of nocturia before treating patients complaining of this disorder. Nocturnal polyuria (NP) is one of many causes of nocturia.

Obstructive sleep apnea syndrome (OSAS) is highly prevalent in older men and is thought to be one of the causes of NP.[5] One of the mechanisms that has been suggested as a contributing factor is hemodynamic stress due to negative intrathoracic pressure during each apnea episode caused by attempts to breathe against an occluded airway. Brain natriuretic peptide (BNP), a diuretic and vasodilatory hormone, is secreted by the cardiac ventricles in response to volume expansion and pressure load.[6] This cardiac hormone increases sodium and water excretion, and also inhibits other hormone systems that regulate fluid volume, vasopressin, and the renin–angiotensin–aldosterone complex. As a result, nocturnal urine production might be increased in older men with OSAS.

The lack of a definite diurnal rhythm in most elderly subjects could to some extent explain the increased diuresis during the night in older adults.[7] Hirayama suggested that leg edema

influenced, though not directly, nocturnal urine volume (NUV) with an associated decrease in antidiuretic hormone (ADH) secretion.[8] Overnight rostral fluid displacement from the legs, related to prolonged sitting, may play a previously unrecognized role in the pathogenesis of obstructive sleep apnea in non-obese men that is independent of body weight.[9,10]

We hypothesized that there are many individuals who potentially have OSAS among older men with NP. The aim of this study was to investigate the impact of OSAS on night-time secretion of BNP and ADH in older men with nocturia accompanied by NP.

MATERIALS AND METHODS

The purpose and methods of this study were approved by the institutional review board and fully explained to the patients, who then provided written informed consent.

A total of 106 male nocturia patients 60 years of age or older, admitted to the Sleep Medicine Center to determine whether or not they had OSAS, were enrolled in this study. Since Ljunggren reported that there is a dose-response relationship between the severity of sleep apnea during the night and the levels of plasma BNP in the morning [6], we excluded patients with a mildly elevated apnea-hypopnea index (AHI) (events/hour) ($5 \leq AHI < 15$). A nocturnal voided volume (NVV) greater than 35% of the 24-hour production (nocturnal polyuria index, $NPi \geq 0.35$) was defined as NP. Patients with NPi less than 0.35 were also excluded from this study. Patients with a history of heart disease, diabetes mellitus with a fasting blood glucose of 200 mg/dL or more, serum creatinine (Cre) greater than 1.5 ng/dL, liver dysfunction, hydronephrosis, post-void residual urine volume greater than 50 mL, active infection, 24-hour voided volume greater than 40ml x weight, or habitual diuretic or lithium use were also excluded from the study.

Patients ate the same meals at 7:00 AM, 12:00 PM, and 6:00 PM as those served in the hospital, which included about 1300mL water and less than 3.5g NaCl per day. They ingested only pure water or Japanese tea to relieve their thirst. All 106 participants underwent full-night polysomnography (PSG) in the Sleep Medicine Center. Blood pressure, blood counts, standard chemistry panel, BNP measurements, and urinalysis were conducted routinely. The participants' heights and weights were measured and the body mass index (BMI) was calculated for each patient. The post-void residual urine volume and

the presence of hydronephrosis were determined by ultrasonography. A frequency volume chart (FVC) was recorded on the same day that PSG was performed. NUV was defined as the total amount of urine voided between 10:00 PM and 6:00 AM, including the first voided volume after waking. A single urine sample voided at 6:00 AM was obtained from all patients and then stored at -20°C until analysis. To evaluate ADH and sodium secretion during the night, urinary ADH (u-ADH), sodium (u-Na), and Cre (u-Cre) were measured according to previously reported methods.[11] Urinary osmolality was also determined. u-ADH and u-Na were adjusted by the u-Cre level (u-ADH/u-Cre and u-Na/u-Cre) to decrease the volumetric influence of urine production.

Polysomnographic Evaluations

PSG consisted of continuous recordings from 6 electroen- cephalographic (EEG) leads, 2 electrooculographic leads, 5 electromyographic leads (2 submental and bilateral anterior tibialis and unilateral MAS muscles), nasal cannula with a pressure transducer and thermal sensor for nasal airflow, strain gauges for thoracic and abdominal movements, pulse oximetry, and electrocardiography. Simultaneous audio-video recording was made. Subjects went to bed at their usual bedtime or before 23:30, and the recording was terminated after 6:30. Apnea and hypopnea were defined following the rules of the American Academy of Sleep Medicine.[12] An apnea was defined as $\geq$ 90% reduction in air flow for $\geq$ 10 sec; hypopnea as $\geq$ 50% reduction of airflow for $\geq$ 10 sec associated with arousals or with $\geq$ 3% reduction in oxygen saturation. The AHI was calculated as the mean number of obstructive apneas and hypopneas per hour of sleep.

Statistical analysis

The Mann-Whitney U test was used for intergroup comparisons. A $p<0.05$ was considered statistically significant. The Stat View program, version 5.0, was used to conduct all statistical analyses.

RESULTS

Patient characteristics

Twenty-three patients were excluded, 18 because they had an AHI ($5 \leq AHI < 15$) indicating mild OSAS and 5 with NPi under 0.35, from the analysis. The characteristics of the eligible 83 patients are listed in Table 1. The mean patient age was 69.4±5.9 years. Fifty-one patients had hypertension. However, none of the patients had been diagnosed with chronic heart failure.

Sleep measurements in OSAS patients and non-OSAS patients as a control group are shown in Table 2. There was no significant difference in age. Patients with OSAS had significantly higher BMI ($p<0.0001$), higher systolic blood pressure ($p=0.0396$), and higher AHI ($p<0.0001$) than those without OSAS.

As to blood counts and standard chemistry panels, no significant differences were detected. BNP was significantly higher in the OSAS group than in the control group (48.6±41.4 vs. 30.7±31.5, $p=0.0006$).

On urinalysis, OSAS patients showed significantly higher u-Na/u-Cre secretion than controls (24.7±11.3 vs. 16.2±5.1, $p<0.0001$). Urine osmolality was also higher in OSAS patients than in the controls (616±172 vs. 516±174, $p=0.0285$). There was no significant difference in the ratio of secretion of u-ADH to u-Cre (u-ADH/u-Cre) (6.7±10.4 vs. 6.8±7.8, $p= 0.3617$) between the two groups.

The FVC revealed no significant differences in NUV or 24-hour urine production between the two groups (OSAS vs. Control: 712±271 vs. 688±213, p=0.7294 and 1500±491 vs. 1470±328, p=0.7284, respectively).

There were significant differences in nocturia and 24-hour frequency (OSAS vs. Control: 2.2±2.1 vs. 2.5±1.0, p=0.0115 and 8.2±2.7 vs. 11.4±2.5, p<0.0001, respectively) between the OSAS and control groups. Maximum voided volume was greater in OSAS patients than in control patients (OSAS vs. Control: 372±137 vs. 289±61, p=0.0048).

COMMENT

NP and nocturia in older adults reduce QOL and should be urgently addressed; these disorders are considered to be associated with various factors and the causes have not yet been fully elucidated. NP is reportedly one of many causes of nocturia.[2] Considering NP due to an abnormal circadian rhythm of urine production, it is important to decide whether the abnormality stems from an effect on water diuresis or solute diuresis[13] Circadian rhythm deficiency of ADH[7] and an increase in the diuretic hormones, such as atrial natriuretic peptide (ANP) and BNP, which are used in screening or monitoring for heart failure, are thought to be important etiologies of NP.[14]

While the association with OSAS is reportedly one cause, there have been no reports applying ADH and BNP as objective indices. In this study, we endeavored to elucidate the cause of NP by incorporating these two indices.

OSAS patients generally have a poor sleep, because of the sleep disorders breathing, and likely to go to bathroom many time at night. In this study, there were significant differences in nocturia and 24-hour frequency (OSAS vs. Control: 2.2±2.1 vs. 2.5±1.0, $p=0.0115$ and 8.2±2.7 vs. 11.4±2.5, $p<0.0001$, respectively) between the OSAS and control groups. We think that the reason of these counterintuitive results are due to the less maximum voided volume in the group without OSAS than that with OSAS, i.e., a less functional bladder capacity contributed to this results.

Following ANP, BNP was the second uretic peptide isolated from the pig brain. It is primarily secreted from the ventricle when a pressure load or a volumetric load is applied; with its vasodilating and diuretic actions, BNP plays an important role in adjusting systemic fluid volume and blood pressure. Ljunggren et al.[6] reported that BNP shows a positive correlation with the severity of sleep apnea. While the half-life of BNP is only approximately 20 minutes, that of ANP is even shorter at just 10 minutes; therefore, in order to detect the effects of OSAS, samples must be collected quickly before subjects get out of bed, i.e., immediately after resolution of the non-respiratory condition. Accordingly, BNP, which has a longer half-life, was collected at time of awakening in this study, considering that this allows the effect of OSAS to be determined more definitively. The plasma BNP level is very low in healthy people, whereas it increases in patients with cardiac failure according to its severity. In this study, BNP levels were high in both the OSAS and the non-OSAS group, at 48.6±41.4 and 30.7±31.5, respectively. However, none of the patients had evidence of cardiac failure. As Ouslander et al.[15] reported that BNP levels increase with aging, their advanced ages are considered to have been among the causes of high BNP levels at baseline in both of our groups. We thought the high levels of BNP might increase nocturnal urine production on both groups in this study. In addition, the BNP levels were higher in the OSAS than in the non-OSAS group and this was attributed to a mechanism unique to OSAS[6], i.e., excessive secretion of BNP from the ventricle due to hemodynamic stress induced by lowered pressure in the thoracic cavity and increased venous flow, which occurs when patients with airway obstruction inhale. In other words, fluid retention is more serious in OSAS patients than in non-OSAS patients. This

resulted in natriuresis, which led to high levels of u-Na and urine osmolality in the OSAS group on urinalysis.

We used u-ADH instead of plasma ADH to measure the amount of ADH secretion during the night. The u-ADH parameter reportedly represents an integrated value of periodic ADH secretion.[16-18] In addition, ADH is more stable in urine than in plasma. Moreover, our previous study found plasma ADH to simultaneously have a strong significant correlation with u-ADH. The u-ADH level in the urine collected at 6 hours showed a strong significant correlation with the timed single-voided urine sample obtained immediately after the 6-hour urine collection.[11] This indicates that the u-ADH at 6 AM represents nocturnal ADH secretion.

If OSAS predisposed NP patients to have more serious fluid retention, ADH secretion is likely to be lower in OSAS group. However, there was no difference in ADH secretion between OSAS and non-OSAS groups in this study. It was thus assumed that OSAS has no direct effect on the secretion of ADH. Asplund et al.[7] reported decreased ADH secretion in association with aging and that this was an the effect of cerebral infarction, etc. Hirayama et al.[8, 19] reported that NP in older adults is caused by leg edema and that decreased ADH secretion is indirectly associated with this effect. ADH secretion was low in our OSAS group as well as in our non-OSAS group. It is not possible to determine in this study the reasons for low ADH levels, which might have been attributable to direct factors affecting hormone secretion such as cerebral infarction reported by Asplund et al., or leg edema indirectly imposing negative feedback on the pituitary gland. However, since this study

involved elderly patients, there is a possibility of associations among decreased ADH secretion, NP, and leg edema, and these factors may combine to exacerbate NP.

There are reports stating that fluid retained in the legs during the day moves to the upper body when patients are supine at night, causing laryngeal edema, etc., which can also cause OSAS even in non-obese people.[9, 10] According to the BMI classification advocated by WHO, our series of patients with and without OSAS are sub-classified as overweight when BMI is 26.4±3.2 and as normal weight when BMI is 23.2±3.3, respectively. Although there is a statistical difference between these two groups, neither can be categorized as obese. Thus, OSAS due to obesity alone is not the cause of NP. Our observations indicate that slim patients can also have OSAS.

NP in older adults should not be viewed as a single disorder; it can be caused by combinations of various factors, such as natriuresis induced by OSAS, decreased ADH secretion of various etiologies, or fluid transfer from leg edema. Therefore, at the time of treatment, NP should be examined not only by conducting a detailed medical interview and confirming physical findings but also by observing objective indices such as urination diaries and blood test data. It is also considered to be necessary to differentiate OSAS from its underlying causes.

CONCLUSIONS

Our data suggest that increased nocturnal urine production in elderly patients might be due to natriuresis resulting from increased BNP secretion and decreased ADH secretion, associated with aging, although there was no difference in nocturnal urine production between nocturia patient groups with OSAS and without OSAS. Therefore, we consider OSAS to have no marked effect on ADH secretion. Further, our results showed that older men with NP and OSAS did not compensate their excess fluid imbalance, presented with decreased secretion of ADH and u-Na/u-Cr level, but with the increased BNP. When treating elderly patients with NP, OSAS must be included in the differential diagnosis and treated adequately first to improve the excess secretion of BNP. NP patients accompanied with OSAS should avoid ADH therapy.

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Table 1. Patient Characteristics

	Mean SD	Minimum Maximum
Age (y)	69.4±5.9	(60-86)
Weight (Kg)	67.7±10.5	(31-89)
Height (cm)	164.3±8.9	(143-185)
BMI (Kg/m^2)	25.1±3.6	(14.3-34.6)
Blood pressure (mmHg)		
Systolic	138.2±19.4	(103-200)
Diastolic	80.0±13.2	(51-110)
Na (mEq/L)	140.8±2.5	(135-148)
K (mEq/L)	4.2±0.4	(3.5-5.4)
Cl (mg/dL)	104.5±3.0	(99-111)
Ca (mg/dL)	9.3±0.5	(8.1-10.4)
Blood sugar (mg/dL)	96.1±6.3	(80-118)
Creatinine (mg/dL)	0.9±0.2	(0.6-1.4)
BNP (pg/mL)	41.3±38.5	(4.3-221)
24 hour frequency	9.5±3.0	(5-19)
24 hour voided volume (mL)	1487.9±429.5	(650-2650)
Nocturia	2.3±1.7	(0-11)
Nocturnal urine volume (mL)	702.3±247.7	(300-1650)
Nocturnal polyuria index	0.48±0.11	(0.35-0.76)
Maximum voided volume (mL)	337.6±119.4	(170-700)
u-AVP/u-Cre (pg/mL/Cr)	6.7±9.4	(0.6-59.8)
u-Na/u-Cre (mEq/L/Cr)	21.2±10.1	(6.2-66.0)
Urinary Osmolarity (mOsm/L)	574.9±178.6	(185-950)

BMI: body mass index, Na: sodium, K: potassium, Cl: chlorine, Ca: calcium, BNP: brain natriuretic peptide, Cre: creatinine

Table 2. Comparisons of each parameters between patients with and without OSAS

Baseline Parameters	OSAS		P Value
	With (n=49)	Without (n=34)	
Age (y)	69.4 ± 6.8	69.4 ± 4.4	0.4046
BMI (kg/m^2)	26.4 ± 3.2	23.2 ± 3.3	<0.0001
Blood pressure (mmHg)			
Systolic	142.1 ± 20.6	132.9 ± 16.4	0.0396
Diastolic	82.4 ± 12.8	76.8 ± 13.3	0.0804
AHI	36.3 ± 14.3	3.6 ± 0.9	<0.0001
Na (mEq/L)	140.9 ± 2.4	140.7 ± 2.6	0.434
K (mEq/L)	4.3 ± 0.5	4.0 ± 0.4	0.1189
Cl (mEq/L)	105.0 ± 3.5	103.8 ± 2.2	0.1424
Ca (mEq/L)	9.3 ± 0.4	9.2 ± 0.5	0.4257
Creatinine (mg/dL)	0.9 ± 0.2	0.8 ± 0.1	0.0624
Blood sugar (mg/dL)	96.1 ± 7.2	96.2 ± 4.8	0.4874
BNP (pg/mL)	48.6 ± 41.4	30.7 ± 31.5	0.0006
Urinary analysis			
u-Na/u-Cre (mEq/L/Cr)	24.7 ± 11.3	16.2 ± 5.1	<0.0001
u-K/u-Cre (mEq/L/Cr)	4.0 ± 3.3	3.9 ± 3.6	0.3544
u-AVP/u-Cre (pg/mL/Cr)	6.7 ± 10.4	6.8 ± 7.8	0.3617
Urine Osmolarity (mOsm/L)	616 ± 172	516 ± 174	0.0285
Frequency volume chart			
Nocturnal voided volume (mL)	712 ± 271	688 ± 213	0.7249
Nocturia	2.2 ± 2.1	2.5 ± 1.0	0.0115
24-hr Voided volume (mL)	1500 ± 491	1470 ± 328	0.7284
24-hr Frequency	8.2 ± 2.7	11.4 ± 2.5	<0.0001
Nocturnal polyuria index (%)	0.49 ± 0.11	0.47 ± 0.11	0.7042
Maximum voided volume(mL)	372 ± 137	289 ± 61	0.0048

OSAS: obstructive sleep apnea syndrome, BMI: body mass index, AHI: apnea-hypopnea index, Na: sodium, K: potassium, Cl: chlorine, Ca: calcium, BNP: brain natriuretic peptide, Cre: creatinine