

# NOCTURNAL POLYURIA VERSUS OVERACTIVE BLADDER IN NOCTURIA

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## ABSTRACT

The purpose of this article is to review the current state of knowledge on contributions of nocturnal urine overproduction and overactive bladder to the syndrome of nocturia. We review the recent literature and current state of the art in differential diagnosis, pathophysiology, and classification of nocturia. We found that multiple pathologic factors may result in nocturia, including cardiovascular disease, diabetes mellitus or insipidus, third spacing of fluid, sleep apnea, lower urinary tract obstruction, primary sleep disorders, and behavioral and environmental factors. Thus, nocturia may be attributed to nocturnal polyuria (nocturnal urine overproduction), diminished nocturnal bladder capacity, or both. Distinction between these conditions is made by a simple arithmetic analysis of the 24-hour voiding diary. Understanding the manifold origins of nocturia will lead to rational treatment of specific contributing pathophysiologic factors. *UROLOGY* 60 (Suppl 5A): 28–32, 2002. © 2002, Elsevier Science Inc.

One of the most common reasons for interrupted sleep in the general adult population is nocturia—waking during the night to urinate.<sup>1,2</sup> Many individuals with nocturia, particularly elderly men, have other lower urinary tract symptoms, such as urinary frequency, weak stream, urgency, and incontinence. In women, these symptoms are often believed to result from aging, childbirth, or just “being a woman.”<sup>3,4</sup> Nocturia refers both to the simple notion of urinating during the night and to the more complex idea involving an excess of some sort. It is unclear whether the excess refers to the volume of urine being produced or voided or to the number of occasions on which urine is passed. What constitutes an excessive frequency or volume for nocturnal urination has not been well defined for any age group.<sup>5–9</sup>

Most nocturic patients are elderly and are more likely to be exposed to serious health risks because nocturia causes fatigue caused by sleep deprivation, which increases the chance of traumatic injury through falling.<sup>10,11</sup> In a study that examined nighttime falls in elderly people, those with nocturia were at a significantly greater risk of falling, with risk increasing from 10% to 21% with  $\geq 2$

micturitions per night.<sup>12</sup> Such falls often lead to fractures, particularly hip fractures, a serious consequence of an already bothersome condition.

Pathologic conditions that cause nocturia include cardiovascular disease, diabetes mellitus and insipidus, lower urinary tract obstruction, and awakening to void for other reasons, such as anxiety or primary sleep disorders.<sup>11,13–15</sup> Behavioral and environmental factors that contribute to nocturia include consumption of diuretic medication, caffeine, alcohol, or excessive fluid shortly before retiring for the night.<sup>11</sup> Prostatic disease and neurogenic and unstable bladders have been reported to lead to frequent nocturnal rising.<sup>11,13</sup> Nocturia may additionally result from stroke, congestive heart failure, peripheral edema (eg, from venous insufficiency or nephrotic syndrome), and myeloneuropathy secondary to vertebral disk disease or spondylosis.<sup>16</sup>

The underlying pathophysiologic conditions that account for nocturia can be described in 4 broad categories: (1) nocturnal polyuria (NP) or nocturnal urine overproduction, (2) low nocturnal bladder capacity (NBC), (3) mixed (a combination of NP and low NBC), and (4) polyuria. These categories are derived from the 24-hour voiding diary in which the patient tabulates each voided volume and its corresponding time. We carefully counsel each patient in the procedure for diary procurement and confirm that the diary obtained is representative of the typical situation for that patient.

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Polyuria, defined as 24-hour urine output >2500 mL (or >40 mL/kg per 24 hours),<sup>14,17</sup> may cause nocturia through generally increased urine production wherein nocturnal urine output exceeds functional bladder capacity (FBC), much the same as the situation for NP. However, polyuria and NP are not mutually inclusive.

### NOCTURNAL POLYURIA

The increased production of urine at night experienced in NP is offset by lowered daytime urine production, such that the 24-hour urine volume remains normal.<sup>6</sup> A reason for this diurnal change is thought to be a disruption of the diurnal variation in secretion of arginine vasopressin (AVP). AVP, normally secreted in a diurnal pattern, is partly responsible for regulation of urine production.<sup>18</sup> Because AVP increases the resorption of water from the renal tubule, higher concentrations of AVP occurring at night result in the production of lower volumes of concentrated urine.

A change in the diurnal pattern of AVP secretion has been noted in elderly patients.<sup>13,14,19</sup> However, there is controversy surrounding the exact role of AVP in nocturia in elderly patients because other contributory factors—such as benign prostatic hyperplasia,<sup>20</sup> bladder dysfunction, and abnormal thirst perception—may coexist.<sup>21,22</sup> Plasma AVP levels are often undetectable during the night in elderly patients with nocturia, thus implying a cause-and-effect relation between AVP secretion and NP.<sup>13,23</sup>

In the renal inner medullary collecting duct, vasopressin regulates aquaporin-2 (AQP2), which is present in intracellular vesicles and the apical plasma membrane. Short-term regulation of AQP2 occurs by vasopressin-induced trafficking of AQP2-containing vesicles to the apical plasma membrane.<sup>24</sup> Long-term regulation is such that prolonged (>24-hour) increase in circulating vasopressin in turn leads to increased cellular levels of AQP2.<sup>25</sup> In addition, AVP causes the vasopressin V2 receptor in collecting duct cells to activate G protein, which in turn stimulates adenylate cyclase-mediated conversion of adenosine triphosphate to cyclic adenosine monophosphate. The latter activates protein kinase A, which stimulates permeability of AQP2 water channels.<sup>26</sup> Vasopressin “escape” is associated with relative vasopressin resistance of the collecting duct cells manifested by decreased intracellular cyclic adenosine monophosphate levels.<sup>27</sup> Factors that cause diuresis via antidiuretic hormone (ADH) inhibition include prostaglandin E<sub>2</sub>, hypercalcemia, lithium, and tetracycline.

Nocturia in a large proportion of elderly men with lower urinary tract symptoms is caused by NP and natriuresis.<sup>14</sup> Interestingly, a positive correlation has been observed between nocturnal urine volume (NUV) and daytime mean arterial blood

pressure. Although significant negative correlation has been found between NUV and plasma angiotensin II, NP is associated with decreased plasma AVP levels.<sup>14</sup> A possible explanation for NP and natriuresis in these patients is that pressure-induced lesions in the renal medulla and distal tubular system may be caused by long-lasting urinary tract obstruction. This may interfere with normal circadian renal handling of sodium by decreasing daytime sodium excretion.<sup>14</sup>

### OBSTRUCTIVE SLEEP APNEA

Respiratory disease associated with increased airway resistance, such as obstructive sleep apnea (OSA), is associated with increased renal sodium and water excretion mediated by plasma atrial natriuretic peptide levels.<sup>14,28</sup> The prevalence of OSA is about 2% in women and 4% in men.<sup>29</sup> The mechanism for elevated atrial natriuretic peptide release associated with OSA has been demonstrated as being caused by increased right atrial transmural pressure that results from hypoxia-induced pulmonary vasoconstriction.<sup>28</sup> Hence, nocturia in a population of patients may result from OSA and secondary NP.<sup>30</sup>

Polysomnographic sleep studies are therefore recommended in patients with nocturia suspected of being related to OSA. Patient selection is based on increased risk as follows: patients with morbid obesity, snoring, acromegaly, asthma, hypertension, type 2 diabetes mellitus, and craniofacial abnormalities may be submitted for sleep studies because of their 30% to 40% chance of having OSA.<sup>29,30</sup>

### ACCUMULATION OF THIRD-SPACE FLUID

NP may be occasioned by third spacing of fluid in the lower extremities caused by right-sided congestive heart failure, lower-extremity venous stasis disease, hypoalbuminemia, and excessive salt intake. Detailed history and physical examination, as well as adjunctive testing, such as cardiac echography and nuclear testing, should be used in patients with nocturia found to have NP who are at risk for cardiac disease.

### POLYURIA, DISORDERS OF THIRST, AND DIABETES INSIPIDUS

Polyuria (defined as 24-hour urine output in excess of 2500 mL or >40 mL/kg per 24 hours) is related to increased intake, so that polyuria and polydipsia (at least in the steady state) are closely related. Polyuria thus results in both day and night urinary frequency caused by global urine overproduction in excess of bladder capacity. Causes of polyuria include diabetes mellitus and insipidus (in turn caused by deficient production of vasopressin by the pituitary or by primary nephrogenic water loss), lithium-induced polydipsia or polyuria,<sup>31,32</sup> and primary thirst disorders.<sup>33</sup>

Although polyuria causes increased NUV similar to the situation for NP, treatment is directed at reduction in both water intake and its resultant output through specific measures, such as insulin replacement, voluntary restriction of water intake, or supplementary administration of vasopressin analogs where appropriate.

The causes of diabetes insipidus are generally classified into 2 categories: central (neurogenic) and renal (nephrogenic). In the case of the former, there is a lack of production of vasopressin (ADH) from the posterior pituitary, most often caused by damage to the hypothalamus as a result of surgery, infection, tumor, or head trauma. Nephrogenic diabetes insipidus is caused by defective renal responsiveness to adequate circulating levels of ADH so that the renal tubules are incapable of water reabsorption, leading to dehydration and excessive thirst with secondary polydipsia. Long-term lithium therapy is a special case of (usually) reversible nephrogenic diabetes insipidus. Psychogenic polydipsia presents as diabetes insipidus caused by compulsive water drinking. There may be an associated secondary nephrogenic component to diabetes insipidus in these patients due to washout of the countercurrent multiplier gradient responsible for renal concentration of urine. This defect may reverse with psychiatric treatment of the underlying compulsion to drink excess volumes of water. Dipsogenic polydipsia results from central neurologic abnormalities caused by brain trauma, tumor, surgery, or radiation therapy.

Patients with primary thirst disorders may present with global polyuria and secondary NP.<sup>31</sup> Diagnosis may be made by careful diary evaluation of intake and urinary output, in addition to use of both the water deprivation and renal concentrating capacity tests. The overnight water deprivation test compares urine osmolality at the hour of sleep with that after an overnight fast. Normal fasting urine osmolality indicates both normal pituitary AVP production and renal concentrating ability. Thus, a normal overnight water deprivation test result indicates that the origin of polyuria is some form of polydipsia. An abnormal overnight water deprivation test result is followed by the renal concentrating capacity test, which takes place as follows: In adults, 40  $\mu$ g of desmopressin is administered intranasally. The bladder is emptied, and a urine sample for osmolality is obtained 3 to 5 hours later. Water intake is restricted for the first 12 hours after drug administration (to avoid hyponatremia from desmopressin in patients with dipsogenic polydipsia). The reference level for normal urine osmolality after desmopressin administration or overnight water deprivation is 800 mOsm/kg. A post-desmopressin administration urine osmolality of <550 mOsm/kg suggests nephrogenic or chronic central diabetes insipidus, whereas urine osmolality

of 550 to 800 mOsm/kg is consistent with psychogenic or dipsogenic polydipsia. However, after several days of desmopressin administration, patients with central diabetes insipidus develop normal concentrating capacity.<sup>32,34</sup>

### NOCTURIA CAUSED BY DIMINISHED NOCTURNAL BLADDER CAPACITY

Nocturia caused by diminished NBC is of 2 general types: decreased FBC and decreased NBC. In both conditions, NUV exceeds bladder capacity and the patient is awakened by the need to void because the bladder does not hold enough. The FBC is the largest volume voided as recorded in the micturition diary. If the FBC is less than NUV, nocturia ensues.<sup>35</sup>

To quantify NBC, several terms need to be defined: nocturia index (Ni) and the NBC index (NBCi). The Ni is NUV divided by FBC; the first morning void is included in the NUV. The Ni minus 1 (rounded up to the nearest integer if the quotient is not initially an integer) equals the predicted number of nightly voids (PNV). The NBCi is defined as the difference between the PNV and the actual nightly voids (ANV). The significance of this is that the greater the NBCi, the more nocturia may be attributed to overactive bladder (OAB; diminished NBC, sensory urge disorders, detrusor overactivity). For example, if the NUV is 1000 mL and the FBC is 500 mL, the Ni is  $1000/500 = 2$ ; this patient would have a PNV equal to 1 ( $Ni - 1 = 1$  in this case), and he or she would be expected to void once per night, the first 500 mL during sleep hours, and then awaken and void the second 500 mL with the first morning void. With this example, if the patient actually arose 7 times to void the same 1000 mL, he or she would have an NBCi of 6 ( $7 [ANV] - 1 [PNV]$ ). This patient, for whatever reason, has significantly diminished bladder capacity during sleep hours. Thus, a high NBCi indicates either diminished NBC or a more severe global sensory urgency. The advantage of NBCi over the absolute NBC (in milliliters) as a measure of nocturnal OAB is that the NBCi can be compared among different patients, regardless of size or differential urine production. The causes of decreased NBC (and NP and polyuria) are listed in Table I.

The relation between nocturia and detrusor instability as a urodynamic diagnosis has been previously studied.<sup>36</sup> In a prospective study of 137 male and female patients, those with and without detrusor instability were compared with regard to differences in NBC, FBC, NUV, percentage of nocturnal output compared with 24-hour output, and the number of nocturnal voids. There were no significant differences in any of these parameters whether the patient did or did not have urodynamically demonstrated detrusor instability. It was con-

**TABLE I. Causes of nocturia**

Condition	Cause
Nocturnal polyuria	<ul style="list-style-type: none"> <li>● Congestive heart failure</li> <li>● Abnormal diurnal secretion of arginine vasopressin</li> <li>● Third spacing: varicose veins, nephrosis</li> <li>● Late-night diuretic administration</li> <li>● Obstructive sleep apnea</li> </ul>
Polyuria	<ul style="list-style-type: none"> <li>● Diabetes mellitus</li> <li>● Diabetes insipidus (central, nephrogenic)</li> <li>● Polydipsia (dipsogenic, psychogenic)</li> </ul>
Diminished nocturnal bladder capacity	<ul style="list-style-type: none"> <li>● Neurogenic bladder</li> <li>● Cystitis: bacterial, interstitial, tuberculous, radiation</li> <li>● Cancer of bladder, prostate, urethra</li> <li>● Learned voiding dysfunction</li> <li>● Anxiety disorders</li> <li>● Pharmacologic: xanthines (theophylline, caffeine); <math>\beta</math>-blockers</li> <li>● Bladder calculi</li> </ul>

cluded that the origin of nocturia could not be related to daytime detrusor instability. Nocturnal urodynamic studies would need to be performed to identify nocturia caused by detrusor instability occurring during the hours of sleep.

#### MIXED CAUSES FOR NOCTURIA

Many patients with nocturia are found to have a combination of NP and low NBC. We term this a *mixed* origin of nocturia. A recent study<sup>37</sup> of nocturia in elderly patients determined that older patients with nocturia tend to have higher NUVs and lower FBCs than their counterparts without nocturia. However, the ratio between NUV and FBC (otherwise known as the Ni<sup>38</sup>) allowed a more significant discrimination of the origin of nocturia in elderly patients than either variable alone: In patients with nocturia, the mean NUV was twice the FBC, whereas in patients without nocturia, the mean NUV was approximately the same as the FBC. This study thus demonstrated that the origin of nocturia in elderly (and presumably nonelderly) patients can be attributed to the disparity between nocturnal urine output and ability to store such output during the hours of sleep.

#### REFERENCES

1. Middlekoop HA, Smilde-van den Doel DA, Neven AK, *et al*: Subjective sleep characteristics of 1485 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* 51: M108–M115, 1996.
2. Asplund R, and Åberg HE: Micturition habits of older people: voiding frequency and urine volumes. *Scand J Urol Nephrol* 26: 345–349, 1992.
3. Umlauf MG, Goode S, and Burgio KL: Psychosocial issues in geriatric urology: problems in treatment and treatment seeking. *Urol Clin North Am* 23: 127–136, 1996.

4. Fultz NH, and Herzog AR: Epidemiology of urinary symptoms in the geriatric population. *Urol Clin North Am* 23: 1–10, 1996.
5. Donahue JL, and Lowenthal DT: Nocturnal polyuria in the elderly person. *Am J Med Sci* 314: 232–238, 1997.
6. Asplund R: The nocturnal polyuria syndrome (NPS). *Gen Pharmacol* 26: 1203–1209, 1995.
7. Asplund R, and Åberg H: Nocturnal micturition, sleep and well-being in women of ages 40–64 years. *Maturitas* 24: 73–81, 1996.
8. Shah PJR: The assessment of patients with a view to urodynamics, in Mundy AR, Stephenson TP, and Wein AJ (Eds), *Urodynamics: Principles, Practice and Application*. Edinburgh, Churchill Livingstone, 1994, pp 85–93.
9. Hennessy CH, and Shen JKM: Sources of unreliability in the multidisciplinary team assessment of the elderly. *Eval Rev* 10: 178, 1986.
10. Barry MJ, Fowler FJ, O’Leary MP, *et al*: The American Urological Association Symptom Index for benign prostatic hyperplasia. *J Urol* 148: 1549–1557, 1992.
11. Barker JC, and Mitteness LS: Nocturia in the elderly. *Gerontologist* 28: 99–104, 1988.
12. Stewart RB, Moore MT, May FE, *et al*: Nocturia a risk factor for falls in the elderly. *J Am Geriatr Soc* 40: 1217–1220, 1992.
13. Saito M, Kondo A, Kato T, *et al*: Frequency-volume charts: comparison of frequency between elderly and adult patients. *Br J Urol* 72: 38–41, 1993.
14. Matthiesen TB, Rittig S, Norgaard JP, *et al*: Nocturnal polyuria and natriuresis in male patients with nocturia and lower urinary tract symptoms. *J Urol* 156: 1292–1299, 1996.
15. Asplund R, and Åberg HE: Micturition habits of older people. *Scand J Urol* 26: 345–349, 1992.
16. Sullivan MP, and Yalla SV: Urodynamic assessment of benign prostatic hypertrophy, in Romas NA, and Vaughan ED (Eds), *Alternate Methods in the Treatment of Benign Prostatic Hyperplasia*. Berlin, Springer-Verlag, 1993, pp 66–89.
17. Weiss JP, Stember DS, and Blaivas JG: Nocturia in adults: classification and etiology. *Neurourol Urodyn* 17: 467–472, 1998.
18. Baylis PH: Osmoregulation and control of vasopressin secretion in healthy humans. *Am J Physiol* 235: R671–R678, 1987.

19. Kikuchi Y: Participation of atrial natriuretic peptide (hANP) levels and arginine vasopressin (AVP) in aged persons with nocturia. *Jpn J Urol* 86: 1651–1659, 1995.
20. Bruskwitz RC, Larsen EH, Madsen PO, *et al*: 3-year follow-up of urinary symptoms after transurethral resection of the prostate. *J Urol* 136: 613–615, 1986.
21. Phillips PA, Bretherton M, Johnston C, *et al*: Reduced osmotic thirst in healthy elderly men. *Am J Physiol* 261: R166–R171, 1991.
22. Stachenfeld NS, Mack GW, Takamata A, *et al*: Thirst and fluid regulatory responses to hypertonicity in older adults. *Am J Physiol* 271: R757–R765, 1996.
23. Asplund R, and Åberg H: Diurnal variation in the levels of antidiuretic hormone in elderly subjects with nocturia. *J Intern Med* 229: 131–134, 1991.
24. Inoue T, Terris J, Ecelbarger CA, *et al*: Vasopressin regulates apical targeting of aquaporin-2 but not of UT1 urea transporter in renal collecting duct. *Am J Phys* 276: F559–F566, 1999.
25. Valenti G, Laera A, Pace G, *et al*: Urinary aquaporin 2 and calciuria correlate with the severity of enuresis in children. *J Am Soc Nephrol* 11: 1873–1881, 2000.
26. Nishimoto G, Zelenina M, Li D, *et al*: Arginine vasopressin stimulates phosphorylation of aquaporin-2 in rat renal tissue. *Am J Physiol* 276: F254–F259, 1999.
27. Ecelbarger CA, Chou CL, Lee AJ, *et al*: Escape from vasopressin-induced antidiuresis: role of vasopressin resistance of the collecting duct. *Am J Physiol* 274: F1161–F1166, 1998.
28. Yalkut D, Lee LY, Grider J, *et al*: Mechanism of atrial natriuretic peptide release with increased inspiratory resistance. *J Lab Clin Med* 128: 322–328, 1996.
29. Partinen M: Epidemiology of obstructive sleep apnea syndrome. *Curr Opin Pulm Med* 1: 482–487, 1995.
30. Krieger J, Petian C, Sforza E, *et al*: Nocturnal pollakiuria is a symptom of obstructive sleep apnea. *Urol Int* 50: 93–97, 1993.
31. Widerlov E, Sjoström R, and Soderberg U: DDAVP and lithium-induced polyuria/polydipsia. *Lancet* 2: 1080, 1977.
32. Abyholm G, and Monn E: Intranasal DDAVP test in the study of renal concentrating ability in children with recurrent urinary tract infections. *Eur J Pediatr* 130: 149–154, 1979.
33. Aronson AS, and Svenningsen NW: DDAVP test for estimation of renal concentrating capacity in infants and children. *Arch Dis Child* 49: 654–659, 1974.
34. Miller M, Dalakos AM, Gellerman H, *et al*: Recognition of partial defects in antidiuretic hormone secretion. *Ann Intern Med* 73: 721–729, 1970.
35. Abrams P, Blaivas JG, Stanton S, *et al*: The standardisation of terminology of lower urinary tract function. International Continence Society Committee on Standardisation of Terminology. *Scand J Urol Nephrol Suppl* 114: 5–19, 1988.
36. Sakamoto K, Weiss JP, and Blaivas JG: Etiology of nocturia: relationship to nocturnal bladder capacity and detrusor instability. Abstracts of the International Continence Society Meeting, August 2000; Tampere, Finland; p 360.
37. Rembratt A, Weiss J, and Robertson G: Pathogenesis of nocturia in the elderly: relationship of functional bladder capacity to nocturnal urine output [abstract]. *J Urol* 165(suppl): 250, 2001.
38. Weiss JP, and Blaivas JG: Nocturia. *J Urol* 163: 5–12, 2000.

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## DISCUSSION FOLLOWING DR. WEISS' PRESENTATION

**Joseph G. Ouslander, MD (Atlanta, GA):** Do you know whether people who void less have a sleep disorder? Often, the prevalence of sleep disorders in older people is so high that they may be waking up from a sleep disorder and then voiding. We have been studying this problem in older people. They may get up 2 or 3 times a night, and it does not bother them at all because they go right back to sleep.

Many older people have venous insufficiency. We treat those people with support stockings, leg elevation, and sometimes a late afternoon diuretic agent. We find that some of them get better. The people whom I see in my clinic will not and cannot keep an accurate frequency volume diary. So what I do is determine whether someone is complaining primarily of nocturia but actually has frequency and urgency during the day. If this patient has a negative workup, I will treat them with a bladder relaxant at night.

**Jeffrey P. Weiss, MD (New York, NY):** Men too?

**Dr. Ouslander:** Men are different. These are mostly women.

You have to be very careful with older men. I do not use anticholinergic medication in 80- and 90-year-old men except in very limited circumstances. I have seen too many go into irreversible urinary retention.

**Dr. Weiss:** I think the key in what you are doing in treating nocturia is matching nocturnal urine output with nocturnal bladder volume. Therefore, if you can get the nocturnal urine output down and the nocturnal bladder capacity up, you win. Neither of those is easy; thus, nocturia is really hard to treat, as is overactive bladder (OAB). Therefore, we are looking for better drugs and better methodologies. However, in general, I think the message is to try to determine what you can do to match nocturnal urine volume with nocturnal bladder capacity.

**David R. Staskin, MD (New York, NY):** Urologists tend to treat men with nocturia with an  $\alpha$ -blocker when the problem may be OAB. You are treating bladder outlet obstruction. The patient may develop more peripheral edema with the  $\alpha$ -blocker and the nocturia may get worse.