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ORIGINAL ARTICLE

Determinants of nocturia severity in men, derived from frequency–volume charts

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Abstract

Objective. Nocturia may be characterized by indices derived from the frequency–volume chart (FVC). The objective of this study was to determine how these parameters relate to the severity of nocturia in men with and without lower urinary tract symptoms (LUTS). *Materials and methods.* A retrospective analysis of FVCs was performed in two cohorts of men: those presenting with LUTS in a New York ambulatory urology clinic and those from the longitudinal population-based Krimpen study. Nocturnal urine volume (NUV), nocturia index (Ni), nocturnal polyuria index (NPi), nocturnal maximal voided volume (nMVV) and sleep duration were derived from FVCs. Comparisons were made using Spearman's rank correlation coefficient between actual number of nightly voids (ANV) and the other diary parameters. *Results.* Eighty-eight consecutive men who presented with LUTS completed a 24 h FVC [median age 70 years, interquartile range (IQR) 64.5–74.5, median ANV 2, IQR 1.5–4]. Nocturnal voiding frequency and volume were analyzed in 1082 community-dwelling men (median age 61 years, IQR 56.1–66.4, range 49.4–78.2; median ANV 1.5, IQR 1.0–2.0, range 0–4.5). Both cohorts demonstrated strong correlations between nocturia severity (represented as ANV) and Ni (0.797, 0.658 for cohorts 1 and 2, respectively). There were moderate correlations between nocturia severity and NPi (0.545, 0.394), NUV (0.463, 0.432) and sleep duration (0.306, 0.272). The nMVV correlated poorly with nocturia severity (0.159, 0.146). *Conclusions.* Treatment of nocturia should aim to match nocturnal urine production with bladder capacity. Given the lack of known effective pharmacotherapy for low bladder volume, the first attempt nocturia treatment could focus on volume reduction.

Keywords:

Lower urinary tract symptoms, nocturia, quality of life, voiding diary

History

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Introduction

Nocturia is a highly bothersome and prevalent lower urinary tract symptom (LUTS) [1–3]. Patient-reported outcome instruments allow physicians and researchers to measure the subjective impact of nocturia on patients. These include the Nocturia Quality-of-Life (NQoL) questionnaire [4], the American Urological Association Symptom Index (AUASI) [5] and the generic 15D Healthcare Related Quality of Life (15DHRQoL) instrument [6]. The Finnish National Nocturia and Overactive bladder (FINNO) study, a Finnish population-based study, found nocturia to be associated with a significant decrease on all dimensions of the 15DHRQoL. Furthermore, bother (as determined by the AUASI) was found to be significantly increased with two or more voids nightly [7]. These findings are supported by a community-based study of Taiwanese adults with nocturia, which found an inverse correlation between episodes of nocturia and quality of life as measured by the NQoL questionnaire. The impact on quality of life was greatest for patients with at least two episodes per night [8].

The negative impact of nocturia is not limited to quality of life; it has economic implications as well. A study using data from the Boston Area Community Health Study and the US Bureau of Labor Statistics to estimate the economic burden of nocturia found that workers experiencing nocturia were less productive, as measured by the Work Productivity and Activity Impairment questionnaire. The study concluded that the cost of nocturia to the USA was 63.5 billion dollars per year [9]. A clinical review by Bosch and Weiss found that 2–16.6% of men aged 20–40 years and 4.4–18% of women aged 20–40 years experience two or more nightly voids, and that the prevalence increases with age, ultimately surpassing 50% [3]. The United Nations Department of Economic and Social Affairs projects 32% of the world population to be over the age of 60 by 2050, suggesting an increase in the healthcare burden of nocturia [10].

The 2002 International Continence Society report proposed the first standardization of nocturia terminology, defining the condition as the complaint that the individual has to wake at night one or more times to void, with each void being preceded and followed by sleep [11]. Various factors contribute to nocturia, including local diseases such as

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benign prostatic hyperplasia and overactive bladder; systemic diseases such as diabetes mellitus, congestive heart failure and obstructive sleep apnea; and behavioral habits such as excessive intake of water, salt, alcohol and caffeine [11–13]. Nocturia can be divided into four proposed mechanistic groups: 24 h polyuria (urine output exceeding 40 ml/kg in a 24 h period), nocturnal polyuria (urine produced from first going to bed to the first morning void exceeding 33% of 24 h urine output), bladder storage problems (strict criteria for normal and abnormal have yet to be defined) and mixed (i.e. a patient with nocturnal polyuria and bladder storage problems) [11]. Although patient-reported outcome questionnaires can be helpful in evaluating symptoms and their frequency, severity and impact on quality of life, they are prone to recall bias [14] and do not allow derivation of objective quantifiable values. Frequency–volume charts (FVCs) and bladder diaries are key non-invasive diagnostic tools in evaluating the etiology of nocturia, given the wide array of possible contributors [11,15].

An understanding of which diary-based parameters best correlate with nocturia severity may help to guide future research. As such, the objective of the current study was to determine which diary-derived parameters are most closely related to the severity of nocturia in men. To test the robustness of the associations, two different samples were used: one including patients visiting a tertiary center complaining of LUTS, and one including men from the general population, not necessarily being patients. Such information could then be utilized to direct future nocturia therapy.

Materials and methods

After receiving institutional review board approval, a retrospective analysis of FVCs was performed in two separate cohorts: patients presenting with a chief complaint of LUTS at a tertiary ambulatory urology clinic and men from the population-based Krimpen study. The tertiary ambulatory urology clinic was part of the Veterans Affairs hospital system, which serves a mostly male population. As such, only males were included in this cohort. The data were collected from 2009 to 2012. Patients were included regardless of their postvoid residual volume and comorbid medical or surgical conditions.

The first cohort was comprised of 88 men whose initial presentation to a tertiary outpatient urology center was with a chief complaint of subjective LUTS. That is, these men presented complaining of frequency, urgency, dysuria, nocturia, poor stream, hesitancy, terminal dribbling, incomplete voiding or incontinence. The majority of these men had nocturia (83 out of 88, 94%) These men were provided with measuring containers, and they completed a bladder diary with instructions to document the time and volume of each void over a 24 h period, and the time of rising in the morning and retiring to bed at night, and to answer specific questions about storage and emptying symptoms. There were no restrictions on the type or timing of food and fluid intake in these individuals, nor were any medications added or subtracted from their baseline regimen upon presentation. The bladder diary provided information including 24 h urine volume (24UV), 24 h total number of voids, actual number of nightly voids (ANV), sleep duration in hours, maximum voided volume (MVV), nocturnal maximum voided volume (nMVV) and nocturnal urinary volume (NUV). From the FVC variables, the nocturia index [Ni, calculated as (NUV/MVV)] and nocturnal polyuria index [NPi, calculated as (NUV/24UV)] were derived.

The Krimpen study was a longitudinal study of urogenital tract dysfunction and its impact on general health status. The design of this study has been described in great detail elsewhere [16,17]. In brief, men aged 50–78 years in a Dutch municipality were investigated. Men without radical prostatectomy, prostate cancer, bladder cancer or neurogenic bladder disease, who were able to complete questionnaires and attend the health center, were invited for the study. At baseline participants completed a 113-item questionnaire, including the International Prostate Symptom Score (IPSS), and visited the local general practice health center for medical examination. Then, urological measurements (serum prostate-specific antigen, digital rectal examination, transrectal prostatic ultrasound, uroflowmetry and postvoid residual urine volume) were taken at the urological outpatient department of the Erasmus Medical Centre Rotterdam, The Netherlands. Participants subsequently completed a 3 day FVC. Follow-up FVCs were completed at 2.1, 4.2 and 6.5 years after baseline. The FVCs at baseline were used for the present analysis.

Comparisons were made using Spearman's rank correlation coefficient [calculated for the clinical sample (cohort 1) using Microsoft Excel® and for the general population (cohort 2) using IBM Statistical Product and Service Solutions® program], with ANV as the independent variable and nocturia index, nocturnal poyuria index, NUV, nMVV and sleep duration (h) as dependent variables. Spearman's rank correlation coefficient was selected because the data were non-parametric. The authors believe that a diary parameter with a strong Spearman's rank correlation coefficient may serve as a potential therapeutic target. Strong and moderate correlation were defined as a Spearman's coefficient greater than 0.6 and 0.2–0.6, respectively. Statistical significance was considered at $p < 0.05$.

Results

Eighty-eight consecutive men who presented with LUTS completed a 24 h FVC [median age 70 years, interquartile range (IQR) 64.5–74.5, range 27–88; median ANV 2, IQR 1.5–4, range 0–15]. The ethnic composition of this cohort was 48% African American, 36% Caucasian, 9% Latino and 7% other.

In total, 1597 community-dwelling men (95% of the responders) completed a 3 day FVC. However, owing to missing data regarding sleeping hours ($n = 375$) and to meeting exclusion criteria ($n = 143$), nocturnal voiding frequency and volume could be analyzed in only 1082 men (median age 61 years, IQR 56.1–66.4, range 49.4–78.2; median ANV 1.5, IQR 1.0–2.0, range 0–4.5). Strong correlation was shown for nocturia index in both study populations (0.797, $p < 0.001$, and 0.658, $p < 0.001$, in cohorts 1 and 2, respectively). For the other parameters, only a modest correlation was present. Table 1 shows the Spearman's rank coefficient

Table 1. Results of analysis comparing average number of nightly voids to various voiding-diary derived parameters for the clinical sample and the general population.

Voiding-diary derived parameter	Clinical sample: correlation coefficient vs ANV (Spearmans rho)	Significance (two-tailed)	General population: correlation coefficient vs ANV (Spearmans rho)	Significance (two-tailed)
Ni	0.797	$p < 0.001$	0.658	$p < 0.001$
NPi	0.545	$p < 0.001$	0.394	$p < 0.001$
NUV	0.463	$p < 0.001$	0.432	$p < 0.001$
Sleep (h)	0.306	$p = 0.011$	0.272	$p < 0.001$
nMVV	0.159	$p = 0.169$	0.146	$p < 0.001$

Comparisons were made using Spearman's rank correlation coefficient calculated for the clinical sample using Microsoft Excel® and for the general population using IBM Statistical Product and Service Solutions program.
ANV = actual number of nightly voids; Ni = nocturia index; NPi = nocturnal polyuria index; NUV = nocturnal urinary volume; nMVV = nocturnal maximum voided volume.

and associated significance between ANV and the various FVC parameters for each cohort.

Discussion

History taking and physical examinations alone are insufficient to determine the etiology of nocturia. FVCs and bladder diaries are key non-invasive diagnostic tools in evaluating the etiology of nocturia and are recommended by the International Continence Society in the work-up for a patient complaining of nocturia [11,15]. The current study used FVCs and bladder diaries to evaluate the correlation between nocturia severity, represented as ANV, and other diary-derived variables. The importance of evaluating nocturia severity based on ANV has been highlighted in previous investigations, which demonstrated that subjective quality of life is significantly impacted with two or more nightly voids. Furthermore, as the number of voids increases, subjective quality of life decreases [7,8].

The nocturia index is defined as NUV divided by functional bladder capacity (defined as the single largest voided volume, or MVV). A nocturia index greater than 1 implies that urine output exceeds the bladder's maximal storage capacity and therefore the patient will either awake to void or have enuresis [18]. In the present study, within both cohorts, nocturia index was the only diary parameter strongly correlated with nocturia severity (0.797 and 0.658 in cohorts 1 and 2, respectively). In other words, the data suggest that 66–80% of the variation in nocturia severity is explained by the variance in nocturia index. These findings are supported by a linear regression analysis performed by Homma et al., which showed that 68% of the variation in nocturia severity is accounted for by the nocturia index [19].

The logical corollary to these findings is that therapies aimed at decreasing the nocturia index may be efficacious in the treatment of nocturia, which can be achieved through either decreasing nocturnal urine production or increasing the nocturnal functional bladder capacity. In both cohorts of this study, nocturia severity correlated poorly with bladder capacity (0.159 and 0.146 in cohorts 1 and 2, respectively), while nocturnal urine production correlated moderately with nocturia severity (0.463 and 0.432 in cohorts 1 and 2, respectively). This suggests that therapies aimed at decreasing nocturnal urine production (e.g. antidiuretic or timed, late afternoon diuretic therapy and decreased evening fluid intake) may be more efficacious in the treatment of nocturia than those that increase bladder volume (e.g. antimuscarinics, α-blockers and β-agonists). Current data on the therapy of nocturia support this notion. A study examining the effects of behavioral therapy, including evening fluid restriction, demonstrated a significant decrease in nocturic episodes and an average reduction of 106 ml in nocturnal urine volume, after two behavioral modification education sessions [20]. In contrast, a recent study showed mirabegron to have increased voided volume by 11 ml/void relative to placebo [21]. For a patient with nocturia three times nightly, such pharmacotherapy would make room for only 33 ml extra urine storage on average, less than one-third the effect of a decrease in nocturnal urine volume after behavioral therapy alone, as referenced above. Hence, until effective strategies to increase nocturnal bladder become available, the authors believe that the first attempt at treating nocturia should focus on volume reduction.

Limitations of this study included the sample size of the clinical sample, the diversity of both samples, and the fact that an FVC rather than a bladder diary was used for the vast majority of patients. The FVC simply records the time and amount of each void, but does not annotate symptoms. This means that there is no way to determine whether a nocturnal void occurs because of a bladder event, i.e. whether the patient is awakened by an urge to void or is awakened by something else and voids out of convenience before going back to sleep. A properly annotated bladder diary can make this distinction. Furthermore, AUASI data were not available for the clinical sample, which limited the researchers' ability to stratify patients based on symptom score. Although there were 1082 subjects in the general population cohort, only 88 subjects were included in the clinical cohort. The diversity was limited in that all of the subjects were men, and all of the patients in the second cohort were Caucasian men from a single community. The authors recommend a follow-up study with a larger sample size and a more diverse population, which should include women and patients from multiple centers.

In conclusion, in both men seeking treatment for LUTS and community-dwelling men with and without LUTS, there exists a strong correlation between nocturia voiding frequency and the nocturia index. Furthermore, there is

moderate correlation between nocturia severity and polyuria index, and sleep duration. The nMVV did not correlate with nocturia severity. These findings suggest that the therapeutic strategy for nocturia should entail balancing nocturnal urine production with bladder capacity by decreasing nocturnal urine production. In practical terms, until effective strategies to increase nocturnal bladder capacity become available, the authors believe that the first attempt at treating nocturia should focus on nocturnal urine volume reduction. A follow-up multicenter study of both genders could be undertaken to improve the generality of these conclusions.

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References

[1] Anderson SO, Rashidkhani B, Karlberg L, Wolk A, Johansson JE. Prevalence of lower urinary tract symptoms in men aged 45–79 years: a population-based study of 40 000 Swedish men. BJU Int 2003;94:327–31.

[2] Coyne KS, Zhou Z, Bhattacharyya SK, Thompson CL, Dhawan R, Versi E. The prevalence of nocturia and its effect on health-related quality of life and sleep in a community sample in the USA. BJU Int 2003;92:948–54.

[3] Bosch JL, Weiss JP. The prevalence and causes of nocturia. J Urol 2010;184:440–6.

[4] Abraham L, Hareendran A, Mills IW, Martin ML, Abrams P, Drake MJ, et al. Development and validation of a quality-of-life measure for men with nocturia. Urology 2004;63:481–6.

[5] Barry MJ, Fowler FJ, O'Leary MP, Bruskewitz RC, Holtgrewe HL, Mebust WK, et al. The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. J Urol 1992;148:1549–57; discussion 64.

[6] Sintonen H. The 15D instrument of health-related quality of life: properties and applications. Ann Med 2001;33:328–36.

[7] Tikkinen KA, Johnson TM, Tammela TL, Sintonen H, Haukka J, Huhtala H, et al. Nocturia frequency, bother, and quality of life: how often is too often? A population-based study in Finland. Eur Urol 2010;57:488–96.

[8] Yu HJ, Chen FY, Huang PC, Chen TH, Chie WC, Liu CY. Impact of nocturia on symptom-specific quality of life among community-dwelling adults aged 40 years and older. Urology 2006;67:713–18.

[9] Holm-Larsen T, Weiss JP, Langkilde LK. The economic impact of nocturia. Neurourol Urodyn 2014;33:S10–14.

[10] United Nations. Department of Economic and Social Affairs, Population Division. World population ageing 2013. New York: United Nations; 2013. 114):11–12.

[11] van Kerrebroeck P, Abrams P, Chaikin D, Donovan J, Fonda D, Jackson S, et al. The standardization of terminology in nocturia: report from the Standardization Sub-committee of the International Continence Society. Neurourol Urodyn 2002;21:179–83.

[12] Weiss JP, Blaivas JG. Nocturia. J Urol 2000;163:5–12.

[13] Wein A, Lose GR, Fonda D. Nocturia in men, women and the elderly: a practical approach. BJU Int 2002;90:28–31.

[14] Coughlin SS. Recall bias in epidemiologic studies. J Am Epidemiol 1990;43:87–91.

[15] Abrams P, Klevmark B. Frequency volume charts: an indispensable part of lower urinary tract assessment. Scand J Urol Nephrol Suppl 1996;179:47–53.

[16] Blanker MH, Bohen AM, Groeneveld FP, Bernsen RM, Prins A, Ruud Bosch JL. Normal voiding patterns and determinants of increased diurnal and nocturnal voiding frequency in elderly men. J Urol 2000;164:1201–5.

[17] Blanker MH, Bernsen RM, Bosch JL, Thomas S, Groeneveld FP, Prins A, et al. Relation between nocturnal voiding frequency and nocturnal urine production in older men: a population-based study. Urology 2002;60:612–16.

[18] Weiss JP, Blaivas JG, Stember DS, Brooks MM. Nocturia in adults: etiology and classification. Neurourol Urodyn 1998;17:467–72.

[19] Homma Y, Yamaguchi O, Kageyama S, Nishizawa O, Yoshida M, Kawabe K. Nocturia in the adult: classification on the basis of largest voided volume and nocturnal urine production. J Urol 2000;163:777–81.

[20] Cho SY, Lee SL, Kim IS, Koo DH, Kim HJ, Oh SJ. Short-term effects of systematized behavioral modification program for nocturia: a prospective study. Neurourol Urodyn 2012;31:64–8.

[21] Nitti VW, Auerbach S, Martin N, Calhoun A, Lee M, Herschorn S. Results of a randomized phase III trial of mirabegron in patients with overactive bladder. J Urol 2013;189:1388–95.