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## Nocturia and complementary indices: determination and quantification of the cause of nocturia by frequency-volume charts in women with lower urinary tract symptoms

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**Abstract** We evaluated differences between women with lower urinary tract symptoms (LUTS) with and without nocturia in terms of voiding habits, urine production and voided volumes in order to determine and quantify the cause of nocturia by using frequency-volume (FV) charts. At the initial visit, all patients underwent a detailed clinical evaluation including an International Prostate Symptom Score assessment, received a thorough explanation from the study coordinators, and were requested to complete a 3-day FV chart. Of the 123 women enrolled, 106 (86.2%) 20–83 years old (median age 55.0) completed the study. Nocturnal urine volume was higher in nocturics than in non-nocturics, but this was not statistically significant. Total daytime voided volume was lower in nocturics than in non-nocturics ( $P=0.030$ ) but with no detectable difference in total voided volume. To identify possible risk factors, we examined age and night time parameters including the nocturnal bladder capacity index (NBCI), nocturnal polyuria index (NPI) and nocturia index (NI) by univariate logistic analysis. When nocturia was defined as voiding at least twice per night, age and NI were found to be associated with it by univariate analysis. These two variables were further analyzed using a multivariate logistic model to determine their association with nocturia. In the multivariate analysis, a positive association was observed between age and nocturia. Patients 50 years or older had a 3.9-fold higher risk [odds ratio (OR) 3.86; 95% confidence interval (CI) 1.60–9.31;  $P=0.003$ ] of voiding

at least twice per night than those younger than 50 years. In the same model, patients with NI greater than 1.5 had a 4.5-fold higher risk of voiding at least twice per night (OR 4.59; 95% CI 1.80–11.17;  $P=0.001$ ). FV charts are valuable for determining the cause of nocturia in women with LUTS. Our findings suggest that age and the NI may be important variables in the evaluation of nocturia in women with LUTS.

**Keywords** Nocturia · Bladder · Voiding diary · Urination disorders

### Introduction

Patient-completed frequency-volume (FV) charts are commonly used in clinical trials as a primary tool for measuring subjective symptoms of the lower urinary tract. These measures are deemed noninvasive and inexpensive. The FV chart is usually recorded during the patient's normal daily activities in his or her environment. It provides not only the frequency of voiding, but also urinary volume per void and total urinary volume during the day and night. Therefore, it can also provide important information on a patient's voiding problem, which is not easily identified by other means.

Nocturia is a bothersome symptom, because it may result in sleep disturbance, daytime fatigue, a lower level of general well-being and the risk of nightly falls [1]. Nocturia may be attributed to nocturnal polyuria, diminished nocturnal bladder capacity, or both. Women have nocturia more often than men [2, 3], and the few of studies on female nocturia question whether male and female nocturia have identical etiologies [4]. To date, however, the literature on female nocturia is sparse, whereas male nocturia has been studied rather extensively because of an association with lower urinary tract symptoms (LUTS). Furthermore, published reports on the value of the FV chart for determining the cause of nocturia in women with LUTS are lacking. We

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hypothesized that one could classify the etiology of nocturia, for example as nocturnal polyuria and/or detrusor overactivity based on the data from FV charts. To test this hypothesis, we evaluated differences between women with and without nocturia in terms of voiding habits, urine production and voided volumes. Our primary goal was to determine and quantify the cause of nocturia by using FV charts in women with LUTS.

## Materials and methods

We prospectively enrolled 123 women referred for the evaluation of LUTS. All individuals were evaluated on an outpatient basis. At the initial visit, all patients underwent a detailed clinical evaluation, comprising a complete history, physical examination, an International Prostate Symptom Score (IPSS) assessment, urinalysis, urine culture, uroflowmetry and post-void residual urine measurement. Subsequently, patients received a thorough explanation from the study coordinators and were requested to complete a 3-day FV chart, including the time and volume of each void, and their bedtime and waking time. Subjects were asked not to alter their usual fluid intake and voiding habits during the study. Since sleeping habits vary markedly between subjects and individually from day-to-day, night time was defined as the time from going to bed to rising in the morning for each night registered [5]. All diaries were completed before any further diagnostic or therapeutic intervention was undertaken. The protocol was approved by our institutional review board and all patients signed an informed consent agreement.

Study inclusion criteria were an age of 20 years or older and the ability to communicate, understand and comply with the study requirements. Exclusion criteria were a confused state or depression, urinary tract infection, medication known to affect voiding, neurogenic bladder dysfunction, pregnancy, restricted mobility and those who were working primarily at night. Patients with an incomplete workup due to charts with missing dates, non-consecutive days or only 2 days of data were also excluded. Of the 123 women enrolled, 106 (86.2%) 20–83 years old (median age 55.0) completed the study.

Diaries from 44 non-nocturics and 62 nocturics were analyzed. The number of nightly voids was measured using the IPSS questionnaire and estimated voiding volumes were means taken over 3 days. Nocturics were defined as patients that voided at least twice per night and non-nocturics as those with one or less voids per night [6]. When assessing a FV chart, the first morning void was included in the nocturnal urine volume since this void had been excreted by the kidneys during sleep. Thus, nocturnal urine volume was defined as volume of nightly voids plus the first morning void. However, the first morning void was considered a normal diurnal voiding episode. We evaluated three complementary indices of nocturia based on the FV charts: the nocturnal bladder capacity index (NBCI), the nocturnal polyuria index (NPI), and the nocturia index (NI). The NBCI was defined as the difference between the predicted number of nightly voids and the actual number of nightly voids, and reflects nocturnal bladder capacity. When the nocturnal bladder capacity index is greater than 2, nocturia may be attributed to a diminished nocturnal bladder capacity [7]. NPI and NI are measures of nocturnal urine overproduction. The NPI was defined as nocturnal urine volume divided by the 24-h urine volume [8]. When the NPI is greater than 0.35, increased nocturnal urine production will cause nocturia. The NI was defined as the nocturnal urine volume divided by the functional bladder capacity [8]. When the NI is greater than 1.5, nocturia may occur due to increased nocturnal urine production.

Associations between parameters were calculated using the Spearman-rank correlation. We then compared clinical parameters between patients with and without nocturia, i.e., voiding at least twice per night. Statistical comparisons of continuous data were performed using the Mann-Whitney U-test. The receiver operating characteristic (ROC) curve was used to determine the predictive

ability of variables for nocturia, and areas under the ROC curves were estimated. To assess the possible effect of variables on nocturia, univariate logistic regression analysis was performed. In this univariate analysis, variables with  $P < 0.05$  were entered into a multivariate model. Associations between variables and nocturia are described using maximum likelihood estimates of the relative risk and by 95% confidence intervals based on logistic regression models. Confidence intervals were based on the standard errors of the coefficients and a normal approximation. A commercially available computer software package (SPSS, Chicago, Ill.) was used for the analysis. A 2-tailed  $P$  value of  $< 0.05$  was considered significant.

## Results

We evaluated the correlation coefficients between the number of nocturnal voids in the FV charts and degree of nocturia (question no. 7) in the IPSS. These parameters were significantly correlated with each other ( $r = 0.627$ ,  $P < 0.001$ ). Median IPSS of the total group was 14.0 (range 1–34) and the median quality of life score was 5.0 (range 0–6). Nocturnal urine volume was higher in nocturics than in non-nocturics but this was not statistically significant. Total daytime voided volume was lower in nocturics than in non-nocturics ( $P = 0.030$ ) but with no detected difference in total voided volume. Maximum daytime voided volume ( $P = 0.045$ ), mean daytime voided volume ( $P = 0.002$ ), maximum voided volume ( $P = 0.006$ ) and mean voided volume ( $P = 0.002$ ) were significantly lower in nocturics than in non-nocturics (Table 1).

The predictive ability of variables for nocturia is shown in Table 2. The area under the curve shows the probability that the predictive ability of NI is higher than that of the other variables. The areas under the ROC curve for nocturia were 0.68, 0.67, 0.61 and 0.73 for age, NBCI, NPI and NI, respectively.

To identify possible risk factors that influence nocturia, we examined age and night time parameters including NBCI, NPI and NI by univariate logistic analysis. When nocturia was defined as voiding at least twice per night, age and NI were found to be associated with it by univariate analysis. These two variables were further analyzed using a multivariate logistic model to determine their association with nocturia, and a positive association was observed between age and nocturia. Patients 50 years old or older had a 3.9-fold higher risk [odds ratio (OR) 3.86; 95% confidence interval (CI) 1.60–9.31;  $P = 0.003$ ] of voiding at least twice per night than those younger than 50 years. In the same model, a higher NI was positively related to nocturia. Patients with an NI greater than 1.5 had a 4.5-fold higher risk of voiding at least twice per night (OR 4.59; 95% CI 1.80–11.17;  $P = 0.001$ ). These results are presented in Table 3.

## Discussion

Increased well-being is promoted by fewer voids and a better quality of sleep [9]. However, the incidence of

**Table 1** Comparison of variables (medians and range) between patients with and without voiding at least twice per night. IPSS International Prostate Symptom Score, probabilities refer to Mann-Whitney U-tests

	Number of nocturia (IPSS no. 7)		<i>P</i>
	≤ 1	≥ 2	
No. of patients	44	62	
Age (years)	46.5 (20.0–74.0)	59.0 (23.0–83.0)	0.002
Night time parameters			
Nocturnal bladder capacity index	0.0 (0.0–1.0)	0.0 (0.0–3.0)	< 0.001
Nocturnal polyuria index (%)	0.3 (0.0–0.7)	0.4 (0.1–0.7)	0.062
Nocturia index	1.1 (0.1–3.8)	1.6 (0.4–10.6)	< 0.001
Nocturnal urine volume (cc)	375.0 (20.0–800.0)	447.0 (90.0–1500.0)	0.197
Daytime parameters			
Maximum daytime voided volume (cc)	250.0 (60.0–600.0)	230.0 (30.0–400.0)	0.045
Mean daytime voided volume (cc)	192.9 (88.9–373.3)	168.7 (46.3–303.3)	0.002
Total daytime voided volume (cc)	1037.0 (170.0–2400.0)	830.0 (95.0–2330.0)	0.030
Total parameters			
Maximum voided volume(cc)	315.0 (140.0–650.0)	260.0 (30.0–680.0)	0.006
Mean voided volume (cc)	192.9 (88.9–373.3)	168.7 (43.3–303.3)	0.002
Total voided volume (cc)	1365.0 (660.0–2410.0)	1344.0 (185.0–2650.0)	0.700

**Table 2** Areas under the receiver operating characteristic curves demonstrating the ability of variables to predict voiding at least twice per night (IPSS no. 7)

	Areas under the curve (95% confidence interval)	<i>P</i>
Age	0.681 (0.577–0.784)	0.002
Nocturnal bladder capacity index	0.673 (0.572–0.774)	0.002
Nocturnal polyuria index	0.607 (0.498–0.716)	0.062
Nocturia index	0.731 (0.634–0.828)	< 0.001

nocturia and the total number of voiding episodes increases with age. Because of this correlation with increasing age, nocturia is often viewed as a natural part of aging, although it may occur at any age. Age-related physiological changes can alter the regular pattern of urine excretion and lead to an increased nocturnal frequency of voiding. Additionally, aging is associated with anatomical and physiological changes of the urinary tract, which predispose towards increased urinary frequency without affecting urine volume. Whenever, nocturia is present, clinicians should try to identify its causes by a taking a thorough history, as well as making a physical examination with pertinent complimentary

tests. Once the specific cause or causes are found, most cases can be satisfactorily managed using behavioral, pharmacological or surgical therapies [10].

FV charts are widely used by clinicians interested in voiding dysfunction. These charts have the advantage of being recorded at home in the subject's environment and do not interfere with an individual's daily habits. FV charts, which are completed daily by the patient over a certain number of days, facilitate history-taking, allow the clinician to obtain information about voiding frequency, nocturia, the mean volume of urine passed, and provide documentation on voiding patterns to be established in the patient's environment and during various daily activities. FV charts remain the most valid instrument for diagnosing nocturia in elderly men [11].

Our study confirms the importance of FV charts for the evaluation of nocturia in female patients. We analyzed the relationship between nocturia and age with three complementary indices of nocturia in women with LUTS. As expected, age differences were found to be related to episodes of nocturia. Interestingly, of the complementary indices, only NI was found to be an independent predictor of voiding at least twice per night. This result indicates that female nocturia is related to excess overnight urine production (nocturnal polyuria).

**Table 3** Univariate and multivariate risk factors of voiding at least twice per night (IPSS no. 7)

	Odds ratio (95% CI)	<i>P</i>	Adjusted odds ratio (95% CI) <i>P</i>	<i>P</i>
Age (years)				
≥ 50	3.783 (1.659–8.626)	0.002	3.860 (1.600–9.312)	0.003
< 50	1.000			
nocturnal bladder capacity index				
> 2	1.017 (0.000–4.070)	0.706		
≤ 2	1.000			
nocturnal polyuria index (%)				
≥ 35	1.489 (0.679–3.265)	0.320		
< 35	1.000			
Nocturia index				
> 1.5	4.407 (1.855–10.473)	0.001	4.490 (1.804–11.174)	0.001
≤ 1.5	1.000			

Nocturia may be caused by a diminished nocturnal bladder capacity. The relationship between nocturia and detrusor instability, as a means of urodynamic diagnosis, has been studied [12]. In a prospective study, those with and without detrusor instability were compared with respect to differences in nocturnal bladder capacity, functional bladder capacity, nocturnal urine volume, percentage of nocturnal output compared with 24-h output, and the number of nocturnal voids. No significant differences were observed in any of these parameters, regardless of whether the patient did or did not have urodynamically demonstrated detrusor instability. It was concluded that the origin of nocturia could not be related to daytime detrusor instability. Thus, nocturnal urodynamic studies are required to identify the cause of nocturia by detrusor instability occurring during the hours of sleep [13].

We excluded women with restricted mobility from the analysis. Guite et al. [14] studied the effect of posture on nocturnal urine output in elderly women and found that there was no difference between day and night time urine output for days spent in bed, but that nocturnal output was greatly increased when the subjects spent the day sitting in a chair. This supports the theory that edema in dependent limbs is required for the circulation, and that excess water is excreted at night when the subject is prostrate. This edema could represent a degree of sub-clinical cardiac failure and may explain why healthy individuals with nocturnal polyuria have high levels of circulating atrial natriuretic peptide [15].

Many patients with nocturia are found to have a combination of nocturnal polyuria and a low nocturnal bladder capacity. A recent study of nocturia in elderly patients found that older patients with nocturia tend to have a higher nocturnal urine volume and lower functional bladder capacity than their counterparts without nocturia [16]. However, the ratio between nocturnal urine volume and functional bladder capacity (NI) allowed a more significant discrimination of the origin of nocturia in elderly patients than either variable alone. The present study supports this result. Women with nocturia had smaller maximum voided volumes than those without nocturia (260 ml vs 325 ml,  $P=0.006$ ). Nocturnal urine volume was higher in nocturics than in non-nocturics but this difference was not statistically significant (447 ml vs 375 ml,  $P=0.197$ ). NI was found to be significantly greater in nocturics than in non-nocturics (1.6 versus 1.1,  $P<0.001$ ) (Table 1). Furthermore, among the complementary indices of nocturia, only NI was found to be positively related to nocturia (Table 3). Our results demonstrate that the NI may be superior to the NPI for identifying relative nocturnal urine overproduction as the suspected explanation for nocturia in female patients.

The present study was not population-based and thus the subjects may not be representative of the general population since they might have been more interested

in, or had more concern about, LUTS including nocturia than the general population. Additional studies involving the general population are needed to confirm these findings. Additionally, our study included only Korean women. Therefore, the results may not be applicable to patients of other races or cultures and further studies in these areas are warranted.

In conclusion, we believe that it is possible to determine and quantify the cause of nocturia by using FV charts for females. In the present study, age and NI were found to be independent predictors of voiding at least twice per night in these patients. Our findings suggest that age and the NI may be important variables in the evaluation of nocturia in women with LUTS.

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