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

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OBJECTIVE To investigate the impact of obstructive sleep apnea syndrome (OSAS) on night-time secretion of brain natriuretic peptide (BNP) and antidiuretic hormone (ADH) in older men with nocturia accompanied by nocturnal polyuria.

MATERIALS AND METHODS One hundred six men with nocturia aged ≥60 years underwent full-night polysomnography to determine whether they had OSAS. Blood count, standard chemistry panel, BNP, urinary ADH, urinary creatinine (u-Cre), and urinary osmolarity were measured at 6:00 AM, and a frequency volume chart was recorded on the same day that polysomnography was performed.

RESULTS We evaluated 83 patients after excluding 18 with mild OSAS and 5 with nocturnal polyuria index <0.35. Participants with OSAS had higher apnea-hypopnea index ($P < .0001$) than those without OSAS. Body mass index and systolic blood pressure were higher in OSAS patients than those in the control group. BNP was higher in the OSAS patients than in the control patients (48.6 ± 41.4 vs 30.7 ± 31.5; $P = .0006$). On urinalysis, OSAS patients showed higher urinary sodium and u-Cre secretion than controls (24.7 ± 11.3 vs 16.2 ± 5.1; $P < .0001$). Urine osmolarity was also higher in OSAS patients than in the control patients (616 ± 172 vs 516 ± 174; $P = .0285$). There was no significant difference in urinary ADH and u-Cre (6.7 ± 10.4 vs 6.8 ± 7.8; $P = .3617$) between the 2 groups.

CONCLUSION Our results indicated that older men with nocturnal polyuria and OSAS did not compensate their fluid imbalance presented with decreased secretion of ADH but increased BNP level. UROLOGY 84: 892–897, 2014. © 2014 Elsevier Inc.

Nocturia, defined by the International Continence Society as having to wake up ≥1 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, 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 have been suggested as contributing factors is hemodynamic stress because of negative intrathoracic pressure during each episode of apnea 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 et al[8] suggested that leg edema influenced, although not directly, nocturnal urine volume (NUV) with an associated decrease in

Financial Disclosure: *The authors declare that they have no relevant financial interests.*

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Submitted: November 5, 2013, accepted (with revisions): February 28, 2014

http://dx.doi.org/10.1016/j.urology.2014.02.073
0090-4295/14

antidiuretic hormone (ADH) secretion. 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 nonobese men that is independent of body weight.[9,10]

We hypothesized that there are many individuals among older men with NP who potentially have OSAS. 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 aged ≥60 years, admitted to the Sleep Medicine Center to determine whether they had OSAS, were enrolled in this study.

As Ljunggren et al[6] 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, we excluded patients with a mildly elevated apnea-hypopnea index (AHI; events per hour; 5≤AHI<15). A nocturnal voided volume >35% of the 24-hour production (NP index [NPi] ≥0.35) was defined as NP. Patients with NPi <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, serum creatinine (Cre) >1.5 ng/dL, liver dysfunction, hydronephrosis, postvoid residual urine volume >50 mL, active infection, 24-hour voided volume >40 mL × 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 1300 mL water and <3.5 g 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 postvoid residual urine volume and the presence of hydronephrosis were determined by ultrasonography. A frequency volume chart 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), urinary sodium (u-Na), and urinary Cre (u-Cre) were measured according to previously reported methods.[11] Urinary osmolality was also determined. The u-ADH and u-Na levels 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 electroencephalographic leads, 2 electrooculographic leads, 5 electromyographic leads (2 submental and bilateral anterior tibialis and unilateral masseter muscles), nasal cannula with a pressure transducer and thermal sensor for nasal air flow, strain gages for thoracic and abdominal movements, pulse oximetry, and electrocardiography. Simultaneous audio-video recording was made. Patients 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 ≥90% reduction in air flow for ≥10 seconds; hypopnea as ≥50% reduction of air flow for ≥10 seconds associated with arousals or with ≥3% reduction in oxygen saturation. The AHI was calculated as the mean number of obstructive apneas and hypopneas per hour of sleep.

Table 1. Patient characteristics

Characteristic	Mean ± SD (Range)
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 (mm Hg)	
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)
Cre (mg/dL)	0.9 ± 0.2 (0.6-1.4)
BNP (pg/mL)	41.3 ± 38.5 (4.3-221)
24-hr frequency	9.5 ± 3.0 (5-19)
24-hr 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-ADH/u-Cre (pg/mL/Cre)	6.7 ± 9.4 (0.6-59.8)
u-Na/u-Cre (mEq/L/Cre)	21.2 ± 10.1 (6.2-66.0)
Urinary osmolarity (mOsm/L)	574.9 ± 178.6 (185-950)

BMI, body mass index; BNP, brain natriuretic peptide; Ca, calcium; Cl, chlorine; Cre, creatinine; K, potassium; Na, sodium; u-ADH, urinary antidiuretic hormone; u-Cre, urinary creatinine; u-Na, urinary sodium.

Statistical Analysis

The Mann-Whitney *U* test was used for intergroup comparisons. A $P < .05$ was considered statistically significant. The StatView program, version 5.0 (SAS institute, Cary, NC), was used to conduct all statistical analyses.

RESULTS

Patient Characteristics

Twenty-three patients were excluded, 18 because they had an AHI (5≤ AHI <15) indicating mild OSAS and 5 with NPi <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 ($P < .0001$), higher systolic

Table 2. Comparisons of each parameter 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	.4046
BMI (kg/m^2)	26.4 ± 3.2	23.2 ± 3.3	<.0001
Blood pressure (mm Hg)			
Systolic	142.1 ± 20.6	132.9 ± 16.4	.0396
Diastolic	82.4 ± 12.8	76.8 ± 13.3	.0804
AHI	36.3 ± 14.3	3.6 ± 0.9	<.0001
Na (mEq/L)	140.9 ± 2.4	140.7 ± 2.6	.434
K (mEq/L)	4.3 ± 0.5	4.0 ± 0.4	.1189
Cl (mEq/L)	105.0 ± 3.5	103.8 ± 2.2	.1424
Ca (mEq/L)	9.3 ± 0.4	9.2 ± 0.5	.4257
Cre (mg/dL)	0.9 ± 0.2	0.8 ± 0.1	.0624
Blood sugar (mg/dL)	96.1 ± 7.2	96.2 ± 4.8	.4874
BNP (pg/mL)	48.6 ± 41.4	30.7 ± 31.5	.0006
Urinary analysis			
u-Na/u-Cre (mEq/L/Cre)	24.7 ± 11.3	16.2 ± 5.1	<.0001
u-K/u-Cre (mEq/L/Cre)	4.0 ± 3.3	3.9 ± 3.6	.3544
u-ADH/u-Cre (pg/mL/Cre)	6.7 ± 10.4	6.8 ± 7.8	.3617
Urine osmolarity (mOsm/L)	616 ± 172	516 ± 174	.0285
Frequency volume chart			
Nocturnal voided volume (mL)	712 ± 271	688 ± 213	.7249
Nocturia	2.2 ± 2.1	2.5 ± 1.0	.0115
24-hr voided volume (mL)	1500 ± 491	1470 ± 328	.7284
24-hr frequency	8.2 ± 2.7	11.4 ± 2.5	<.0001
Nocturnal polyuria index (%)	0.49 ± 0.11	0.47 ± 0.11	.7042
Maximum voided volume (mL)	372 ± 137	289 ± 61	.0048

AHI, apnea-hypopnea index; OSAS, obstructive sleep apnea syndrome; other abbreviations as in Table 1.

blood pressure ($P = .0396$), and higher AHI ($P < .0001$) 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; $P = .0006$).

On urinalysis, OSAS patients showed significantly higher u-Na and u-Cre secretion than controls (24.7 ± 11.3 vs 16.2 ± 5.1; $P < .0001$). Urine osmolarity was also higher in OSAS patients than in the controls (616 ± 172 vs 516 ± 174; $P = .0285$). 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; $P = .3617$) between the 2 groups.

The frequency volume chart revealed no significant differences in NUV or 24-hour urine production between the 2 groups (OSAS vs control: 712 ± 271 vs 688 ± 213; $P = .7294$ and 1500 ± 491 vs 1470 ± 328; $P = .7284$, respectively).

There were significant differences in nocturia and 24-hour frequency (OSAS vs control: 2.2 ± 2.1 vs 2.5 ± 1.0; $P = .0115$ and 8.2 ± 2.7 vs 11.4 ± 2.5; $P < .0001$, 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; $P = .0048$).

COMMENT

NP and nocturia in older adults reduce quality of life 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 because of 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]

Although 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 2 indices.

OSAS patients generally have a poor sleep because of the sleep disorders, breathing, and likely having to go to bathroom many times 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; $P = .0115$ and 8.2 ± 2.7 vs 11.4 ± 2.5; $P < .0001$, respectively) between the OSAS and control groups. We think that the reason of these counterintuitive results are because of the less maximum voided volume in the group without OSAS than that with OSAS, that is, a less functional bladder capacity contributed to this results.

After 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. Although the half-life of BNP is approximately only 20 minutes, that of ANP is even shorter at just 10 minutes; therefore, to detect the effects of OSAS, samples must be collected quickly before patients get out of bed, that is, immediately after resolution of the non-respiratory condition. Accordingly, BNP, which has a longer half-life, was collected at the 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, the patients' 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] that is, excessive secretion of BNP from the ventricle because of 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 osmolarity 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 the effect of cerebral infarction, and so forth. 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,[7] or leg edema indirectly imposing negative feedback on the pituitary gland. However, because 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, and so forth, which can also cause OSAS even in nonobese people.[9,10] According to the BMI classification advocated by World Health Organization, our series of patients with and without OSAS are subclassified as overweight when BMI is 26.4 ± 3.2 kg/m^2 and as normal weight when BMI is 23.2 ± 3.3 kg/m^2, respectively. Although there is a statistical difference between these 2 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.

CONCLUSION

Our data suggest that increased nocturnal urine production in elderly patients might be because of 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. Furthermore, 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 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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EDITORIAL COMMENT

Nocturia is one of the most bothersome lower urinary tract symptoms. In many ways, nocturia can be considered a "geriatric syndrome."[1] The condition is highly prevalent among older adults, is generally considered to be multifactorial, and leads to negative clinical outcomes. In some patients, it develops in part because of accumulated effects of decreased function in multiple organ systems. In addition, a number of clinical conditions outside the genitourinary system are also commonly associated with nocturia including congestive heart failure, electrolyte imbalances, diabetes insipidus, and pulmonary and peripheral edema. Certain medications including calcium channel blockers, angiotensin-converting enzyme inhibitors, and diuretics can be associated with nocturia, particularly if taken in the late afternoon or evening. Use of alcohol or caffeine before bedtime can also increase the risk for nocturia. Nocturnal polyuria can also lead to nocturia because of the increased volume of urine production at night.

Obstructive sleep apnea has been shown to be associated with nocturia for several reasons. People with this condition make abnormally high levels of atrial natriuretic peptide but lower levels of antidiuretic hormone (ADH). This leads to increased urine production at night and subsequent nocturia. This study demonstrated that levels of brain natriuretic peptide were elevated in elderly men with nocturia. This substance acts as both a diuretic and vasodilatory agent. It was interesting to note that in this study cohort, urinary secretion of ADH did not differ significantly between the nocturia and control groups, and ADH levels were generally low among these elderly men. As the authors suggest, this may have more to do with differences in functional bladder capacity between the groups.

In addition, the obstructive breathing pattern leads to multiple episodes of apnea during the night that tend to cause disruption of rapid eye movement sleep. It can be difficult to determine if affected patients are waking during the night because of the increased bladder volume and need to urinate or other factors disrupting sleep. Either way, the effect is poor overall sleep hygiene and symptomatic complaints of nocturia. Treatment of obstructive sleep apnea with continuous positive airway pressure can help with the primary condition and subsequently improve nocturia symptoms.

Nocturia can lead to substantial negative side effects on both general and health-related quality of life. People with nocturia frequently experience both sleep disruption and sleep deprivation leading to fatigue, daytime sleepiness, and depression. Treatment of underlying health conditions can certainly help to improve these associated symptoms. This article helps to clarify some of the factors associated with development of nocturia among older men. Better understanding of the etiologies of nocturia in older adults can help to develop future targets for treatment of this condition. Nocturia is a complex geriatric syndrome, and successful treatment may require a variety of targeted therapies.

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http://dx.doi.org/10.1016/j.urology.2014.02.075
UROLOGY 84: 896, 2014.

REPLY

As the editorial comment emphasizes the importance of understanding the multiple etiologies of nocturia, various physical conditions and comorbidity diseases involve nocturia mutually in older men. Nocturnal polyuria (NP) is a condition that is most frequently encountered in routine clinical practice. For instance, fluid accumulation in the lower extremities

forming leg edema is considered to be not only a source of NP, but also a cause of obstructive sleep apnea syndrome (OSAS). We intended to clarify the effect of OSAS on NP in older male patients with nocturia. At first, we supposed that differences in the patients' background and biochemical index such as a urinary antidiuretic hormone (ADH) level and osmolarity were found in NP patients with and without OSAS. NP patients with OSAS showed a low urinary level of ADH similarly to that without OSAS. However, the brain natriuretic peptide level is significantly high in the group with OSAS. This indicates that older men with both NP and OSAS need their proper fluid balance first by improving heart failure or congestive condition. Therefore, although continuous positive airway pressure can improve the sleep troublesome conditions due to OSAS, it may not decrease nocturnal urine volume to the level that we expect. Still, it is very important to examine the etiologies of NP in older men from various perspectives. We shall elucidate the correlations between edema and NP and OSAS via a treatment intervention in the future study.

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http://dx.doi.org/10.1016/j.urology.2014.02.076
UROLOGY 84: 896–897, 2014.