Obstructive Sleep Apnea, Nocturia and Polyuria in Older Adults

Mary Grace Umlauf, RN, PhD[1]; Eileen R. Chasens, RN, DSN[2]; Robert A Greevy, MS[3]; John Arnold, RPh[4]; Kathryn L. Burgio, PhD[5]; Dennis J. Pillion, PhD[4]

[1]University of Alabama School of Nursing, [2]University of Pennsylvania School of Nursing, [3]Wharton School of Business, University of Pennsylvania, [4]University of Alabama at Birmingham School of Medicine, [5]Geriatric Research Education and Clinical Center, VAMC, Birmingham AL

Study Objective: The purpose of this study was to examine the relationship between nocturia and obstructive sleep apnea (OSA) in community dwelling older men and women

Design: A repeated measures design was employed over a 24-hour period.

Setting: The study was conducted in a clinical research center.

Participants: Thirty community-dwelling elders (mean age=65.5, SD=8.4 years) with symptoms of nocturia and sleep disordered breathing, volunteered to participate. Both men (n=13) and women (n=17) and minority subjects (African-Americans, n=19; Caucasian, n=11) were included in the study.

Interventions: NA

Measurements: Blood specimens were collected every 4 hours, except for an 8-hour collection period overnight. Urine specimens were collected ad libitum and at the end of each data collection interval. Urine and blood specimens were analyzed for ANP and AVP content. Polysomnography was conducted using a full 18-channel montage. Apnea was defined as a decrease in airflow of ≥ 90% for a minimum of 10 seconds. Hypopnea was defined as ≥ 30% decrease in airflow and desaturations required a ≥ 3% decrease in oxygen saturation for a minimum of 10 seconds. The apnea hypopnea index (AHI) was calculated as the sum of apneas and hypopneas divided by hours of sleep.

Results: Twenty of the thirty subjects were found to have clinically diagnosable OSA (AHI ≥5). AVP excretion was not correlated with changes in AHI levels. Conversely, total urine output, plasma ANP and urine ANP excretion were significantly higher among subjects with higher AHI levels (>15).

Conclusion: In subjects with elevated AHI (>15), nighttime urine production and ANP excretion are elevated.

Key Words: obstructive sleep apnea, polyuria, homeostasis, atrial natriuretic factor, vasopressin, nocturia

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INTRODUCTION

NOCTURIA IS DEFINED AS A VOLUNTARY VOIDING THAT OCCURS AFTER AN INDIVIDUAL HAS GONE TO SLEEP. Nocturia is often reported as a source of sleep disturbance in older adults. Many older adults have bladder control problems in addition to other ailments. In otherwise healthy adults, nocturia is sometimes viewed only as a bothersome symptom of an underlying bladder problem, rather than as a serious contributor to morbidity/mortality, as a result of an increased likelihood of hip fractures associated with a fall.[1] Older men who have nocturia are often assumed to have benign prostatic hypertrophy and older women with nocturia are often assumed to have an unstable bladder or reduced bladder capacity associated with aging.[2] However, nocturia may occur as a result of overproduction of urine, rather than diminished bladder capacity or prostatic hypertrophy. Sleep researchers have demonstrated that nocturia is more common in patients with obstructive sleep apnea (OSA).[1, 3, 4] A gap exists in our understanding of the relationship between urine production and OSA.

Nocturnal Urine Production

Normally, nocturnal urine production is < 20% of the daily urine output in young adults, and < 30% of the daily urine output among older adults.[5] Nocturnal urine production is controlled in part by fluid intake before going to bed and by the secretion of hormones including vasopressin (AVP) and atrial natriuretic peptide (ANP). AVP secretion is increased when a person is lying in the prone position; the net effect of this AVP secretion is diminished urine production during the sleep interval.[6]

Schatzl and colleagues have reported that 10% of the general population over age 20 has nocturia two or more times per night.[7] In the 50-59 age group, 58% of men and 66% of women experience nocturia. In those over age 80, 72% of men and 91% of women report nocturia.[8] It is not known precisely why nocturia increases with age but several possible explanations have been described. Prostatic hypertrophy may cause nocturia by several mechanisms, such as obstructing the bladder outlet and preventing complete bladder emptying, or by causing detrusor over-activity.[9] However, this explanation is not consistent with the observation that nocturia is apparently insensitive to some treatments for BPH[10] and does not resolve after prostatectomy.[11-13] Nocturia in females must be explained in terms exclusive of any prostatic contribution.[14] Women have an increasing prevalence of nocturia between ages 40-64 years, which is not related to parity.[15] Although little attention has been paid to the contribution of OSA to development of nocturia in females, it is noteworthy that the rate of sleep apnea in women doubles (47% versus 21%) after menopause [16] and estrogen has been shown to reduce the risk of both nocturia and sleep disorders.[17, 18]

Hypothesis

Although nocturia can be attributed to a number of conditions, the purpose of this study was to examine the relationship between over-production of urine and obstructive sleep apnea. A major hypothesis of this proposal is that nocturia may actually be a result of the diuretic hormone response to obstructive respiratory events. The physiological events surrounding the generation of negative pressures in the thorax caused by partial or full obstruction of the airway and sustained ventilatory effort (repeated Mueller maneuvers) causes the heart to receive a false signal of volume overload (Figure 1). The hormonal response to this signal is increased ANP secretion and diminished AVP secretion. Hence OSA causes the body to increase urine production. Earlier studies have

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Address correspondence to: Dr. Mary Umlauf, University of Alabama School of Nursing, 1530 3r d Ave. South, NB 215, Birmingham, AL 35294-1210, Ph: (205) 934-7532, email: mgumlauf@uab.edu

reported that older men experience a shift in urine volume production from day to night.[19, 20] This study expands on earlier work by Krieger and colleagues,[21-24] who documented diurnal and nocturnal diuresis along with OSA, to focus on the excretion of AVP and ANP during the overnight period.

METHOD

Subjects

A sequential recruitment design was used to solicit symptomatic community dwelling older adults to participate in a study of nocturia and sleep disorders. An initial sample of 1000 older adults was surveyed by mailed questionnaire to recruit volunteers for intensive clinical interviews and ultimately a 24-hour stay on a metabolic unit.[25] Names and addresses of potential subjects were obtained from a large university sponsored, health promotion and medical referral program offered free to adults over age 55 in Birmingham, Alabama. Sampling procedures excluded persons who lived outside of the greater Birmingham area. Random sampling from the membership list was targeted to achieve a balance by sex and by ethnicity, African-American and white. Cross section sampling by age was also achieved by targeting three potential subject groups: persons age 55-64 years (n=450), 65-74 years (n=450) and 75 years and older (n=100). The survey packet included a cover letter explaining the study, a copy of the questionnaire with a return addressed stamped envelope and a reply card for listing their name and phone number if the respondent was interested further study participation including in face-to-face clinical exams and, potentially, an overnight stay in the General Clinical Research Center (GCRC). The cover letter also stated that eligible subjects would be reimbursed for their time to participate in the latter two stages of the study. A follow-up reminder postcard was sent 7 to 10 days after the surveys were mailed to encourage participation. It was anticipated that this procedure for sample recruitment would likely exclude persons who were less motivated and less symptomatic, as well as persons who were not able or unwilling to travel to the downtown university area to participate in a research study. This procedure yielded 176 survey respondents, approximately half (n=87) were willing to come to the GCRC to complete additional survey instruments and undergo additional health screening. As previously reported, analysis of survey responses using generalized logistic regression modeling showed that higher levels of nocturia (> 1 event per night) in binary form were statistically associated with poor sleep quality (OR = 2.3, CI = 1.4-3.8, $p<0.01$), gender (women, OR = 2.4, CI – 1.1-5.1, $p<0.05$), ethnicity (African- American, OR = 2.3, CI = 1.1-4.9, $p<0.05$), and symptoms of urinary urgency and frequency (OR = 1.7, CI = 1.1-2.6, $p<0.05$). [25]

Using the pool of initial postal volunteers, 60 older adults (approximately 50%/50% male/female, White/African-American) were invited to participate in clinical interviews if they reported sleep disturbances and nocturia (>1 event per night by postal survey). The following tests and measures were completed during the clinical interviews: battery of sleep questionnaires, a 3-day nocturia bladder diary, glycosolated hemoglobin (HbA_{1c}) by finger stick, measurement of height, weight, and blood pressure. An initial phone contact was made to identify exclusionary conditions as follows: (a) had continuous urinary incontinence, (b) used external urinary collection equipment, (c) medical diagnosis of renal failure, (d) required insulin to control their diabetes, (e) were under medical treatment for sleep disorders, or (f) were institutionalized. As determined during the clinical examination, the following conditions also precluded participation in the final phase of the study, the 24 hour observation at the GCRC: (a) were taking diuretic medications after 12:00 noon, (b) had a resting oxygen saturation <90% (indicative of cardiac or pulmonary disorders), (c) had a positive urine dipstick test for leukocytes and nitrites (indicative of bacteriuria), or (d) were psychologically or cognitively impaired.

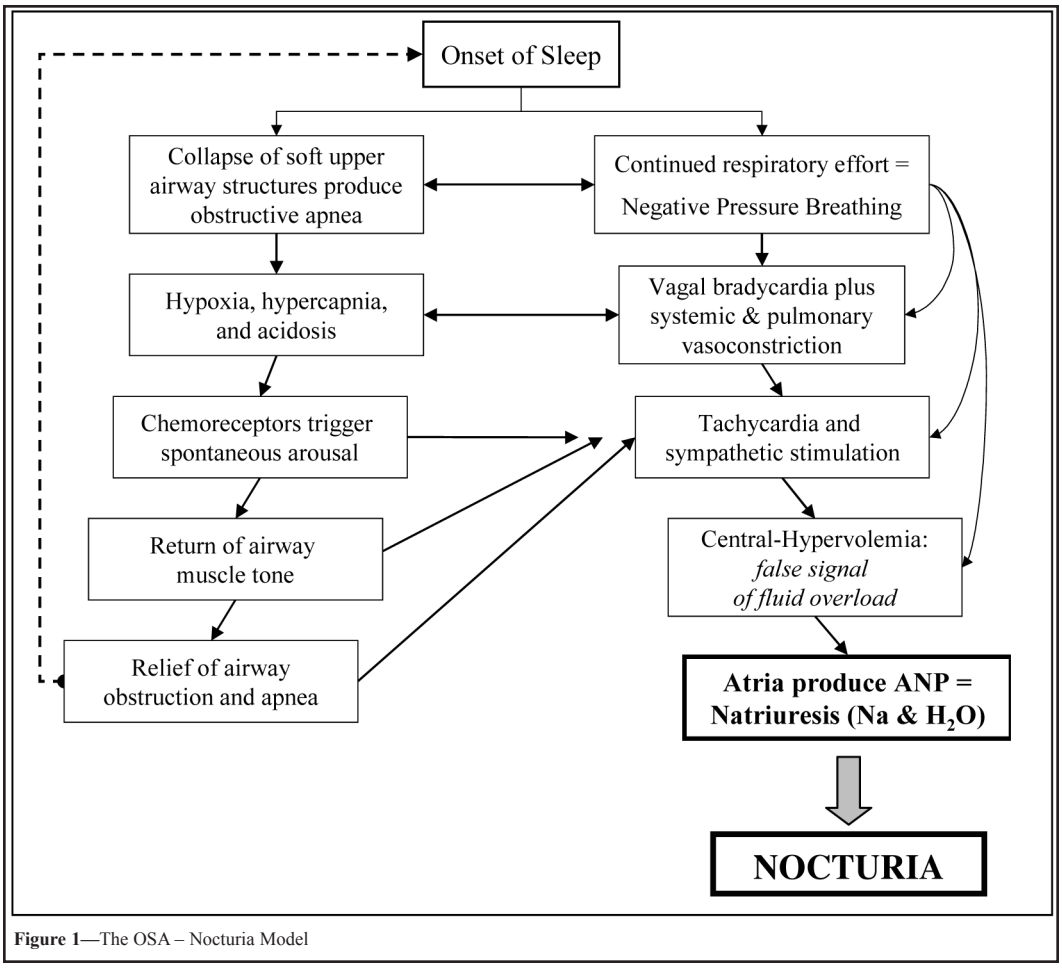

Figure 1—The OSA – Nocturia Model

Subjects with elevated HbA_{1c} levels (>7%) were not automatically disqualified from study participation as long as they had an existing diagnosis of diabetes, were under medical treatment and did not require insulin. Two subjects were referred to their primary medical care providers for elevated HbA_{1c} levels and were subsequently diagnosed and treated for diabetes. Eligible subjects were recruited for the second phase of the study if they were still willing and able to participate when contacted by the recruiter for scheduling.

As the final step in the protocol, 30 subjects (mean age 65.5, SD=8.4) completed the 24-hour observation period, which included full montage polysomnography (EEG, EKG, leg movement, oxygen saturation), continuous measures of intake, and urine output, measures of body water composition by bioimpedance and sequential blood sampling for ANP and AVP 6 times over the total observation period (2pm, 6pm, 10pm, 6am, 10am, 2pm).

Measurements

The study was conducted in the National Institute of Health funded UAB GCRC. All subjects were seen

by a doctor or nurse practitioner for a history and physical prior to admission to rule out uncontrolled heart disease, hypertension, or any acute disease that might pose a risk for the subject or compromise the study. Subjects were allowed to take prescribed medications brought from home. Unless subjects requested a special diet, a regular diet was served during the admission. Subjects were only restricted from food or caloric beverages from 10:00 p.m. until 6:00 a.m. the next morning.

Strict intake and output procedures were followed to create five observation intervals (2pm-6pm, 6pm-10pm, 10pm-6am, 6am-10am, 10am-2pm). Subjects voided at 2pm the first day, then ad-lib, and at the end of each observation interval. Voided volumes were pooled for each observation interval and specimens for assay were taken from these five volumes. This procedure provides an automatic averaging of metabolite excretion per urine collection interval and permits interpolation into minute volume (MV). Urine was refrigerated during the collection intervals, and a new urinal or specimen pan was used for each collection period to prevent the contamination of specimens with urine from an earlier period.

Blood specimens were collected from a venous port (saline lock) while the subject was seated, except at 10:00 pm and 6:00 am when the patient was in reclining in bed. Blood specimens collected at 10:00 p.m., 6:00 a.m. (fasting), and 10:00 a.m. (2 hour postprandial) included a blood glucose, insulin level, and urine glucose. A serum creatinine level was also obtained on admission to verify adequate renal function. Glucose, insulin and creatinine assays were conducted in a standard hospital laboratory. Blood specimens for AVP and ANP were collected in iced tubes prepared with anticoagulant and protease inhibitors (EDTA). The plasma was immediately centrifuged, separated and frozen at -70°C for batch processing. The AVP and ANP assays were performed in a research laboratory using commercially available radioimmunoassay kits according to the manufacturer's specifications (Diagnostic Systems Laboratories, Inc., Webster, Texas and Amersham Biosciences, Inc., Piscataway, NJ). HbA_{1c} level, a reflection of glucose control over the previous 90-120 days, was measured by finger stick blood sampling using a DCA2000 Analyzer and Hemoglobin A_{1c} Reagent Kit (Bayer Diagnostics, Inc., Tarrytown, NY) according to the recommended procedure. Estimates of body water composition were obtained by using bioelectrical impedance analysis (RJL Systems, Inc, Clinton Township, MI) at each of the six measurement intervals.

A certified polysomnography technician conducted the sleep study, although subjects determined their own bedtime for sleep. Sleep studies were conducted in the General Clinical Research Center by certified technicians using a digital polysomnography system (Sandman, Nellcor Puritan Bennett (Melville Ltd., Ontario, Canada) that recorded central and occipital electroencephalogram (EEG) derivations (C3, C4, O1, O2), bilateral electrooculogram (left outer canthus and right outer canthus), submental and anterior tibialis electromyogram (EMG), electrocardiogram, nasal/oral airflow using a thermistor, respiratory effort using chest and abdominal inductance belts, and finger pulse oximetry (Nellcor, Pleasanton, CA). The sleep recordings were scored using the Rechtschaffen and Kales criteria.[26] An apneic event was defined as a decrease in airflow of >90% for a minimum of 10 seconds. A hypopneic event was scored if airflow decreased ≥30%, and desaturations required a 3% reduction in oxygen saturation for a minimum of 10 seconds. The apnea hypopnea index (AHI) was calculated as the sum of apneas and hypopneas divided by hours of sleep. Subject with an AHI of 5 or more was considered as having a diagnosable case of OSA.

RESULTS

Both men (n=13) and women (n=17), and minority subjects (African-Americans, n=19; Caucasian, n=11), participated in the study and the mean age was 65.5 (SD 8.4; range 51-91). None of the subjects were apnea free, and two-thirds of the sample (n=20) had clinically diagnosable OSA (AHI≥5). Although 10 subjects had a diagnosis of diabetes and HbA_{1c} >7.0%, 8 of these 10 had no glucosuria, and only two members of this subsample had trace amounts of glucosuria overnight. Hence, in these diabetic subjects, elevated blood glucose concentrations were not causing increased urine production as a result of osmotic diuresis. Nocturnal urine production, obesity and sleep problems were pronounced in many subjects (Table 1). The BMI for the entire sample was in the obese range (Mean = 32.9, SD 7.4) with a broad range of values (22-52). No significant differences were measured when urine output data or AHI data from African-American men or women were compared with comparable data from Caucasians.

Nocturia, defined as the number of voidings after going to bed, and self-rated health, were self-reported using a 3-day home bladder diary during the subject screening process. Nocturia values showed a mean=3.0, SD=1.1, range=1-6.1. Nocturia was positively associated with AHI (r=. 52, p=0.004) but negatively associated with self-rated health (r= -.37, p=0.04). No statistically significant associations were found in this population between nocturia and two variables that could impact on urine production, i.e. age and BMI. Comparisons were made between men and women using the Mann-Whitney test, but no differences were found when testing nocturia, self-rated health, or the rate of overnight urine output (minute volume).

An ordinal logistic regression was computed to test the association of AHI levels (Minimal: AHI<5, Mild: AHI 5-14.9, Moderate and Severe: AHI >15) and percent of urine produced overnight while controlling for age, BMI, HbA_{1c}, and gender (Table 2). Association with AHI levels was examined using Wald's test. The ordinal logistic regression showed that percentage of overnight urine output was the only variable associated with AHI level (p=0.046). The estimate of the effect was moderately large. That is, on average and holding all other variables constant, increasing nighttime urine output by +10%, increases the odds of being in a more severe AHI group by 2.12 times (95% CI =1.01-4.46).

A second ordinal logistic regression to predict AHI level was computed including nocturia but excluding percent of urine produced overnight. Association with AHI Level was examined using Wald's test. The ordinal logistic regression showed that nocturia (p=0.043) was a significant predictor of AHI level and that the estimate of the effect was also moderately large. That is, on average and holding all other variables constant, increasing nocturia by one event per night increases the odds of being in a more severe AHI group by 2.44 times (95% CI =1.11-5.38). Secondarily, the Wald test for BMI yielded p=0.045.

Table 1—BMI, Overnight Urinary Output and AHI by Ethnicity and Gender

	n	BMI		Night Output (ml)		AHI		AHI ≥ 5
		Mean (SD)	Range	Mean(SD)	Range	Mean (SD)	Range	
African-American								
Men	7	32.5(7.2)	24.7-47.7	963 (418)	335-1644	14.4 (10.5)	1.7-33.0	6
Women	12	35.2 (9.6)	22.4-52.0	854 (303)	450-1370	10.3 (10.5)	0.7–22.9	6
White								
Men	6	30.4 (3.2)	26.9-35.9	853 (222)	520-1100	17.3 (22.9)	0.9-62.9	4
Women	5	31.0 (5.2)	25.3-38.6	609 (326)	240-1050	11.5 (10.3)	4.5-28.4	4
Total	30	32.9(7.5)	22.4-52.0	838 (327)	240-1644	12.8 (13.4)	0.7-62.9	20

Table 2—Age, BMI, Overnight Urine Output, Total Sleep Time (TST) and Sleep Efficiency (SE) by AHI Level

	AHI < 5 N = 10		AHI 5-14.9 N=11		AHI > 15 N=9		Total Sample N=30	
	Mean(SD)	Range	Mean(SD)	Range	Mean(SD)	Range	Mean(SD)	Range
Age	67(12)	57-91	63(6)	51-74	67(5)	61-77	65(8)	51-91
BMI	32.0(7.5)	25.3-52 3	30.1(4.5)	22.4-38.7	37.4(8.7)	28.5-49.5	33(7.4)	22.5-52
Output	707(263)	240-1100	844(359)	335-1644	977(327)	335-1370	854(359)	240-1644
TST	254(59)	182-332	271(76)	164-459	268(48)	178-348	264(62)	164-459
SE (%)	66(14)	43-87	67(12)	48-84	73(12)	48-91	68.5(13)	43-91

Urinary AVP and ANP concentrations were measured and the data were multiplied by the urine volume and divided by the time interval to determine total AVP and ANP output per minute (Figure 2). Data were stratified between the 3 AHI levels (Minimal, Mild, and Moderate-Severe) by 8-hour intervals (afternoon: 2pm–10pm, night: 10pm–6am, morning: 6am–2pm). The results were evaluated using Wilcoxon and Kruskal-Wallis rank sum tests. No significant variations were found by interval (p= 0.43) or by group (p= -0.80).

Circadian differences in plasma and urinary measures of ANP and AVP were tested using the Friedman test. This statistic provides a comparison of the 24 hours of data at one time based on ranks. None of the five interval (urine) measures or six timed (plasma) values showed significantly high or low ranks when testing the total sample at once. The Mann-Whitney and the Kruskal Wallis tests were used to compare subjects with milder apnea (AHI<15) to those with moderate and severe apnea (AHI≥15). These statistics compare data from individual time points (plasma) or intervals (urine) between groups based on ranks. No group differences were found for plasma or urinary AVP. However, when direct measurements of the concentration of ANP found in plasma and urine were made, subjects with AHI≥15 had significantly higher plasma ANP values ($p<0.05$) at 6pm, 6am, 10am and 2pm and higher urinary ANP values ($p<0.05$) during the 10pm- 6am and 10am-2pm intervals, than individuals with AHI<15 (Table 3).

Comparison of Plasma and Urinary Measures of ANP and AVP

To test the utility of using continuous collection of urine to track changes in ANP and AVP during sleep and for circadian studies, comparisons were made using both plasma values and total amount excreted in urine by interval. The plasma measurements were added together to create a sum total for the 24-hour period. Urinary measures for each time interval were then multiplied by their respective urine output volumes and those products were added together to create a 24-hour urinary total. The totals were transformed with the natural log function to compensate for the positively skewed distribution and to make the data suitable for analysis. The correlations between urinary and plasma measures of ANP were significant (r=0.63, p=0.0003), but AVP values were not (r=0.28, p=0.128).

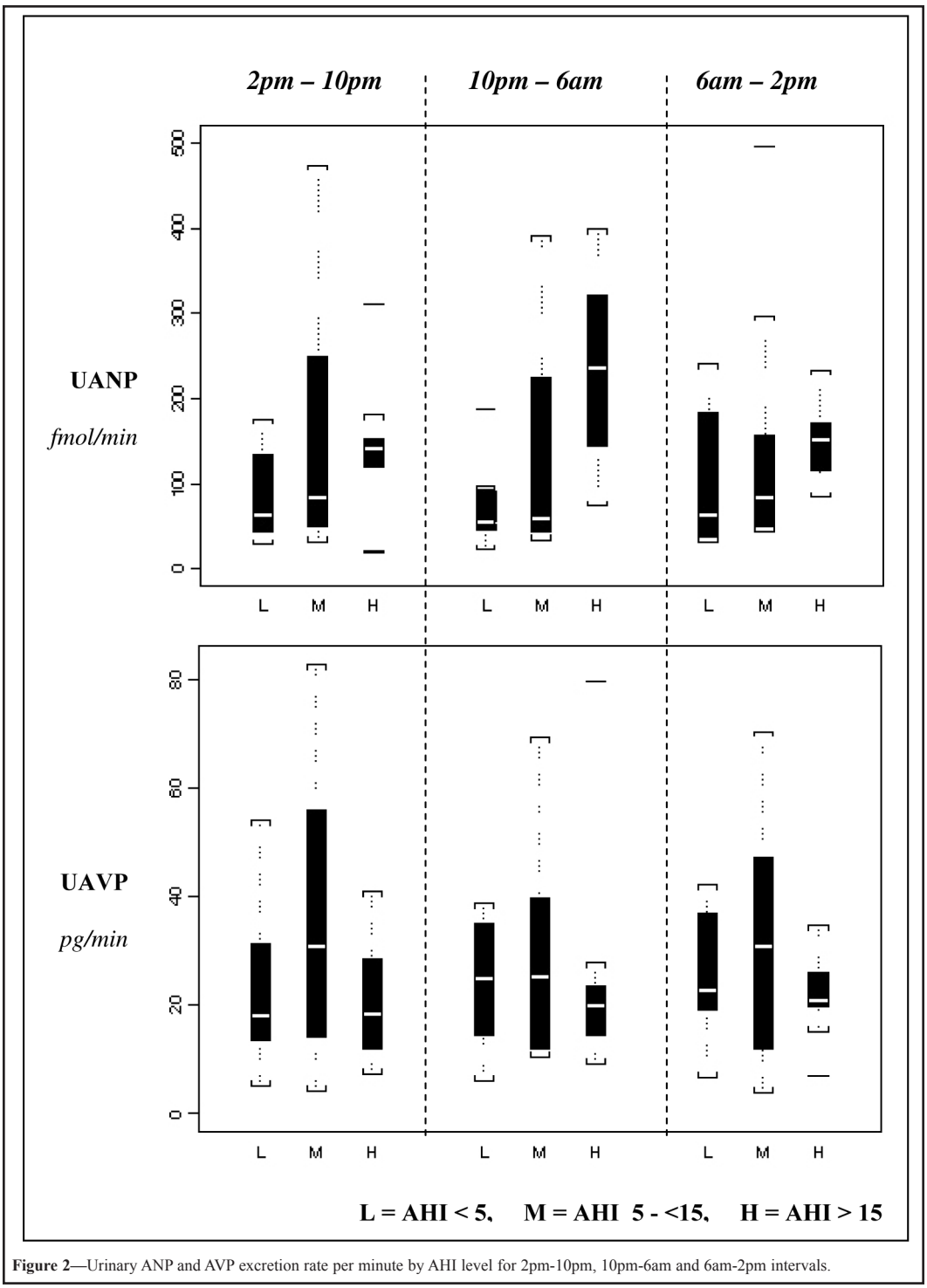

Figure 2—Urinary ANP and AVP excretion rate per minute by AHI level for 2pm-10pm, 10pm-6am and 6am-2pm intervals.

DISCUSSION

Consistent with the findings of Krieger and colleagues regarding sleep clinic patients,[21-24] the data suggest an association between nocturia, nocturnal polyuria and AHI. Based on the original conceptualization of Sullivan and Issa,[27] a model has been developed to illustrate the complex set of events surrounding OSA leading to polyuria (Figure 1). Although OSA can cause hypoxia and trigger arousals from sleep, it also generates extreme negative intrathoracic pressures that directly impact cardiovascular performance.[28] Paradoxical respiration is the outward manifestation of the vigorous contractions of the diaphragm in the presence of an obstructed airway. That is, a given obstructive apnea event begins with the collapse of the airway and ends with the reopening of the airway following arousal. During a single obstructive apnea event several diaphragmatic contractions may occur without air exchange that generate fluctuating pressures in the thorax. Guilleminault [29] documented that esophageal pressures can drop as low as -80 to -90 cm H_20 during a single obstructive apnea event. The effect of these acute pressure swings is an increased systolic transmural pressure and left ventricular after-

load.[30] Venous return is also increased, thereby causing distention of the right atrium and ventricle. This distention also shifts the interventricular septum, impairs left ventricular diastolic filling and reduces stroke volume during each apnea.[31] Hypoxia and hypercapnea ensue and stimulate sympathetic outflow and also increase left ventricular afterload.[30] As a result of these vacillating intracardiac pressure changes, the heart responds to the distention as a false sign of fluid overload. The normal physiological response to atrial stretch is to excrete ANP, which is a natriuretic, diuretic, and vasorelaxant cardiac hormone.[32] Exocytosis of ANP by the atria can be increased by acidosis[33] and reduced oxygen tension.[34] ANP also inhibits the secretion of AVP, the rennin-angiotensin-aldosterone system,[35] and aldosterone while increasing glomerular filtration.[36, 37] Studies have shown that ANP is chronically elevated in individuals with congestive heart failure at rest,[38, 39] episodically elevated during periods of apneic sleep[40] and predictive of mortality among elders with known cardiovascular disorders.[41]

In the current study, glucose control, glucosuria, gender, BMI, and age were not significantly correlated with AVP and ANP in the analysis. Obesity, and diabetes are frequently observed as comorbid conditions with OSA, but recent studies have found that OSA is statistically independent from serum leptin concentrations,[42] glucose intolerance [43] and insulin resistance.[43, 44] Even though BMI is known to be associated with OSA,[42] the lack of statistical association observed in this sample could result from the small sample size or the consequence of including mostly obese subjects who were selected based on symptomology. Although gender did not predict AHI level, men have a greater risk for OSA and BPH is both normal and prerequisite to prostatism. However, this was not a random sample from the general population and sampling was limited to 30 older adults deliberately chosen by ethnicity and gender who demonstrated the symptom of interest, nocturia.

Significant elevations in ANP excretion were found in the sample when comparing between levels of AHI. Urine ANP levels were higher overnight and in early morning intervals (10p-6a; 6a-10a) among the group with AHI >15. Although AVP is normally expected to become elevated at night, no statistical differences were noted over the 24 hour observation period, nor when comparing by separate time intervals or by levels of AHI. Contrary to supposition, in this study neither ANP nor AVP were related to age of subject. This circadian observation of the variations of ANP and AVP in subjects with nocturnal polyuria and apnea are consistent with previous investigations and raise issues regarding the chronic impact of OSA on volume homeostasis. For example, Krieger and colleagues [21-24] have shown that OSA is associated with diurnal and nocturnal diuresis in sleep clinic populations, was significantly higher in OSA patients than in healthy subjects, and frequency of nocturnal voids decrease after treatment with CPAP. [24] Others have found that patients with diagnosed OSA may present with 4-7 episodes of nocturia per night. [45] Many other investigators have also demonstrated that nocturia and enuresis frequently resolves with effective treatment of OSA.[46-49] Further, Asplund and colleagues have compared AVP in older adults with and without nocturia.[3, 50] Their findings also document a lack of circadian variation among persons with nocturia, which was reduced when subjects were given the antidiuretic hormone analog, DDAVP (desmopressin) before bedtime. However, DDAVP is only effective for 6-8 hours and there is no residual improvement in nocturia when the drug is not taken. In addition, hyponatremia can be a fatal side effect of DDAVP in both older adults [51] and children.[52] A common theme among the reported serious side effects is the onset of hyponatremia within the first 1-2 days of use among patients who had never taken the drug previously,[53, 54] which suggests that an undetected condition causing daytime fluid retention and nocturnal excretion, like OSA, could play a part in this type of consequence.

Table 3—Plasma and urine ANP per milliliter of specimen by AHI level and time interval.

	Urine ANP (fmol/mL)	
Interval	AHI < 15 n=21	AHI >15 n=9
1400-1800	96 ± 33	123 ± 35
1800-2200	92 ± 28	109 ± 21
2200-0600	74 ± 16	121 ± 22*
0600-1000	89 ± 31	113 ± 25
1000-1400	83 ± 30	121± 23*
	Plasma ANP (fmol/mL)	
Time	AHI < 15 n=21	AHI >15 n=9
1800	9.3 ± 1.7	27.2 ± 6.5*
2200	16.5 ± 2.5	30.2 ± 8.6
0600	13.4 ± 4.5	28.5 ± 5.3*
1000	12.1 ± 2.9	29.3 ± 8.0*
1400	8.2 ± 0.8	34.5 ± 8.8*

(*p<0.05)

Collectively, these findings suggest that conditions of airway compromise during sleep may be a potent contributor to nocturia in men or in women. The question arises if persons with nocturnal polyuria and OSA have a circadian disturbance in water homeostasis, not just excessive urine output at night. This is consistent with recent clinical reports documenting the common clinical presentation of leg edema, pulmonary hypertension with OSA and proposing that lower extremity edema is a potential clinical marker of OSA.[55-57] The interplay of overnight elevations in ANP and the suppression of overnight AVP suggest a circadian alteration in body water management, which may be caused directly or indirectly by OSA. The normal cycle of water excretion follows fluid intake; thus demonstrating a greater output during the waking hours. The subjects in our sample apparently have a forward phase shift of the normal pattern of urine excretion. That is, less output earlier in the day when fluids are consumed and more output after 6:00 pm and at night when there should be no intake.

From a methodological perspective, the ability to use urine specimens to track ANP can aid in the design of future studies of the effect of OSA and/or its treatment on urine production, edema, and hydration. The findings of this study offer support for the use of urinary measures of ANP over plasma values, which demands a rigorous specimen management procedure. The comparison of urinary and plasma AVP measures are less compelling and warrant additional testing in future studies. Further, the management of plasma AVP specimens, compared to ANP specimens, is not as cumbersome and time sensitive because the latter are much more quickly and extensively degraded by serum proteases. However, capturing excretion patterns of both hormones is an important tool in tracking the circadian effect of OSA on water metabolism. Thus, future studies are needed with larger samples to fully validate the technique and clarify issues of water homeostasis in OSA.

CONCLUSION

Many health care providers are unaware of the cardiovascular impact of sleep-disordered breathing. OSA has an insidious natural history and the damage occurs many times each night over a period of years. Thus, the impact of OSA is not just sleep deprivation; it is also a repetitive noxious cardiovascular event. In addition, OSA natriuresis has only recently been identified as a mechanism for nocturnal polyuria (nocturia, enuresis and incontinence). Since a wide variety of disorders can cause changes in the secretion of natriuretic and anti-natriuretic peptides, further research on the secretion of these peptides in persons with OSA has the potential to improve our understanding of nighttime urine production under normal and abnormal conditions.

REFERENCES

1. Stewart RB, Moore MT, May FE, Marks RG, Hale WE. Nocturia: a risk factor for falls in the elderly. J Am Geri Soc 1992;40:1217-20.
2. Harvard Health Letter. Nocturia: When nature calls at night. Harvard Health Letter 1999;24:6.
3. Asplund R, Aberg H. Nocturnal micturition, sleep and well-being in women of ages 40-64 years. Maturitas 1996;24:73-81.

4. Pressman MR, Figueroa WG, Kendrick-Mohamed J, Greenspon LW, Peterson DD. Nocturia. A rarely recognized symptom of sleep apnea and other occult sleep disorders. Arch Int Med 1996;156:545-50.
5. van Kerrebroeck P, Abrams P, Chaikin D, et al. The standardisation of terminology in nocturia: report from the Standardization Sub-committee of the International Continence Society. Neurorology & Urodynamics 2002;21:179-83.
6. Matthiesen T, Tittig S, Norgaard J, Pederson E, Djurhuus J. Nocturnal polyuria and naturesis in male patients with nocturia and lower urinary tract symptoms. J Urol 1996;156:1291-9.
7. Schatzl G, Temml C, Schmudbauer J, Dolezal B, Haidinger G, Madersbacher S. Cross-sectional study of nocturia in both sexes: Analysis of a voluntary health screening project. Urology 2000;56:71-75.
8. Middelkoop HA, Smilde-van den Doel DA, Neven AK, Kamphuisen HA, Springer CP. Subjective sleep characteristics of 1,485 males and females aged 50-93: effects of sex and age, and factors related to self-evaluated quality of sleep. J Gerontol A Biol Sci Med Sci 1996;51:M108-15.
9. Staskin DR. Age-related physiologic and pathologic changes affecting lower urinary tract function. Clin Geriatr Med 1986;2:701-10.
10. Homma Y, Yamaguchi T, Kondo Y, Horie S, Takahashi S, Kitamura T. Significance of nocturia in the International Prostate Symptom Score for benign prostatic hyperplasia. J Urol 2002;167:172-6.
11. Bruskewitz RC, Larsen EH, Madsen PO, Dorflinger T. 3-year followup of urinary symptoms after transurethral resection of the prostate. J Urol 1986; 136:613-5.
12. Lepor H, Rigaud G. The efficacy of transurethral resection of the prostate in men with moderate symptoms of prostatism. J Urol 1990;143:533-7.
13. Neal DE, Ramsden PD, Sharples L, et al. Outcome of elective prostatectomy. BMJ 1989;299:762-7.
14. Weiss JP, Blaivas JG, Stember DS, Brooks MM. Nocturia in adults: etiology and classification. Neurourology & Urodynamics 1998;17:467-72.
15. Asplund R, Aberg HE. Nocturia and health in women aged 40-64 years. Maturitas 2000;35:143-8.
16. Dancey DR, Hanly PJ, Soong C, Lee B, Hoffstein V. Impact of menopause on the prevalence and severity of sleep apnea. Chest 2001;120:151-5.
17. Fantl JA, Wyman JF, Anderson RL, Matt DW, Bump RC. Postmenopausal urinary incontinence: comparison between non-estrogen-supplemented and estrogen-supplemented women. Obstet Gynecol 1988;71:823-8.
18. Bixler EO, Vgontzas AN, Lin HM, et al. Prevalence of sleep-disordered breathing in women: effects of gender. Am J Respir Crit Care Med 2001;163:608-13.
19. Kirkland JL, Lye M, Levy DW, Banerjee AK. Patterns of urine flow and electrolyte excretion in healthy elderly people. Br Med J (Clin Res Ed) 1983;287:1665-7.
20. Rowe JW, Shock NW, DeFronzo RA. The influence of age on the renal response to water deprivation in man. Nephron. 1976;17:270-8.
21. Krieger J, Imbs JL, Schmidt M, Kurtz D. Renal function in patients with obstructive sleep apnea: Effects of nasal continuous positive airway pressure. Arch Intern Med 1988;148:1337-1340.
22. Krieger J, Laks L, Wilcox I, et al. Atrial natriuretic peptide relaease during sleep in patients with obstructive sleep apnoea before and during treatment with nasal continuous positive airway pressure. Clin Sci 1989;77:407-411.
23. Krieger J, Follenus M, Sforza E, Brandenberger G, Peter JC. Effects of treatment with nasal continuous positive pressure on atrial natriuetic peptide and arginine vasopressin release during sleep in patients with obstructive sleep apnea. Clin Sci 1991;8:443-449.
24. Krieger J, Petiau C, Sforza E, Delanoe F, Chamouard V. Nocturnal polyuria is a symptom of obstructive sleep apnea. Urol Int 1993;50:93-97.
25. Umlauf M, Kurtzer E, Valappil T, Burgio K, Pillion D, Goode P. Sleep-disordered breathing as a mechanism for nocturia: preliminary findings. Ostomy/Wound Management 1999;45:52-60.
26. Rechtschaffen A, Kales A. A manual for standardized terminology: Techniques and scoring system for sleep stages of human subjects. Los Angeles: UCLA Brain Information Service/Brain Research Institute, 1968.
27. Sullivan CE, Issa FG. Pathophysiological mechanisms in obstructive sleep apnea. Sleep 1980;3:235-46.
28. Watanabe T, Mikami A, Shigedo Y, et al. Esophageal pressure and apnea hypopnea index in sleep-disordered breathing. Psychiatry Clin Neurosci 2000;54:338-9.
29. Guilleminault C. Sleep apnea syndromes: impact of sleep and sleep states. Sleep 1980;3:227-34.
30. Yan AT, Bradley TD, Liu PP. The role of continuous positive airway pressure in the treatment of congestive heart failure. Chest 2001;120:1675-85.
31. Shiomi T, Guilleminault C, Stoohs R, Schnittger I. Leftward shift of the interventricular septum and pulsus paradoxus in obstructive sleep apnea syndrome. Chest 1991;100:894-902.
32. De Bold AJ, Borenstein HB, Veress AT, Sonnenberg H. A rapid and potent natriuretic response to intravenous injection of atrial myocardial extract in rats. Life Sci 1981;28:89-94.
33. Tavi P, Laine M, Voutilainen S, et al. Potentiation of stretch-induced atrial natriuretic peptide secretion by intracellular acidosis. Am J Physiol 1999;277:H405-12.
34. Klinger JR, Pietras L, Warburton R, Hill NS. Reduced oxygen tension increases atrial natriuretic peptide release from atrial cardiocytes. Exp Biol Med 2001;226:847-53.
35. Espiner EA, Richards AM, Yandle TG, Nicholls MG. Natriuretic hormones. Endocrinol Metab Clin North Am 1995;24:481-509.
36. Cantin M, Genest J. The heart as an endocrine gland. Clin Invest Med 986;9:319-327.
37. Yandle TG. Biochemistry of natriuretic peptides. J Int Med 1994;235:561-76.
38. Shenker Y, Sider RS, Ostafin EA, Grekin RJ. Plasma levels of immunoreactive atrial natriuretic factor in healthy subjects and in patients with edema. J Clin Invest 985;76:1684-7.
39. Raine AE, Erne P, Burgisser E, et al. Atrial natriuretic peptide and atrial pressure in patients with congestive heart failure. N Engl J Med 1986;315:533-7.
40. Lin CC, Tsan KW, Lin CY. Plasma levels of atrial natriuretic factor in moderate to severe obstructive sleep apnea syndrome. Sleep 1993;16:37-9.
41. Wallen T, Landahl S, Hedner T, Hall C, Saito Y, Nakao K. Atrial natriuretic peptides predict mortality in the elderly.[comment]. J Int Med 1997;241:269-75.
42. Schafer H, Pauleit D, Sudhop T, Gouni-Berthold I, Ewig S, Berthold HK. Body fat distribution, serum leptin, and cardiovascular risk factors in men with obstructive sleep apnea.[comment]. Chest 2002;122:829-39.
43. Punjabi NM, Sorkin JD, Katzel LI, Goldberg AP, Schwartz AR, Smith PL. Sleep-disordered breathing and insulin resistance in middle-aged and overweight men. Am. J. Respir. Crit Care Med 2002;165:677-682.
44. Ip MS, Lam B, Ng MM, Lam WK, Tsang KW, Lam KS. Obstructive Sleep Apnea Is Independently Associated with Insulin Resistance. Am. J. Respir. Crit Care Med 2002;165:670-676.
45. Guilleminault C. Clinical features and evaluation of obstructive sleep apnea. In: Kryger MH, Roth T, Dement WC, eds. Principles and practice of sleep medicine. Philadelphia: W. B. Saunders, 1994:667-677.
46. Robson WL, Leung AK. Secondary nocturnal enuresis. Clin Pediatr 2000;39:379-85.
47. Sakai J, Hebert F. Secondary enuresis associated with obstructive sleep apnea. J Am Acad Child Adolesc Psychiatry 2000;39:140-1.
48. Umlauf MG, Burgio KL, Shettar S, Pillion D. Nocturia and nocturnal urine production in obstructive sleep apnea. Appl Nurs Res 1997;10:198-201.
49. Ehlenz K, Firle K, Schneider H, et al. Reduction of nocturnal diuresis and natriuresis during treatment of obstructive sleep apnea (OSA) with nasal continuous positive air pressure (nCPAP) correlates to cGMP excretion. Medizinische Klinik 1991;86:294-6, 332.
50. Asplund R, Sundberg B, Bengtsson P. Desmopressin for the treatment of nocturnal polyuria in the elderly: a dose titration study. Br J Urol 1998;82:642-6.
51. Shindel A, Tobin G, Klutke C. Hyponatremia associated with desmopressin for the treatment of nocturnal polyuria. Urology 2002;60:344.
52. Robson WL, Norgaard J, Leung AK. Hyponatremia in patients with nocturnal enuresis treated with DDAVP. Eur J Pediatr 1996;155:959-962.
53. Odeh M, Oliven A. Coma and seizures due to severe hyponatremia and water intoxication in an adult with intranasal desmopressin therapy for nocturnal enuresis. J Clin Pharm 2001;41:582-4.
54. Bernstein SA, Williford SL. Intranasal desmopressin-associated hyponatremia: a case report and literature review. J Fam Pract 1997;44:203-8.
55. Blankfield RP, Hudgel DW, Tapolyai AA, Zyzanski SJ. Bilateral leg edema, obesity, pulmonary hypertension, and obstructive sleep apnea. Arch Int Med 2000; 160:2357-62.
56. Blankfield RP, Tapolyai AA, Zyzanski SJ. Left ventricular dysfunction, pulmonary hypertension, obesity, and sleep apnea. Sleep Breath 2001;5:57-62.
57. Blankfield RP, Zyzanski SJ. Bilateral leg edema, pulmonary hypertension, and obstructive sleep apnea: a cross-sectional study. J Fam Pract 2002;51:561-4.