The evaluation of voiding patterns

An analysis of frequency-volume charts and symptom scores

	Tijd	Volume in ml
1	9:30	melk 100
2	9:45	Reis 150
3	10:15	zuiker 100
4	12:10	Reis 100
5	13 50	Suiker 50
6	15:10	Suiker 75
7	16:20	water 50
8	18:10	Reis 100
9	20:00	Reis 100
10	21:10	Meel 50
11	11:15	Reis 100
12	05:50	Reis 100
13	06:15	Meel 50
14	09 50	water 50

Ernst van Haarst

Colophon:

ZuidamUithof Drukkerijen

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The evaluation of voiding patterns.
An analysis of frequency-volume charts and symptom scores.

De evaluatie van plaspatronen.
Een analyse van mictielijsten en symptoomscores.
(met een samenvatting in het Nederlands)

Proefschrift

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door

Ernst Peter van Haarst

geboren op 26 april 1963
te Berkel en Rodenrijs

Promotor: Prof.dr. J.L.H.R. Bosch

Aan mijn ouders

Contents

	Tijd	Volume in ml	Verlies (x)
1	[redacted]	[redacted]	
2	08 20	2,50 Suiker	25-3-03
3	10 55	1, Meel	25-3-03
4	13 35	1, Meel	25-3-03
5	16 30	1, Meel	25-3-03
6	19 10	1, Meel	25-3-03
7	22 15	2, Suiker	25-3-03
8	01 15	2,50 Suiker	26-3-03
9	05 30	4, Suiker	26-3-03
10	08 20	3, Suiker	26-3-03
11			
12			
13			
14			
15			
16			

Chapter 1

Introduction

Introduction

Bother due to lower urinary tract symptoms (LUTS) is a core business for many urologists. Apart from history taking and physical examination, numerous attempts have been made to categorise and classify these symptoms. Standardised symptom scores, such as the International Prostate Symptom Score and the overactive bladder questionnaire, are used for that purpose. A large number of reports have assessed voiding patterns and complaints using scores, questionnaires, or interviews. However, history and questionnaires may be influenced by a patient's emotions or bother and recall bias.

A registration of the voiding pattern by recording voiding events in time and volume yields a more objective assessment of urinary frequency and voided volumes. Recordings concerning urgency, incontinence episodes, or fluid intake may be added.

Such recordings have been referred to as a micturition time chart (a simplified version that omits volume recordings), frequency-volume chart (FVC), micturition chart, urinary diary, voiding diary, or bladder diary. The latter was proposed by the International Continence Society [1] to include data on urgency and incontinence episodes because the term is more comprehensive than voiding diary or FVC. However, in several reports this term is used for data on urgency and incontinence only, without time and volume recordings. In this thesis we use the term *FVC,* addressing the basic parameters (time and volume) of the voiding pattern as a collective noun for all formats.

FVCs have become an important part of the evaluation of LUTS, and their use is recommended in several guidelines [2-8]. Most experts would agree that these charts provide invaluable information about several voiding symptoms. A number of parameters can be assessed by the FVC including total number of voids per 24 hours, total number of daytime (awake) voids, total number of nighttime voids, total voided volume, maximum, minimum, and mean voided volume, and, if appropriate, total fluid intake, number of urgency episodes, and number of incontinence episodes. If the FVCs are completed for more than 1 day, patterns of variations over several days may become apparent. Finally, several indexes, reflecting ratios of previous parameters, might be added.

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	Tijd	Volume in ml
1	om 5 uur	2 = + 7/8
2	6 uur	3/8
3		
4		
5	om 9 uur	+ 1/8
6		
7		
8		
9	9 uur	+ 1/8
10		
11		
12	12 uur	7/8
13	13 uur	5/8
14	15 uur	+ 5/8
15	16 uur	3/8

Chapter 2

Frequency-volume charts, a review of the literature through 2011

E.P. van Haarst
J.L.H.R. Bosch

Frequency-volume charts, a review of the literature through 2011

Introduction

The aim of this study is to clarify the use and value of frequency-volume charts (FVCs) by reviewing the literature published through 2011.

Survey of the literature

Methods

1. Search strategy

A structured Medline search for FVCs was performed to identify all literature published through December 2011. The search terms used were *micturition chart, micturition time chart, micturition diary, frequency volume diary, frequency-volume chart, bladder chart, bladder diary, urinary chart, urinary diary, urination chart, voiding chart,* and *voiding diary*. For a detailed query, see the appendix.

2. Search results and categorisation

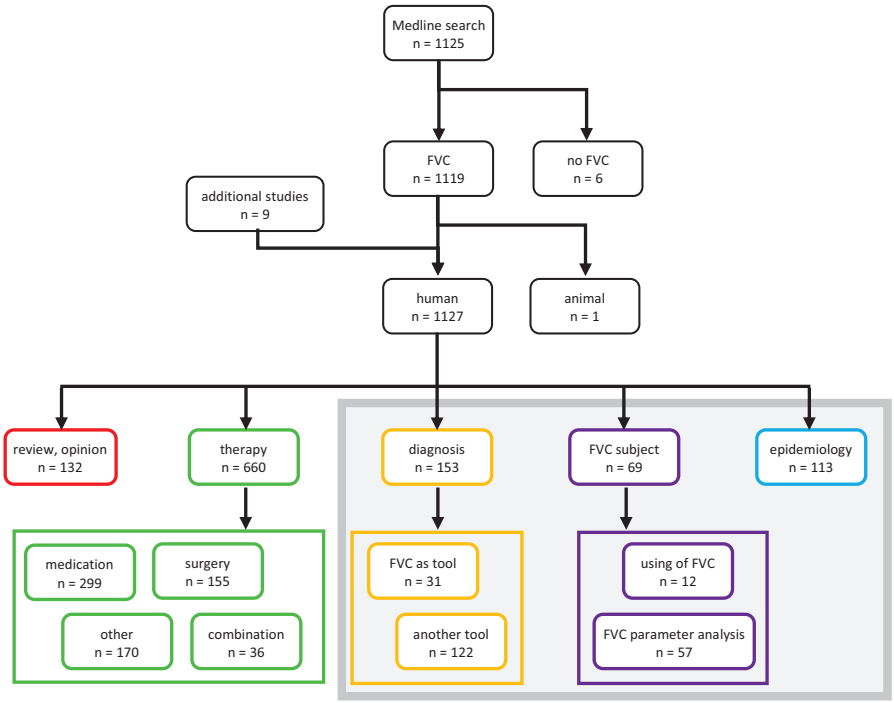
The following terms were not found in Medline: *micturition time chart, frequency volume diaries, urinary charts,* and *urination charts.* The search yielded 1125 articles. Another 9 articles were identified through reference lists of the retrieved articles. In these articles the terms *frequency records* [1], *frequency/volume chart* [2-4], *voided volume chart* [5;6], *frequency-volume charts* (in text only) [7;8], and *home diaries* [9] were used or the more descriptive "number of incontinent episodes per week as recorded on a 7-day diary" [10]. Figure 1 shows the search results and categorisation of publications.

Seven articles were excluded: in 6 articles FVCs were not involved; 1 was an animal study. All remaining 1127 articles were categorised by one of the authors (E.v.H.) by reading titles and abstracts, and, if necessary, the full-text article. Five major categories were identified: FVCs involved in (1) a guideline, review, opinion, or comment; (2) the evaluation of treatment; (3) diagnosis; (4) the analysis of FVCs as such; or (5) reports on epidemiology or aetiology. In the figures the first category is abbreviated to "review, opinion". Excluding that category, 995 original publications involving human studies using FVCs were identified. Categories 2, 3, and 4 were extended with subcategories. Articles addressing the diagnostic process were divided into those in which FVCs were the main diagnostic tool (in figure: "FVC as tool") and in those in which FVCs were used to evaluate other diagnostic tools (in figure: "another tool"), such as questionnaires, symptom scores, urodynamics, or radiologic examinations. Articles considered to have FVCs as a subject as such were divided in the mere study of FVC parameters and in the application in practice of FVCs by clinicians (in figure: "using of FVC"). Several articles would fit in more than one category or subcategory, and distinction was often difficult, especially for categories "FVC parameter analysis," "epidemiology or aetiology," and "FVC as tool." In these cases the most predominant category was chosen as the primary category; the other was noted as a secondary category.

The search revealed 660 publications that addressed the evaluation of treatments for which FVCs were used. For such evaluations, the FVCs before and after treatment are compared.

Medical treatments were found in 299 articles. Since 1995 the number of publications citing the use of FVCs has increased, especially to evaluate therapies (Figure 2). The increase in

Figure 1. Search results and categorization of publications on FVC. For details see text.



reports on medical treatments has been especially notable since 2002, with the major factor the increase in the treatment group. This probably reflects the increasing number of medications that have become available to treat overactive bladder (OAB). Surgical treatments such as prostatic surgery, surgery for urinary incontinence, gynaecologic operations, and sacral nerve stimulation were addressed in 155 publications. We defined a nonmedical nonsurgical group comprising other therapies such as behavioural therapy, physiotherapy, magnetic therapy, radiotherapy, percutaneous tibial nerve stimulation, and the use of urethral or vaginal devices. These were the subject of 177 publications. Finally, in a fourth category, 36 articles with combinations of these previous 3 therapeutic options were entered.

The earliest article, published in 1965, showed the value of a urinary diary in children [11]. Some publications are redundant or show significant overlap, reporting from the same database. Figures 2 and 3 show distribution by year and top 10 by journal of FVC-related articles.

For this review, we excluded reports not concerning adults because pathophysiology, definitions, and magnitude of parameters in children differ importantly from those of adults. The keywords *child* or *adolescent* and *not adult* were found in 110 articles. Moreover, we focused on original studies analysing FVC properties. Studies using FVCs to evaluate therapies, and reviews, opinions and comments were not used. As a result, articles covering the main

categories of epidemiology, diagnosis, or FVC (in Figure 1 indicated by the grey box)were used and reviewed in detail when deemed necessary.

Figure 2. Distributions of original publications by year and category. Some years before 1985 are missing.

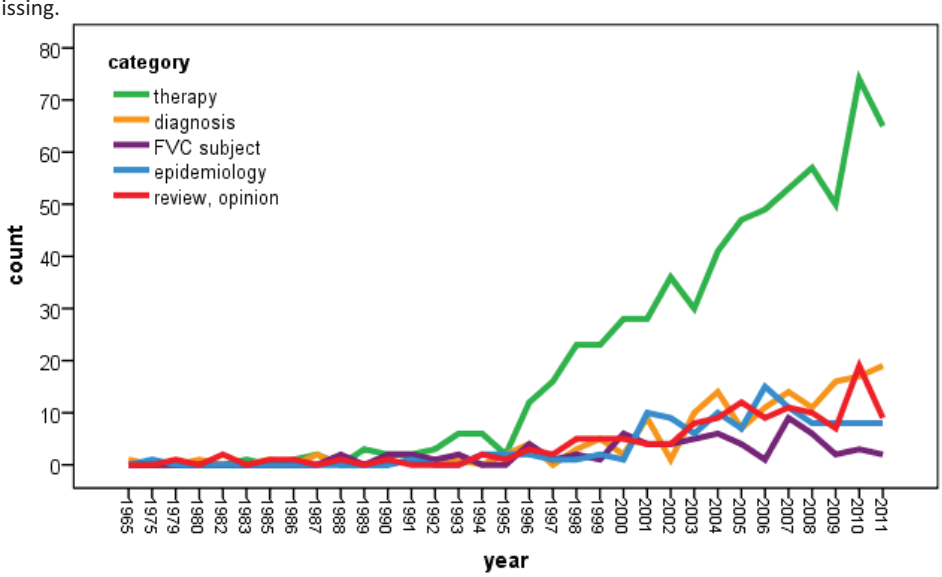
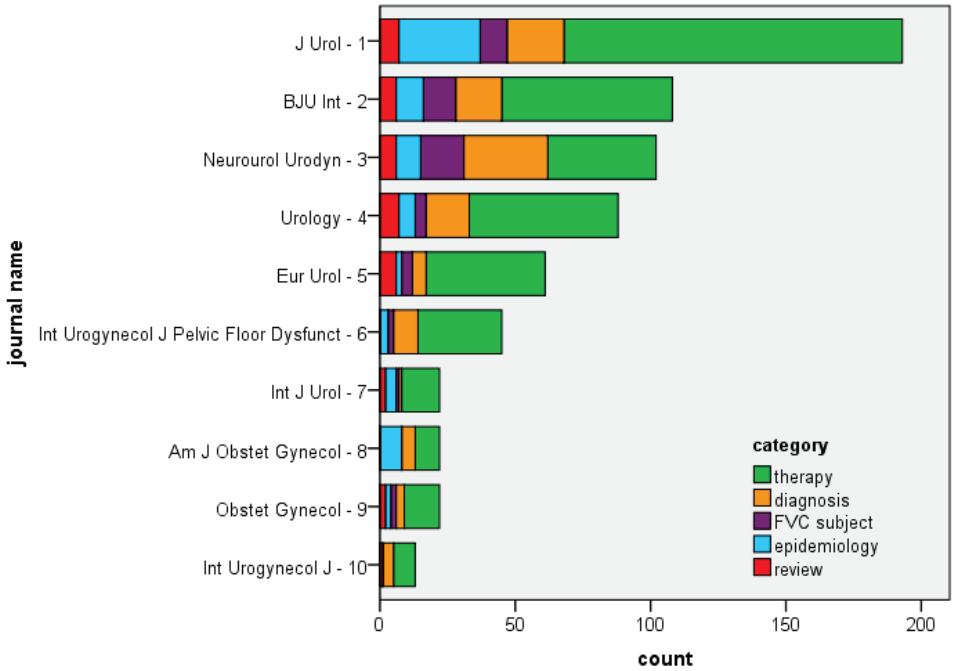


Figure 3. Top 10 journals of FVC-related publications.



Important features of FVC's

Objective recordings versus recall bias

Measurements recorded in FVCs by patients have high accuracy [12].
FVCs have been shown to be reproducible and more accurate when compared with the patient's recall [3;4;13-15]. For nocturia it has been shown that most men were inaccurate in their estimation of the number of episodes per night [16-18].
In women with urinary incontinence, correlation between medical histories and voiding frequency recorded in bladder diaries was reported to be weak in 2 studies (r = 0.31 [19] and r = 0.33 [20]) but moderate in another study (r = 0.61-0.65) and weak for frequency of incontinence (r = 0.41-0.56) [21]. Overestimation or underrecording of incontinence episode frequency in the urinary diary was more pronounced in women who were more bothered by incontinence [22]. The agreement between patient report and physician assessment of urinary incontinence severity is high for mild incontinence but decreases as incontinence severity progresses [23].

The duration of frequency-volume charts

Due to intraindividual variation, FVC recordings differ on different days. The more days recorded, the more likely it will be that the recordings will capture the whole spectrum of variation. Few data have been reported on the intraindividual variation of FVC parameters [12;24;25]. However, these variations have been used in statistical analysis leading to statements on the optimal duration of FVCs. Recommendations for diary duration vary considerably including 24 hours [15;25;26], 3 days [1;27], or 7 days [8;28-30]. This inconsistency is partially explained by differences among study populations, based on diagnosis, age, sex, and geography, and by differences in methods of analysis and in interpretation of the results.
Abrams and Klevmark favoured a 7-day FVC because the week is a unit of time in social terms [28]. Most reports on the optimal duration of an FVC have been based on compliance or reliability rates.

Compliance

Compliance rates have been presented as the percentage of patients that had completed the FVC at the end of the study period and vary from 57% to 100% [31]. In a study of 3-day FVCs in 188 benign prostatic hyperplasia (BPH) patients, 15% did not complete the first day [25]. Of the remaining 160 patients, 91 completed 3 days, resulting in a 3-day compliance of 57% but overall compliance of 48%. In a study of 14-day FVCs in 50 incontinent women, an unusually high compliance rate of 100% was reported [29]. In a group of incontinent men and women, 248 kept a 3-day FVC, and 40 kept a 7-day FVC [32]. Of the 3-day FVCs, 90.7% were complete; this was the case in only 50% of the 7-day FVCs. Therefore, the authors favoured the 3-day FVC.
Ku et al found no differences in compliance rates for FVCs kept for 2, 3, or 7 days by 162 patients with incontinence and lower urinary tract symptoms (LUTS) [33]. However, they showed that the burden of an FVC increased with duration of the FVC. They suggested that the number of days required to evaluate voiding symptoms should be reduced to less than 7 days.
Robinson et al compared two 7-day FVCs of 278 incontinent women [34]. A Minimal Instruction Diary was completed before the initial clinical evaluation, and a second Intensive Instruction Diary was completed after the clinical evaluation. Recordings were made by

placing a checkmark in time-framed columns. Of the subjects, 81% and 56% completed the first and second 7-day FVC, respectively. Pearson correlation coefficients ranged from 0.67 to 0.78 for each of the urinary symptoms, and they were not influenced by diagnosis or fluid intake. It was concluded that the data obtained by the 2 methods of diary use were of equal clinical utility.

Fitzgerald et al invited 220 women to repeat a 1-day FVC after they had been offered a $35 honorarium upon completion of the FVC, hoping to improve compliance [35]. Although most of them indicated they would be interested in participating again, only 137 (62%) completed the second FVC.

Dmochowski et al found no difference in utility between 3-day and 7-day FVCs used to demonstrate the efficacy of anticholinergic treatment, although compliance was significantly lower for the 7-day FVCs [36].

A Spanish study reported that 40% of 748 responding urologists used an FVC of 6 days, 26%, 3 days [37].

Non-Caucasian patients and patients presenting for treatment of pelvic organ prolapse without urinary symptoms were less likely to complete their urinary diary than Caucasians and patients with prolapse and urinary symptoms, respectively [38].

In a study of the postoperative outcome of urinary stress incontinence, only 48% of patients were willing to record a voiding diary, but this was not influenced by the outcome of the operation in individual patients [39].

Of 128 women attending a urogynaecology clinic, 100 (78%) completed a 3-day bladder diary, and its use was evaluated by a specific standardised questionnaire [40]. Compliance and a low mean burden score indicated that women did not experience recording of the FVC as an onerous task.

Reliability

Larsson and Victor compared two 2-day FVCs of 16 women without micturition complaints [41]. Comparison was based on limits of agreement. The authors noticed an increase of the reproducibility of all FVC parameters with increased observation time, and they suggested that the optimal duration might be longer than 4 days.

Wyman et al performed a split-half reliability test of FVCs recorded by 50 incontinent community-dwelling women in 2 consecutive weeks [29]. Correlations varied among different FVC parameters, but it was concluded that 1 week was reliable in assessing urinary frequency.

Groutz et al studied test-retest reliability of 1- to 3-day FVCs recorded in 2 weeks by 109 patients with urinary incontinence and LUTS [15]. They found a reliability of 0.83 for voiding frequency after a 3-day FVC. Although for voided volumes compliance had decreased to 76% by day 3, they preferred a 24-hour FVC because on the second and third days the improvement in reliability was only small compared with the loss in compliance.

In 3-day FVCs in 305 women with interstitial cystitis, Mazurick and Landis correlated the first day with day 2 and 3, and they concluded that a 3-day FVC was of no more benefit than a 1-day FVC [26].

Nygaard et al studied 138 women with stress urinary incontinence who recorded 7-day FVCs [27]. Using the Pearson correlation coefficient, the first 3 days correlated well with the last 4 days, and it was therefore concluded that a 3-day FVC was sufficient.

Gisolf et al found only small variations in the 24-hour mean voided volume in 3-day FVCs recorded by 160 men with LUTS due to BPH, and they concluded that a 24-hour FVC is sufficient and reliable [25].

Van Melick et al studied 2- or 3-day FVCs of 60 women with objective urinary motor urge incontinence [42]. They found small differences between the voiding parameter values calculated from the first FVC and those from all FVCs, and again concluded that a 1-day FVC was sufficient.
Locher et al calculated day-to-day consistency of FVCs of incontinent women recording 14-day FVCs, and they showed that sufficient internal consistency (Cronbach α >0.90) was achieved in 5 days for urgency incontinence and in 7 days for stress incontinence [30]. This study did not account for loss of compliance while judging the FVCs.
Homma et al analysed 1-, 3- and 7-day FVCs of 74 patients with urinary frequency or incontinence [8]. They showed that the intraindividual variability of FVC parameters decreased with increasing duration of the FVC. The magnitude of the decrease was different between different parameters. Thus the optimal length of a diary varies according to the parameter assessed and the precision and sensitivity required. They judged a 7-day FVC to be a reasonable option for most patients with incontinence.
Fitzgerald et al performed a test-retest analysis to estimate the reliability of 1-day FVCs in 137 women without LUTS with an 8-month interval, and they found no significant differences using paired Mann-Whitney tests [35].
Schick et al reported on 7-day FVCs of 84 adult women who consulted a urologist, regardless of their pathology or clinical profile [43]. Means of FVC parameters of 2 to 6 days were compared by correlation to the gold standard of 7 days. They calculated that 4-day FVCs had nearly all its correlations above 0.95 and concluded 4-day FVCs were almost equivalent to 7-day FVCs. They assumed that a decrease of compliance would make the case against recording 7-day FVCs.
In 154 men and women with urinary urge incontinence, Brown et al analysed 7-day FVCs that were repeated after at least 1 week [44]. The diaries exhibited good to excellent reliability, with estimated intraclass correlation coefficients (ICCs) ranging from 0.81 to 0.86. However, diaries completed for 3 and 4 days achieved only slightly lower estimates of reliability (ICC: 0.79-0.84).
Yap et al compared each day of a 3-day FVC of 96 men with LUTS by calculating intraclass correlation coefficients of several parameters. Accuracy varied by parameter and by patient, and therefore it was concluded that a 1-day FVC cannot be used for diagnosis or for evaluation of treatment [45].
In a mini-review on the reliability of FVCs, Yap et al argued that using FVCs of 3 days or longer might be the most defensible policy, but they found no evidence that compliance rates had been accounted for [31]. They concluded that in some reports reliability was overestimated.
Another review by Bright et al focusing on the validation of FVCs summarised that excessive duration reduces patient compliance, but too short a duration may produce unreliable measurements [46]. It was concluded that a validated urinary diary does not yet exist.

Frequency-volume chart content

Apart from the discussion on the optimal duration of FVCs, different opinions exist on their content and layout. It depends on the type of symptoms to be assessed whether the addition of urgency scales and incontinence recordings are required and useful. Layout and content seem to be related to patient and doctor preferences.
Most studies have used paper diaries to collect information. In as early as 1993, Rabin et al found that most of the 25 patients and 25 controls favoured a computerised voiding diary over a written diary [47]. Editorial concerns about fear of technology, especially in elderly or less

intelligent people, were not confirmed in the study. Another study showed improved compliance and more accurate data collection using a computerised voiding diary [48].
Quinn et al compared the use of electronic and paper diaries in a crossover study on 35 patients with OAB [49]. They concluded that data collection was comparable and suggested the electronic diary was an appropriate and easy-to-use alternative to a paper-based method for assessing the symptoms of OAB. Stone et al showed electronic diaries (not specifically voiding diaries) to have a much higher compliance than paper diaries [50]. A Chinese study among 20 healthy young volunteers showed that a wireless and mobile voiding diary monitoring system using smartphones was reliable and feasible [51].

Normal ranges of frequency-volume chart parameters

The table shows the results of a survey of data retrieved from publications referring to adult so-called normal populations or population-based samples. Because most studies were performed in men or in women, and those including both genders often present the data by gender, the data presented were organised by gender too, with 2 exceptions as indicated in the table.
Straightforward comparison of reported data on FVC parameters is hampered not only by differences in the study populations or the FVC duration (1-7 days) but also by the way data are presented:

- Urine production is most often presented as millilitres per 24 hours (or per day or night), but sometimes it is expressed in millilitres per hour [52], millilitres per kilogram [53], or millilitres per hour per kilogram. These aberrant measures are not presented in the table.
- An estimate of the middle value is most frequently indicated by the mean, in some articles by the median. The spread of data may be represented by standard deviation, standard error, standard error of the mean, or quartiles.
- Data may be presented in subgroups, not always summarising overall data. Not included in Table 1 was a population-based study of 224 elderly men and women because FVC data were presented according to nocturic or nonnocturic persons [18].
- *Night* sometimes refers to a fixed time period (23:00 or 24:00 to 7:00 or 8:00), mostly in older publications, but most often it is defined as the time between going to bed and rising the next morning.

Taking medians for means, we calculated weighted means of several parameters, although it seems likely there is some overlap in the presented studies, lending too much influence to the data derived from those studies. The reported mean 24-hour urine production varies between 1256 and 1961 ml, with a weighted mean of 1560 ml. The mean 24-hour frequency varies from 5.6 to 11.4, with a weighted mean of 7.5. The mean voided volume varies from 145 to 294 ml, with a weighted mean of 231 ml.
Several studies reported differences in urine FVC parameters between age groups. Older people have a lower urine production, with a higher proportion of nocturnal urine production [14;53-57]. Gender differences are obvious in the table. Racial differences have been claimed in some studies [58]. A number of reports have focused on FVC parameters related to nocturia [18;56;59-66].

Table. A survey of data retrieved form publications referring to adult 'normal' populations or population-based samples

						Volumes [i]				Frequencies		
	1st author	Year	n	Age [ii]	Day	24-hour	Night	Day	Mean void [iii]	Max [iv]	24-h	Night
	Men and women											
1	Saito [57] < 65 y	1993	85	47 (16-64)	2	1543 (615)	368 (254)	1247 (542)	162 (95)		11.1	1.6
	Saito [57] > 65 y	1993	130	72 (65-84)	2	1550 (610)	490 (285)	1086 (550)	145 (58)		11.4	2.8
2	Palnaes Hansen [12]	1998	18	63 (20-80)	3	1700			179		10	
	Men											
3	Homma [64]	2000	35	60 (24-87)	1	1438 (61)	497 (31)		194 (13)	316 (20)	7.8	1.2
4	Blanker [75]	2001	144	28	3	1506 (1160-1950)			246 (192-349)	400 (300-500)		
5	Blanker [111]	2002	143	61 (50-78)	3	1431 (648)						
6	Latini [112]	2004	284	34 (18-66)	1	1650 (1151-2218)	390 (0-	1110 (1110-2117)	237 (181-333)	382	7	
7	van Haarst [54] [vi]	2004	560	48 (20-88)	1	1718 (753)	519 (282)	1198 (624)	279 (113)	462 (183)	7.11	0.91
8	Parsons [56]	2007	253	46 (19-81)	3		446 (220)	1267 (597)		334 (165)		0.4
9	Tissot [55]	2008	92	46 (20-84)	3	1713 (744)			261 (96)	500 (216)	6.6	1.8
	Women											
10	Larsson [41]	1988	151	43 (19-81)	2	1430 (487)			250 (79)	460 (174)	5.8	1.41
11	Kassis [113]	1993	33	40 (25-56)	7	1473 (386)	409 (130)	1005 (497)			5.6	0.08
	Homma [64]	2000	35	60 (24-87)	1	1332 (59)	406 (26)		175 (8)	277 (16)		
12	Fitzgerald [58]	2002	300	40 (18-91)	1	1759 (797)	[v]	[v]	216 (87)	362 (161)	8.3	0
13	Pauwels [114]	2004	32	49 (38-60)	3	1961			294 (180)		6.68	0.07
	van Haarst [54] [vi]	2004	592	47 (20-87)	1	1762 (763)	535 (295)	1227 (624)	261 (101)	467 (177)	7.59	0.99
14	Amundsen [109]	2007	161	48 (19-81)	3	1730 (721)			245 (91)	514 (190)	7.1	
	Parsons [56]	2007	161	47 (20-84)	3		468 (266)	1261 (591)		332 (149)		0.4
15	Pfisterer [115]	2007	24	50 (22-80)	3	1442 (1288-2239)	438 (316-	1045 (770-1429)			5.9	0.2
16	Miller [116] [vii]	2011	352	50 (35-64)	3	1328 (842)			226 (111)	367 (188)	6.8	2.9
17	Haliloglu [117]	2012	115	31 (18-74)	1	1256 (604)			288 (142)	376 (175)	5.9	2.5

i. Volumes are presented in ml and represent mean values, exceptions for median values accompanied by a range; between brackets is the measure for spread: the standard deviation or range reflecting the interquartile range. Only Homma presented the spread by standard error.
ii. Rounded mean values of age, except the article of Haliloglu, where median age was reported.
iii. Mean voided volume in 24-hour.
iv. Maximum voided volume in 24-hour.
v. Data not shown, in article presented in ml/min.
vi. Some data have not been presented in the original article.
vii. Night was defined as the period from 00:00 to 7:00 a.m.

The application of frequency-volume charts

Clinical correlates of frequency-volume chart parameters

FVCs may be useful in clinical practice to determine a baseline from which a future evaluation can be made. Ideally, FVCs could be useful in the diagnostic process in patients with LUTS. In analysing nocturia, FVCs have been shown to be indispensable for a proper categorisation and thus treatment [67;68]. Although several guidelines recommend using FVCs in the diagnostic work-up of patients with male LUTS/BPH, OAB, incontinence, or bladder pain [69-72], no discriminative values of FVC parameters have been advocated.

Due to the wide variation of FVC parameters within populations, false-positive and false-negative rates will be high, yielding a low predictive value. However, several studies have shown interesting outcomes and are summarised in the subsequent paragraphs.

2. 1. Male lower urinary tract symptoms

In men with LUTS, an overactive detrusor was found in 42% but was not_significantly associated with smaller voided volumes, higher nocturia, or diuria [73]. In men with LUTS treated with transurethral resection of the prostate (TURP), prostate volume, maximal free urinary flow rate, and obstruction grade were only slightly associated with symptom scores and indexes, in contrast to the FVC parameters of mean voided volume, nocturia, and diuria [74]. However, the predictive value of all parameters on the outcome of TURP was poor.

In a large population sample of elderly men, a low functional bladder capacity coincided with higher International Prostate Symptom Score and was lower in men with a reduced maximum flow rate but independent of the postvoid residual volume or prostate volume [75]. Diurnal voiding frequency was higher in men with BPH but was independent of age, in contrast to nocturia [14]. In a follow-up study of this cohort, it was shown that over time and with advancing age, nocturia prevalence increases and maximum and mean voided volume decrease, but 24-hour voided volume did not [76;77].

2. 2. Diabetes

In 110 diabetic women, no differences were found between patients with or without bothersome LUTS concerning urine production derived from 3-day FVCs [78].

2. 3. Urinary incontinence

Comparing women with stress incontinence with women with detrusor overactivity, voiding frequency and leaking volume were significantly higher and mean voided volume was lower in patients with detrusor overactivity than in patients with stress incontinence [79-82]. Differences were even clearer when compared with a reference population [79]. Corrected for the 24-hour urine production, the mean voided volume showed the highest difference [83], whereas in another study nocturia was the best predicting factor [80]. In a comparison of FVCs of women with stress urinary incontinence with FVCs of women without urologic symptoms, the total voided volume, the voiding frequency, the largest single voided volume, and the variability of voided volumes were all shown to be statistically different [3]. In spite of these differences, the authors doubted its importance for diagnostic purposes because the overlap between groups was large for all parameters.

Using normal FVCs combined with history in 555 incontinent patients to diagnose stress incontinence, 18% were shown to have detrusor overactivity [84]. The authors concluded that combining history and bladder diary was too unreliable to omit urodynamic testing.

2. 4. Overactive bladder

In a comparison of 49 women complaining of OAB symptoms with matched controls, it was reported that in the patient group, the median number of voids was higher, 11 vs 7, and the median value for mean voided volume was lower, 171 vs 200 ml [85].

In women with OAB, some studies observed differences in FVC parameters between patients with or without detrusor overactivity. Patients with detrusor overactivity had smaller maximum voided volumes per void, mean 24-hour urine production, and significantly more incontinent episodes [86]. However, other studies did not find differences in FVC parameters and symptom scores, except for a higher occurrence of nocturia with detrusor overactivity [87;88].

Compared with other patients or controls, patients with detrusor overactivity had a smaller functional bladder capacity, higher urgency episode frequency, and larger maximum and mean urge ratings, higher 24-hour frequency, lower maximum volume voided, and mean volume voided per micturition on the bladder diary [79;80;82]. In women with stress, urge, and mixed incontinence, the mean voided volume, which takes into account both frequency of micturition and total voided volume, showed the highest differentiating power and was suggested as the most important parameter when all 3 groups were compared [80].

FVCs used as a diagnostic tool in patients complaining of urinary frequency were shown in combination with urodynamics to help clarify the cause of the increased frequency and to choose a proper treatment [57]. Poor agreement between subjectively estimated urinary frequency and chart-determined urinary frequency has been reported [13]. Moreover, endoscopic vs chart-based measurement of bladder capacity gave different results.

2. 5. Urodynamic studies and FVCs

Although there is a modest correlation between cystometric bladder capacity and the maximum voided volume, the cystometric bladder capacity has been shown to be significantly lower [2;9;88;89]. The lower cystometric bladder capacity was suggested to be an artefact caused by the catheterisation and filling included in the cystometric procedure [88].

In patients with OAB, between patients with or without detrusor overactivity, significant differences were found in cystometric bladder capacity but not in maximum voided volumes [87]. In nearly half of men with LUTS, an unstable bladder was found, but this could not be recognised by FVC parameters [73].

Differences between ambulatory and conventional urodynamic studies were not explained by voiding at FVC-derived modal and maximum bladder capacity because it was shown that urethral resistance and bladder contraction strength were not volume dependent [90].

The predictive value of FVCs to detect detrusor overactivity was judged too low in several studies [2;84;91]. Due to the overlap between groups, a maximum sensitivity of the FVC to detect detrusor overactivity was found to be 52%, with a specificity of 70% [2;91]. The mean voided volume (total voided volume/frequency) was considered a reliable measure of the severity of motor urgency. It was suggested that cystometry mainly gives a qualitative measure of motor urgency, whereas the FVC offers objective and reliable quantitative information of the symptoms and thus supplements the cystometric evaluation. These studies concluded that combining history and bladder diary was too unreliable to omit urodynamic testing.

However, in women with a predominant complaint of stress incontinence, positive cough stress-test results, a postvoid residual urine volume no more than 50 ml, and a FVC-based functional bladder capacity of at least 400 ml, in 97% the diagnosis of stress incontinence was urodynamically confirmed [92].

2. 6. Practical implications

Despite the discouraging findings of most of the previously cited studies, it is conceivable that certain parameters will show better diagnostic properties than others [92]. For example, the median voided volume was reported as the most constant parameter [24;25;41]. Combining data of FVCs with other examinations (e.g., symptom scores, uroflowmetry, and ultrasonography for measurements of the postvoid residual volume or bladder wall thickness) might add to the diagnostic abilities of FVCs, as suggested in several studies of patients with LUTS [64;93-96].

Physicians using frequency-volume charts

With a response rate of 71% of 268 Norwegian gynaecologists, 42% would use an FVC in analysing urinary incontinence [97]. In another Norwegian study, 139 general practitioners (GPs) and 190 gynaecologists responded to a case history questionnaire about female urinary incontinence [98]. Six cases, 3 patients with stress urinary incontinence, 1 with urge incontinence, and 2 with mixed incontinence, were presented. For stress incontinence, 6% of GPs and 21% of gynaecologists would use an FVC. For urge incontinence, the numbers were 18% and 52%, and for mixed incontinence 18% and 45%, respectively. In analysing urinary incontinence, a bladder diary was used by 35% of 264 Dutch GPs [99]. In a large German survey among 2530 physicians (2007 GPs, 304 gynaecologists, 168 internists, only 7 urologists, and 44 others) on diagnosing incontinence in the elderly, a micturition diary was used by 21% of GPs and 43% of gynaecologists [100]. A Spanish study among 748 urologists and 696 primary care physicians on the diagnosis of OAB showed that a micturition diary was used by 43% and 32%, respectively [37]. In the assessment of OAB, a voiding diary was used by 48% of 290 responding Czech gynaecologists and urologists, which was nearly equivalent to 46% using cystoscopy [101]. Of 132 Danish GPs representing a response rate of 54%, 92% sometimes or often included a voiding diary in the urinary incontinence assessment [102]. For the postoperative evaluation of stress incontinent women, 12% of 156 members of the Society of Urodynamics and Female Urology used a bladder diary [103]. Of physical therapists in the United States treating women with localised vulvodynia, 72% used voiding diaries in the assessment of patients [104]. In analysing symptomatic BPH, 17% of Italian urologists used an FVC [105].

Three reports studying patients' use of FVCs were addressed in a paragraph on compliance.

In summary, only 10 studies evaluated when and how often physicians use FVCs. Six studies address their use in relation to incontinence. Most concern the use of FVCs by GPs. In most studies less than half of the physicians use FVCs.

Remarkable findings

Convenience voids were reported to occur frequently in 53 healthy volunteers—during the week in 72% at least 1 convenience void occurred—and decreased the mean voided volume and voiding intervals significantly [106]. The mean voided volumes of convenience voids in patients with OAB with urinary incontinence were significantly smaller than those in other groups [107]. On FVCs, 65% of all voidings were made without desire to void; only 9.5% were with strong desire [108].

Bladder capacity has been reported to be larger in individuals with larger total urine volume [54;56;78;109]. A purposely increased fluid intake was shown to increase bladder capacity in 44 men, suggesting an adaptive mechanism of the bladder to increased volume load [7]. In an elderly population, increased LUTS was related to lower functional bladder capacity [75].

Discussion

This survey of the literature has shown an increasing use of FVCs over the years. However, the number of original articles addressing the value and content of FVC seems to have stabilised by around 20 per year (Figure 1).

With increasing FVC duration, patient compliance decreases while the reliability of data increases. There is a tendency to advise a duration of FVCs for 3 days.

FVCs have been shown to be of value in nocturia. In patients with urinary frequency, the voiding frequency is by definition increased, on the assumption of unchanged urine production. It is therefore no surprise that several studies showed significant differences in mean voided volumes in patients with symptoms of increased voiding frequency compared with subjects with no such symptoms. So far several studies have outlined differences between populations, but there is an obvious lack of clear cut-off points. Due to this lack of diagnostic sensitivity, the use of FVCs by physicians seems to be limited. Nevertheless, several guidelines on LUTS or incontinence advocate the using of FVCs. Information on how FVC data are being processed is sparse.

Appendix

In Medline the following query was used: (micturition chart[tiab] OR micturition charts[tiab]) OR (micturition time chart[tiab] OR micturition time charts[tiab]) OR (micturition diary[tiab] OR micturition diaries[tiab]) OR (frequency volume diary[tiab] OR frequency volume diaries[tiab]) OR (frequency-volume chart[tiab] OR frequency-volume charts[tiab]) OR (fv chart[tiab] OR fv charts[tiab]) OR (bladder chart[tiab] OR bladder charts[tiab]) OR (bladder diary[tiab] OR bladder diaries[tiab]) OR (urinary chart[tiab] OR urinary charts[tiab]) OR (urinary diary[tiab] OR urinary diaries[tiab]) OR (urination chart[tiab] OR urination charts[tiab]) OR (urination diary[tiab] OR urination diaries[tiab]) OR (voiding chart[tiab] OR voiding charts[tiab]) OR (voiding diary[tiab] OR voiding diaries[tiab]).

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	Tijd	Volume in ml
1	12 uur	half voh
2	half twee	paar druppels
3	tegen 3 uur	Eerm
4	vijf uur	klein beetje
5	half zes	1-4 voh
6	half zeven	met zelfde
7	staan	op zelfde
8	8 uur	meer
9	over dag	moet ik
10	meer plassen	
11	soms	helemaal voh
12	en zo	Egen maar
13	dood de hele dag	
14		

Chapter 3

Scope of the thesis

Scope of the thesis

At the end of the 1990s, when we started building the first database that formed the basis of this dissertation, the objective evaluation of symptoms by standardised scoring systems and recording of the voiding pattern by frequency-volume charts (FVCs) were getting more attention. The increasing knowledge about lower urinary tract function and the development of several more specific urologic medications contributed to that trend. To study the possible merits of FVCs, it was clear that urologic science needs reference values, but little was known about normal ranges.

The first goal of our research was to establish normal ranges of FVC parameters as well as of the International Prostate Symptom Score (IPSS) and its correlations. Another goal was to assess the optimal duration of FVCs, taking into account the reliability of FVC parameters as well as patient compliance and its dependency on diagnosis.

Finally, we aimed to critically analyse nocturia, the most bothersome factor in lower urinary tract symptoms. If taking a case history does not bring present nocturia as a problem, then it might be found on the IPSS. Nocturnal polyuria is considered one of the main causes of nocturia. During analysis of our data we were intrigued by the high occurrence of nocturnal polyuria and the disagreement of nocturia recorded by the IPSS and FVC. With a large population-based database, we recognised the opportunity to define normal ranges of the distribution of urine production during the night versus the day. Furthermore, we examined the correlation between IPSS and FVC-derived nocturia.

dag	tijdstip				hoeveelheid urine in milliliters (ml)				urineverlies (x)			
FRI 1 16	X	X	X	X	X	X	X	X	X	X	X	X
SAT 2 17	X	X	X	X	X	X	X	X	X	X	X	X
SUN 3 18	X	X	X	X	X	X	X	X	X	X	X	X
MON 4 19	X	X	X	X	X	X	X	X	X	X	X	X
TUE 5 20	X	X	X	X	X	X	X	X	X	X	X	X
WED 6 21	X	X	X	X	X	X	X	X	X	X	X	X
7 22	X	X	X	X	X	X	X	X	X	X	X	X
8 23	X	X	X	X	X	X	X	X	X	X	X	X
9 24	X	X	X	X	X	X	X	X	X	X	X	X
10 25	X	X	X	X	X	X	X	X	X	X	X	X
11 26	X	X	X	X	X	X	X	X	X	X	X	X
12 27	X	X	X	X	X	X	X	X	X	X	X	X
13 28	X	X	X	X	X	X	X	X	X	X	X	X
14 29	X	X	X	X	X	X	X	X	X	X	X	X

Chapter 4

The 24-h frequency-volume chart in a normal population

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The 24-h frequency-volume chart in a normal population

Abstract

Objective
To determine the variables (e.g. voiding frequency, voided volumes, urine production) and their mutual relationships and differences between age groups and genders, using a frequency-volume chart (FVC) in an adult population (representing all age groups) who denied having any voiding complaints.

Subjects and Methods
In all, 1152 men and women aged > 20 years completed a 24-h FVC; registration started with the first voided volume in the morning and concluded with the first voided volume the next morning. The time of voiding and volume were both recorded, and bedtime hours noted. Each participant claimed to have no voiding complaints. The statistical analysis was aimed at discerning the relationships between the FVC variables, gender and age.

Results
There was a linear increase in mean 24-h voiding frequency and nocturia in men, from 6.0 and 0.5 in the third decade to 8.5 and 1.6 in those aged > 70 years. Contrary to men, in women the mean 24-h frequency declined slightly in the older decades; it increased from 6.9 in the third to 8.2 in the sixth, declining to 7.8 in those aged > 70 years. Nocturia in women increased linearly, although slower than in men, from 0.7 in the third decade to 1.4 in those aged > 70 years. The mean volume/void decreased significantly in both genders, from 313 to 209 ml in men, and from 274 to 240 ml in women. The mean 24- h volume was 1718 and 1762 ml in men and women, respectively. For both genders there was a strong linear association between 24-h urine production and voided volumes.

Conclusion
The volume/void and maximum voided volume decreased significantly with age in both sexes, but more prominently in men. As a result, in men the frequency increased with age, probably reflecting subclinical changes associated with the development of prostatic enlargement. In contrast to men the frequency in women increased initially and decreased in the older groups. A higher 24-h urine production was associated with a higher mean volume/void.

Keywords
frequency-volume chart; female; male; reference values; cross-sectional study

Introduction

A history of voiding complaints in elderly men can be supported by using a symptom score; there is growing interest in female LUTS, where symptom scores are also being used [1;2]. This subjective score may differ from an objective recording and thus the frequency-volume chart (FVC) is recommended as an important diagnostic tool [3-9]. The FVC can give accurate information about 24-h urine output, frequency, nocturia and voided volumes, and most complaints are about these aspects of micturition. The results of a FVC can be used to suggest lower urinary tract dysfunction or conditions such as polydypsia and nocturnal polyuria. The value of the FVC in evaluating voiding complaints has been reported in several studies. The WHO International Consultation and the European Association of Urology recommended FVCs as a tool for evaluating LUTS, but reports on this aspect are scarce [10]. Reported FVC variables are often derived from men with BPH, from population-based studies, or from older groups [11;12]. Remarkably, the voiding patterns of asymptomatic women have been assessed using FVCs [13;14]. Because reference values have not been established in adult populations with no urological symptoms, and in both genders, the accurate interpretation of the FVC is difficult [15]. The objectives of the present study were: (i) to define reference values by age and sex for the different FVC variables (e.g. voiding frequency, mean and maximum voided volumes and 24- h and nocturnal urine production) in a Dutch adult population with no voiding problems; (ii) to determine the mutual relationships and differences among age groups and gender of the FVC variables; and (iii) to investigate the effect of potential co-determining factors, e.g. previous pelvic surgery, comorbidity and particular types of medication, on the FVC.

Subjects and methods

Questionnaires, including forms to keep a voiding diary, were distributed among relatives of patients and hospital employees; data were collected from 1749 volunteers. Essential data were lacking for 104 subjects. Missing volumes (except for the first voided volume of the first day, which was considered to be part of the urine production of the preceding night), and the missing of any time recording, including the times of going to bed and rising, were not accepted. There was a positive answer to the questions ‘do you have micturition complaints now’ and ‘are you being treated for micturition complaints now’ in 574 subjects, and they were excluded; this large number was obviously because the instructions were inappropriate when distributing the questionnaires. Because of overlap in the excluded groups, altogether 597 subjects were excluded.

Thus data for 1152 volunteers (560 men and 592 women, aged ≥ 20 years) were available for analysis. As a consequence of the exclusion criteria all participants denied having voiding complaints and none were under treatment for urological symptoms. The study consisted of two parts; (i) before keeping a record of the FVC, all subjects completed a questionnaire about their self-estimated fluid intake and voiding frequency. Both items could be answered as ‘high’, ‘normal’ or ‘low’, i.e. a subjective impression, as would be obtained when asking a patient in an outpatient clinic. Other items addressed pelvic complaints and their treatment, comorbidity and medication; (ii) the voiding pattern over 24 h was recorded, starting with the first void after rising until the first morning void the next day. During this period the time and volume of each void, and the time of rising on the first and the second day and the time of going to bed, were recorded on a standard form. All subjects were provided with a receptacle

graduated in 25 ml units. The dates and whether they were working days or leisure days were also noted.
The FVC recording period was defined as one whole day and one whole night, the first voided volume in the second morning included, aiming to collect information over 24 h, and in this report this period is referred to as 24-h. From the FVC the following variables were assessed: the voiding frequency in the daytime, night-time and the total frequency; the mean and the maximum volumes of all voids and the total volumes in each period were also calculated. Volumes and frequencies were defined as described by the International Continence Society [16]. However, we made no distinction between bedtime or sleep time and their corresponding night-time frequency and nocturia. The volunteers were only asked to report the time of going to bed and of rising. The nocturnal urine production included all voided volumes during the night with the subsequent first voided volume the next morning. The diurnal urine production is the sum of all voided volumes while the subject is awake and out of bed, minus the first voided volume, which is regarded as part of the preceding night. In the daytime frequency the first void was included, as nocturia does not include the first void in the morning. As a consequence, the mean daytime volume is calculated including the first void.
With frequencies and respective volumes as dependent variables, linear or quadratic regression analysis (LRA or QRA) was used to assess the role of age and gender and their interactions. Interaction tests were used to detect gender differences which were age dependent. The goodness-of-fit of these regression models was checked visually. The mutual relationships between the frequencies and volumes were modelled with multivariate regression analysis with stepwise forward selection. The three categories of the self-estimated drinking behavior and the self-estimated urine production were compared with the categorized 24-h urine production as recorded in the FVC by ANOVA. The subjects were grouped in age decades, and statistical significance defined as $p < 0.05$.

Results

The mean (range) of the registered '24-h' period was 23.57 (18.25–27.57) h; the characteristics of the frequencies and volumes per age decade and gender are summarized in

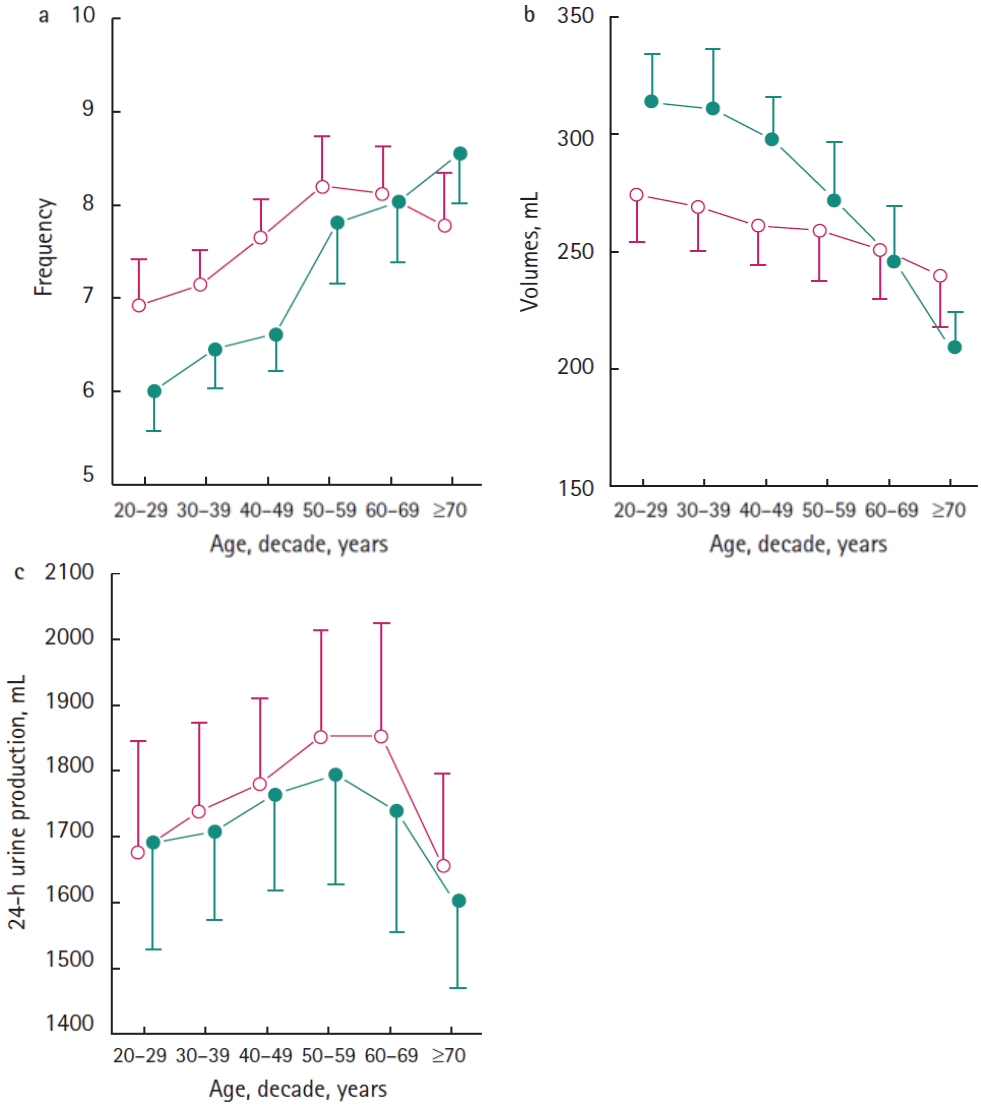
Table 1. Characteristics of frequencies and volumes per age decade and gender.

Age decade	sex	n	Mean (SD) frequency			Mean (SD) volume in ml				
			24-hour	day	nocturia	24-hour*	day*	night*	nocturnal	maximum
20-29	M	85	6.01 (2.00)	5.53 (1.88)	0.48 (0.63)	1690 (747)	297 (92)	390 (161)	469 (258)	491 (152)
	F	102	6.92 (2.54)	6.20 (2.31)	0.73 (0.82)	1677 (860)	258 (101)	361 (176)	473 (231)	479 (186)
30-39	M	114	6.46 (2.31)	5.80 (1.97)	0.66 (0.77)	1707 (720)	298 (142)	380 (178)	472 (239)	510 (201)
	F	127	7.14 (2.11)	6.38 (1.83)	0.76 (0.84)	1739 (767)	257 (110)	335 (172)	473 (286)	475 (172)
40-49	M	128	6.63 (2.33)	5.95 (2.10)	0.67 (0.81)	1765 (839)	280 (112)	387 (170)	514 (268)	503 (184)
	F	119	7.65 (2.29)	6.75 (2.06)	0.84 (0.86)	1711 (711)	243 (90)	349 (158)	510 (260)	475 (169)
50-59	M	83	7.81 (2.99)	6.83 (2.65)	0.98 (0.91)	1794 (758)	258 (112)	339 (142)	539 (327)	465 (196)
	F	98	8.20 (2.66)	6.97 (2.31)	1.23 (0.96)	1853 (805)	241 (108)	356 (191)	582 (314)	470 (183)
60-69	M	67	8.03 (2.67)	6.70 (2.01)	1.33 (1.17)	1738 (745)	227 (95)	323 (134)	602 (309)	414 (156)
	F	81	8.12 (2.29)	6.86 (2.12)	1.26 (1.00)	1852 (780)	226 (92)	355 (169)	620 (359)	445 (181)
70 +	M	83	8.55 (2.44)	6.90 (1.95)	1.65 (1.37)	1602 (604)	189 (69)	276 (107)	579 (315)	349 (131)
	F	65	7.78 (2.26)	6.43 (1.85)	1.35 (1.04)	1655 (566)	216 (89)	324 (145)	612 (270)	439 (170)

* volume/void over the indicated period

Table 1 and Figure 1a,b. The voiding frequencies over 24 h in general increased with age and showed a significant age-dependent gender difference (LRA $p < 0.001$; gender and age interaction test $p = 0.007$), i.e. in both genders the 24-h frequency increased with age, but contrary to men, in women there was a decline from the sixth decade. The daytime voiding frequency and nocturia increased with age (LRA $p < 0.001$), but there were no significant gender differences.

Figure 1. The voiding frequency (a), mean volume/void (b) and 24-h urine production (c) by age decade and gender. **Red open circles**: women; **green closed circles**: men. Errors bars indicate the 95% CI.



Except for the mean night-time volumes and maximum voided volumes in women, in both sexes the mean of the mean volume/void in 24 h (Figure 1b), in the day and in the night-time (Table 1), as well as the maximum voided volume, decreased gradually with age (LRA $p < 0.001$). The mean volume/void was larger in the night than during the day. All these four variables showed significant gender differences independent of age, with a more prominent decrease in men ($p < 0.01$). The ratio between the maximum and the mean voided volumes was about constant through all age groups, at 1.7 in men and 1.8 in women.

The urine production in 24 h related to age had a parabolic curve (QRA, $p = 0.018$; Figure 1c); there was no significant difference between the sexes. The overall mean 24-h volume was 1718 and 1762 ml in men and women, respectively. The urine production in the day had an asymmetric parabolic curve in both sexes, in the older decades decreasing more prominently (QRA, $p = 0.007$ in men and 0.014 in women). The nocturnal urine production showed a slow linear increase (LRA $p < 0.001$), with no gender difference.

The total urine production in 24 h was subdivided into nine categories of 250 ml, from < 750 to > 2500 ml. In these categories the mean and maximum voided volumes were assessed (Figure 2). With increasing 24-h urine production there was a linear increase in the mean and maximum voided volumes (LRA, $p < 0.001$). The maximum voided volume can be used as a rough predictor of the 24-h urine production; mathematically expressed, in men the 24-h

Figure 2. Voided volumes categorized by 24-h urine volume.
Red open circles: maximum; **green closed circles**: 24-h mean; **red closed squares**, daytime mean; **green open circle**: night-time mean). Errors bars indicate the 95% CI.

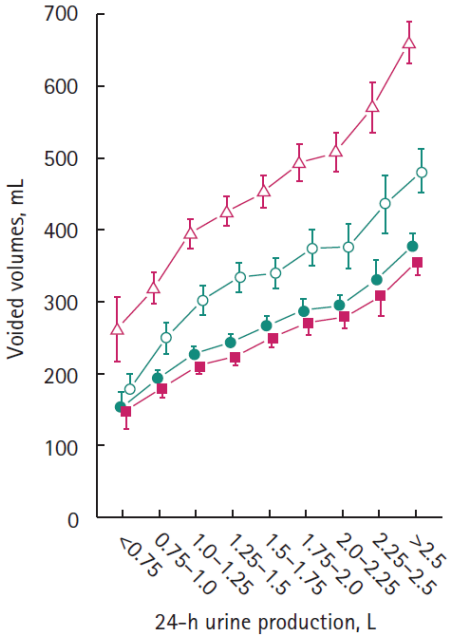
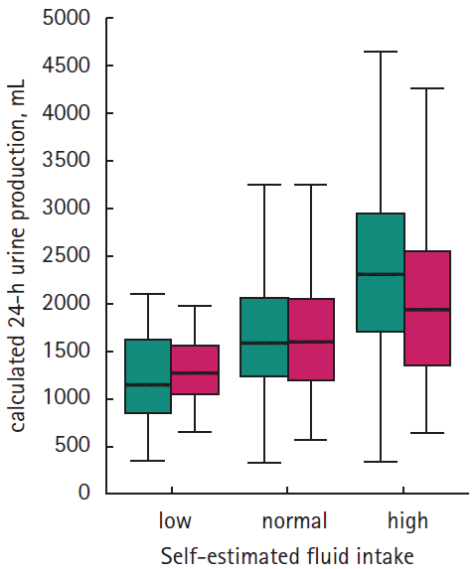


Figure 3. The relationship between the calculated 24-h urine production and self-estimated fluid intake.
The boxes indicate the interquartile ranges, the line the median and the bars the range within 1.5 box lengths. **Green**: women; **red**: men.



urine production was 678 + 2.25 x maximum volume, and in women 572 + 2.55 x maximum volume. A 24-h urine production of < 750 ml was associated with a mean volume/void in men of 166 ml and in women of 146 ml. A total urine production of > 2500 ml had a mean portion size of 376 ml in men and 380 ml in women.
Both the self-estimated fluid intake and the voiding frequency seemed only loosely associated with the calculated urine production and frequency. Although there was a significant difference in the three categories between the mean calculated total urine production (ANOVA $p < 0.001$), the range of volumes showed such a large overlap that the self-estimated volumes are unreliable indicators of the true production (Figure 3).
There was a history of operative interventions in the pelvis in 169 subjects; in this group the respective mean and maximum voided volume were 30 and 40 ml smaller than in the rest of the group who had no such treatment. The voiding frequency was higher in the treated group, but the differences were insignificant. Most people used a leisure day for the FVC recording (920 vs 114 on a working day, with 118 missing values). Most (40%) of the FVCs were recorded during winter, the other seasons being equally represented. There was no significant difference between the type of day or season and the results of the FVC (chi square $p > 0.05$). The numbers of patients with comorbidities and of groups using medication were small; compared to those with neither the results showed no significant differences in the FVC variables.

Discussion

To formulate a frame of reference for patients with voiding complaints we chose subjects who denied any voiding complaints. Thus this group of volunteers differed from a community-based screening population that would contain subjects with such complaints. Nocturia was recently redefined [16]; although in the International Continence Society terminology it is referred to as a complaint, we used nocturia in an asymptomatic population also to describe the number of occasions in the night that they woke to void.
From an FVC it is impossible to have an exact 24 h registration, as voiding times are generally distributed through the day, and the moment of rising is variable. The FVC recording period from 'rising' to 'rising' was influenced by most recording being made by subjects on a leisure day, in some cases resulting in an aberrant scheme with late rising on the first morning and early rising on the next, or vice versa. This aberration was partly caused by our obviously paradoxical instructions, on the one hand requesting a 24-h registration, and on the other instructing the subject to start with the first void after rising on the first morning, and to end with the first void the next morning. This mainly occurred in the youngest subjects, probably reflecting a more irregular lifestyle. As a result, the mean duration of the FVC registration period was 23.5 h. Correcting this by recalculating to exactly 24 h did not alter the curves, trends and significances, but would only slightly increase some absolute values. Therefore we chose not to correct to an exact 24-h period.
Debate remains about the optimum duration of a FVC recording; the discussion is confused by not making a clear distinction between intra-individual and inter-individual variability, both of which may cause sampling error. Increasing the sample size is expected to reduce this sampling error. Schick *et al.* discussed the balance between reliability and compliance of an individual constructing a FVC, showing that by increasing the period of recording the reliability increased and the compliance decreased [17]. In one individual it is likely that a 24-h FVC has more error than a longer recording period but nevertheless, several authors have reported that a short FVC period has high reliability [10;18;19]. Although we have no data on the intra-

individual variance it is very likely that the large range of values in the present study, representing the inter-individual variability, will by far exceed the intra-individual variability. Consequently, in estimating the variables in the present subjects the inter-individual has more weight than the intra-individual variability. Extending the registration period would mainly decrease this intra-individual variability. It is therefore sufficient to have a 24-h FVC, but we realise that keeping the FVCs only over a 24-h period could introduce some bias. The large size of the population sample will minimize the error in estimating the various FVC variables. Considering this, strengthened by the reports cited above, and assuming decreasing compliance of volunteers with increasing duration of measurement, we chose a registration period of 24 h, including first voids in both the first and next morning, to ensure complete recording of the nocturnal voided urine volume.

The 24-h urine production had a weak parabolic curve for both sexes in relation to age (Figure 1c); at the same time the mean and the maximum voided volumes decreased with age, most prominently in men (Figure 1b). Consequently the voiding frequency in 24 h increased with age in men, but there was an increase/decrease in a 'parabolic' curve in women (Figure 1a). Not only the changes with age but also the differences between sexes are interesting. In the older decades in women the 24-h urine production decreased more than the functional bladder capacity, resulting in a later decrease in frequency. In contrast, in men the strong decrease in functional bladder capacity was responsible for the increasing frequencies. Perhaps this suggests changes related to subclinical prostatic enlargement. With increased age, factors such as decreasing compliance of the bladder wall and changes in bladder innervation may be significant [20-23].

We have no explanation for the relatively higher urine production then those reported in other studies. A hypothesis that this was caused by the 89% rate of valid cases of recording on a leisure day, assuming that individuals have more opportunities to drink, had to be rejected because there were no significant difference between the types of recording day. Nor was the season a significant influence. There was also a remarkably high proportion of nocturnal urine production in all age groups; this, along with nocturia, will be assessed in more detail in the near future.

Most striking was the strong significant linear relationship between 24-h urine production and the mean and maximum volumes in all age categories and genders (Figure 2), which could be described mathematically. We have no sure explanation for this; possibly it is an adaptive mechanism of bladder function to urine production, but it is also possible that bladder functional disturbance gives rise to an adaptation in fluid intake. Assessing the effect of increasing urine production in an individual on the voided volumes would be interesting. Further studies are needed to elucidate the relationship between urine production and voided volume.

In taking a patient's history of LUTS they are asked about fluid intake and voiding frequency; this study emphasizes that the answers compare roughly with objective recording of the FVC, but that these answers are to be considered unreliable in individuals. The adequately completed FVC gives good objective estimates of the voiding pattern and is therefore indispensable in the diagnosis and treatment of individual patients. The value of the FVC in evaluating patient groups merits further study. This is especially the case in LUTS, urinary incontinence and other urinary tract dysfunctions. The usefulness of the FVC can be appreciated both in diagnosing functional urinary tract disturbances and in evaluating therapeutic interventions.

In conclusion, in subjects with no voiding complaints the voided volumes decrease with age, and more prominently in men. The voiding frequency also increases with age in men, but in women it increases and then decreases in consecutive age groups. There is a clear relationship between the 24-h urine production and the mean and maximum voided volume for both sexes of all ages. There was no significant influence on the FVC variables of comorbidity or the use of medication. Self-estimated voided volumes are generally unreliable, making the FVC a mandatory tool in the proper evaluation of lower urinary tract function.

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	Tijd	Volume in ml	Verlies (x)
1	7:30	100 ml	15
2	7:30	xx	12
3	8:00	xx	15
4	7:30	xx	15
5	7:30	xx	15
6	7:30	xx	12
7	7:30	xx	15
8	7:30	xx	15
9	7:30	xx	12
10	7:30	xx	10
11	7:30	xx	12
12	7:30	xx	11
13	7:30	xx	15
14	7:30	xx	12
15	7:30	xx	13
16	7:30	xx	15
17	7:30	xx	15
18	7:30	xx	12

Chapter 5

The usability of a 7-day Frequency-Volume Chart

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Submitted

The usability of a 7-day frequency-volume chart

Abstract

Objective
To assess usability by compliance with a 7-day frequency-volume chart (FVC) as to recording of days, voiding times and volumes.

Subjects and methods
Of 500 consecutive urologic outpatients willing to complete a 7-day FVC, 378 forms were evaluable.
Patients were instructed to indicate missed entries for time and/or volume with a coded letter.
Compliance was defined as agreement between the times or volumes recorded and the true frequency (times or volumes recorded plus coded entries).
The mean compliance was calculated, and level of completion by day was computed.

Results
FVCs of 228 men and 150 women were analyzed.
The mean values (SD) were 55 y (16) for age, 13.8 (8.9) for International Prostate Symptom Score, and 1856 ml (828) for 24-h urine production.
At day 7, 28% of the patients had not missed a single entry for time and volume. For all patients as a group compliance with recording time alone decreased from 96% on day 1 to 81% on day 7 (mean 91%); compliance with recording volume alone decreased from 93% to 78% (mean 88%).
No significant relationship between compliance (times or volumes) and any of the FVC parameters was found. From day 2, compliance decreased significantly with each day.
The first 5 days the level of completion was above 80% in most patients.

Conclusion
For the whole group, a 7-day FVC has high compliance with means of 91% and 88% by time and volume, respectively. After day 2 the mean compliance decreases significantly. We consider a minimal level of completion of 80% usable. Therefore, a 2-day FVC is most usable in clinical practice.

Keywords: Frequency-volume charts; Usability; Compliance; self report; Voiding pattern; Urination

Introduction

Frequency volume charts (FVCs) provide an objective impression of a patient's voiding pattern. Indications are that a 7-day FVC provides more reliable information than a 1-day FVC and therefore has higher clinical value [1]. In contrast, the assumption is that compliance (willingness and opportunity to complete the FVC) will decrease with the number of days that need to be recorded [2;3]. Depending on clinical use, Dmochowski noted that a 3-day FVC is sufficient to measure effect of pharmaceutical interventions for overactive bladder [4]. Fitzgerald and Brubaker showed that honorarium on completion resulted in compliance of only 62% [5]. Gisolf concluded that for men with LUTS, a 24-h FVC will be sufficient for monitoring voiding habits [6]. It seems important to establish patients' compliance in relation to the duration of the FVC. Specific research on compliance is scarce [7]. The objective of this study is to determine usability by compliance with a 7-day FVC.

Subjects and Methods

Design

The study was prospectively designed to collect 7-day FVCs from adult urologic patients visiting two outpatient clinics. To avoid selection of patients by invitation, it was decided to invite consecutive patients regardless of the reason for their visit, until 500 patients were recruited. Recruitment period was from June 2008 to January 2009. No records were kept of whom the forms were distributed to, neither of why some patients were unwilling to participate. Later, the records of all patients were reviewed, and each patient was assigned a categorized diagnosis.

Patients received information on the nature of the study and informed consent was achieved. The study was approved by the hospital's ethical committee. Before recording the FVC, the participating patients were asked to record some personal parameters, as well as an International Prostate Symptom Score. Subsequently, the patients received a measuring cup, instructions, and forms on which to record the FVC, one for each day.

During 7 consecutive days, the patients had to record the day of the week, every voiding (time and volume), and the times of waking up and going to sleep, in accordance with the ICS definition of FVC [8]. When they were not able to record the volume or the exact time of a voiding episode, they had to record a coded letter, indicating the reason for the missing record (A: forgotten to measure; B: no opportunity; C: no measuring device; D: incontinence E: other). Purposely, no emphasis was given on any benefit of recording of the FVC with regard to a patient's diagnosis. Records of patients lacking essential data were excluded. We used several methods to assess the usability of the 7-day FVC. Below we will explain the different methods in more detail.

Compliance

Compliance (% of completion) is the agreement between the times or volumes recorded and the true frequency. The total numbers of voiding episodes and voided volumes recorded per day, as well as missed recordings, were computed, resulting in a percentage of completion in time, in volume or both. When recording was interrupted or stopped prematurely, the day count of voiding events was set to the mean of voiding events of completed days, to enable calculations of completion. The better the score, the better the use in clinical practice.

Mean compliance

The first method is the day-by-day mean value of the completion of each patient's recordings. This value represents the overall compliance of the group and has confidence intervals.

Level of completion, daily and cumulative

The second method is the day-by-day number of patients that recorded voiding events above or equal to a predetermined completion level. Arbitrarily, we choose 10-percent levels. Compared to mean compliance, this gives a better impression of the distribution of compliance. Moreover, the latter method may be expressed not only as a daily value but also as a cumulative value. Hereby we took into account the results of previous days: when patient's compliance drops below a certain level, the patient will remain classified to that level, regardless improvement in subsequent days. The results are percentages of patients meeting that criterion.

If, for example, a patient voids nine times in 24-h and misses one volume recording, his compliance in time will be 100% but his compliance in volume will be 8 out of 9, or 89%. For the group, if 8 out of 10 patients record 100% of the events, 1 patient records 92%, and 1 patient records 88%, the first method will show mean compliance of 98%. The second method will show that 80% of the patients fully completed all events, 90% completed 90% or more, and all completed 80% or more. A patient with first day compliance of 100%, second day 80%, third day 100% and fourth to seventh day 70% will be classified to the 100% group in the first day, to the 80% group in the second and third day, and to the 70% group from the fourth day.

Statistical analysis

No formal power analysis was conducted but we aimed to include 400 patients because the standard error of the sample reliability would then be below 0.05. We stratified for five diagnostic groups: 1. benign prostatic hyperplasia (BPH); 2. urinary tract infection (UTI); 3. overactive bladder and urgency or stress incontinence (OAB); 4. LUTS not due to the former 5. a normal group without LUTS.

Between days, completion of recording both time and volume, was compared using linear mixed-effect models for repeated measurements, controlling for age, gender and diagnosis.

To check for completion of the recording of the missing values, the intra-individual variance coefficient was calculated. Assuming that missing recordings of missing values would result in larger intra-individual variation, the 5% highest values of the variance coefficients of the 24-h frequencies and volumes were excluded. Compliance was recalculated and multivariate analysis using mixed-effect models was repeated. These results were compared with previous calculations.

SPSS Statistics v.19.0 (IBM Corp., Armonk, NY, USA) was used for data analysis. Statistical significance was defined as $p < 0.05$.

Results

Population

Of 500 distributed forms, 398 were returned. A response rate of 79.6% in patients who had previously indicated to be willing to participate. 378 FVCs were evaluable, twenty lacked essential data. Table 1 shows patient characteristics. Dispersion of patient by grouped urological diagnosis, age strata and gender are presented in Table 2.

Bedtimes and waking times were both recorded in 84%. Causes of missed episode recordings were A: forgotten to measure (n = 144); B: no opportunity (563); C: no measuring device (359); D: incontinence (43); E: other (124).

Table 1. Patient characteristics

	Total group			Men			Women			
	n	Mean	SD	n	Mean	SD	n	Mean	SD	*p*
Age, year	378	55	16	228	59.1	14.2	150	48.8	16.8	<0.001
BMI	331	25.8	4.3	201	25.8	3.5	130	25.6	5.3	0.95
IPSS	335	13.8	7.9	206	14.0	7.8	129	13.6	8.2	0.62
24-h volume, ml	378	1856	828	228	1855	795	150	1858	877	0.98
24-h frequency	378	9.1	3.5	228	9.1	3.4	150	8.9	3.5	0.47

Table 2. Number of patients by diagnosis, age strata and gender

	no LUTS		BPH		UTI		OAB/inc		other LUTS		Subtotals by sex		Totals by age	
Age, yrs	m	w	m	w	m	w	m	w	m	w	m	w	all	%
<30	1	2	0	0	0	18	0	1	5	2	6	23	29	8%
30-39	9	5	0	0	2	15	3	3	7	4	21	27	48	13%
40-49	11	8	7	0	4	9	5	9	4	2	31	28	59	16%
50-59	9	10	18	0	9	9	5	6	8	4	49	29	78	21%
60-69	17	5	25	0	8	10	3	5	12	5	65	25	90	24%
>=70	7	4	27	0	9	9	4	4	9	1	56	18	74	20%
Subtotals by gender	54	34	77	0	32	70	20	28	45	18	228	150	378	100%
Totals by diagnosis n	88		77		102		48		63					
Totals by diagnosis %	23%		20%		27%		13%		17%		60%	40%	100%	

m = men, w = women
inc = incontinence

Mean compliance

Figure 1 shows the decrease of compliance by day (mixed effect models $p < 0.001$). The overall mean compliance of time is 91%. It occurred only 9 times that volumes were recorded without time recordings. Therefore, compliance of volume recordings were not influenced by lacking time recordings. The overall mean compliance of volume is 88%. The decrease by day was significant, and no differences were found between age strata or gender.

Level of completion

Figure 2 shows the number of patients (in %) by level of completion by day.
The percentage of the number of complete FVCs (all times and volumes recorded) from day 1 to day 7 was 71%, 78%, 73%, 72%, 68%, 63%, and 58%, respectively. A level of completion of 90% is found in more than 80% of patients on the second day, but from the fourth day it drops below 75%. A level of completion of 80% is found on all days in less than 90% of patients, and drops below 80% after 5 days.
Cumulative levels of completion are shown in Figure 3. Of all patients, 104 (28%) recorded every voiding event, for 22 (6%) patients not a single day was complete.

With the duration of FVCs levels of completion decreased ($p < 0.001$) and differed by age and diagnosis (OAB did worse). On the first day women performed better than men, but on the last two days men performed better than woman. Overall, no gender differences were found (mixed effect models $p = 0.07$).
Between 10-year age strata only significant differences were found between the two strata up to 40 years and the other strata of 40 years and older ($p < 0.001$). In general, older patients performed better.
In multivariate analysis using mixed effect models controlling for 10-year age strata, gender and diagnosis, the decrease was still significant.
The intra-individual variances of 24-h frequency and volume were compared by variance coefficient.
Unselecting 63 cases with the 5% highest variance coefficients, minimally improved compliance and level of completion. The decrease in compliance remained ($p < 0.001$).

Figure 1. Compliance with time and volume. Error bars show the 95% confidence.

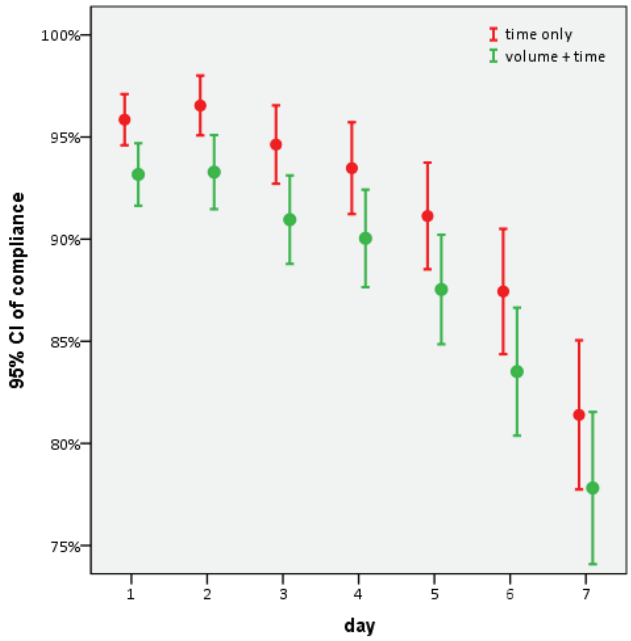
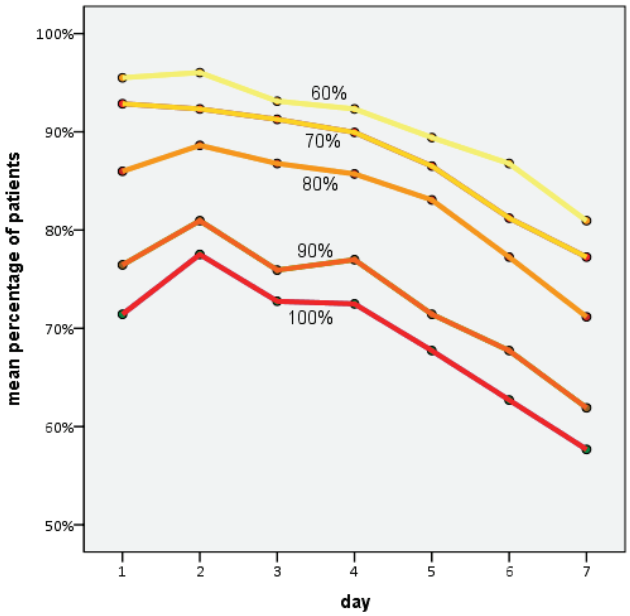
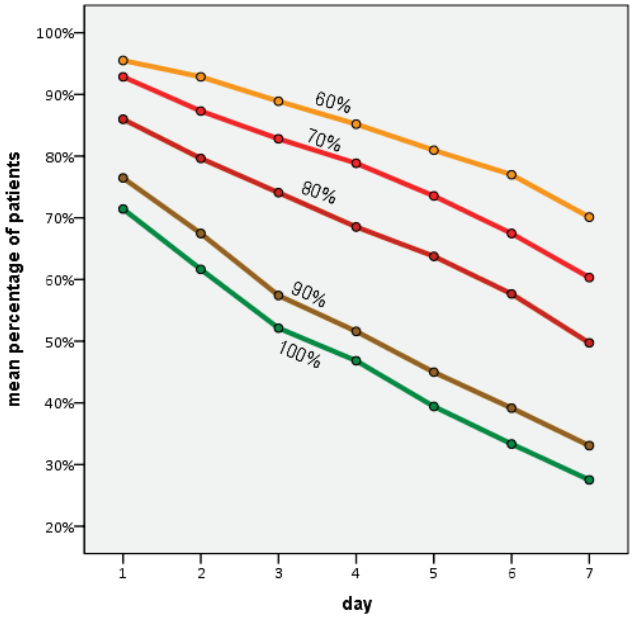


Figure 2. The percentage of patients by level of completion.



Legend
The 100% level of completion (red line) means that all items are fully completed. On the y-axis the amount of patients (in %) is stated.
E.g. 50% level of completion means that only the half of the items are recorded.

Figure 3. The percentage of patients by cumulative level of completion by day.



Discussion

No published studies address compliance with a 7-day FVC. In the present study we evaluated 378 patients. We found mean compliance decreased from 93% to 78%. However, only 71% of FVCs was complete on the first day. From day 2 on, every subsequent day showed lower percentage of completion. The first day had lower compliance than the second day, which likely results from some patients starting as soon as they got the FVC forms – in contrast to instructions – or from a learning effect. In our opinion, a level of completion under 80% will be less usable in many cases. After 4 days the burden of keeping an FVC and loss of information becomes too high.

The decline in compliance after day 2 with the number of FVC days is consistent with other reports [2-4;9]. Yap et al, however, concluded that none of these reports provided enough evidence to prove a relationship between completion and FVC duration [7]. The large sample in our study showed a decline in compliance after day 2. Others have used smaller sample sizes (16–300 patients) than this study. These reports show wide ranges of compliances (57% to 100%)[7]. Our study has a high compliance. We assume that increased convenience due to the possibility to indicate missed values, finally increased compliance.

A possible shortcoming is our recruitment strategy: Unwilling patients were excluded. Mostly patients without voiding complaints, so joining was of no benefit to them. In daily practice, they are not a relevant group with respect to the FVC. A substantial number of participating patients did not return it. Some were not motivated to participate or not able to (illiteracy), some forgot, and others did not return to our department.

The reliability of the participants might limit the results of the study. When patients did not record a missed void with a coded letter, we could not identify a missed episode. Mean urine production, however, is comparable with other studies [10-13]. More important, the variance coefficient did not show significant differences per day. Excluding extreme results did not alter outcome. Obviously it is also possible that the allowance of indicating a missed void by a coded letter can lead to a greater number of missed voids. We did not further elaborate this option. Depending on the requirements of the study data, one might choose to accept a certain percentage of missed values. The implication for clinical studies is that a 7-day FVC is feasible and usable. Although only 28% of the 7-day FVCs were complete, the number of correct measurements was still very high.

Conclusions

The recording of a 7-day FVC has a high usability. The best compliance is found at day 2 (97%). Mean compliance is 91% for a 7-day FVC. The minimal level of completion of 80% is considered usable in clinical practice. Therefore we assume that a 2-day FVC is usable in clinical practice. After 4 days the burden of keeping an FVC and loss of information become too high.

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	Tijd	Volume in ml	Verlies (x)
1	7.45	2 mL	
2	9.29	3 mL	
3	09.59	1 mL + 3 druppels	
4	11.47	1 m + 33 druppels	
5	12.22	1 m + 9 druppels	Bakje
6	17.28	1 m + 23 druppels	
7	20.33	1 m + 63 druppels	
8	23.34	1 m + 23 druppels	
9	00.03		bedje
10	03.23	3 m + 9 druppels	
11	05.42	2 m + 43 druppels	
12	06.52	1½ m + 23 druppels	
13	08.33	2 m + 9 druppels	
14			

Chapter 6

The optimal duration of frequency-volume charts related to compliance and reliability

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The optimal duration of frequency-volume charts related to compliance and reliability

Abstract

Objective
To assess Frequency–volume charts (FVCs) for the yield of additional recorded days and the ideal duration of recording related to compliance and reliability.

Subjects and Methods
Of 500 consecutive urologic outpatients willing to complete a 7- day FVC, 378 FVCs were evaluable. During seven consecutive days every voiding time and volume were recorded. Missed entries were indicated with a coded letter, thereby assessing the true frequency and compliance. Reliability is the agreement of the day-to-day FVC parameters with the 7-day FVC pattern. Single-day reliability was assessed and used in the Spearman–Brown formula.

Results
FVCs of 228 male and 150 females were evaluated. Mean age was 55.2 years (standard deviation [SD]: 16.2 years), and mean 24-hr urine production was 1,856 ml (SD: 828 ml). The percentage of patients with complete FVCs decreased from 78% on day 2 to 58% on day 7, and dropped below 70% after 4 days. Single-day reliability was r = 0.63 for nocturnal urine production, r = 0.72 for 24-hr urine production, and r¼0.80 for mean voided volume. At 5 days, reliability of 90% was achieved for all parameters.

Conclusions
With each additional day, FVCs showed a decrease in compliance and an increase in reliability. At day 3, reliability of 80% was achieved for all FVC parameters, but compliance dropped to 73%. Beyond 5 days, the yield of additional recorded days was limited. We advocate an FVC duration of 3 days, but the duration may be shortened or extended depending on the goal of the FVC.

Key words: compliance; frequency-volume chart; reliability; self report; urinary bladder; urination

Introduction

Frequency-volume charts (FVCs) have become an indispensable tool in the evaluation of lower urinary tract symptoms (LUTS)[1], and several guidelines recommend their use [2-4]. FVCs recording voiding times and volumes will give an impression of a patient's voiding pattern. There is still debate about the optimal duration of the FVC, in order to be representative for a patient.

The longer the FVC is recorded, the better it will reflect the true voiding pattern; however, due to normal variation, which is wide, there is a point after which prolonged recording will yield no additional information. Moreover, with increasing duration of an FVC, compliance—a patient's willingness or ability to record properly—will decrease.

Statements concerning the duration of FVCs vary from 1 to 7 days and are based on compliance or reliability (or their presumed relation). Abrams and Klevmark favored a 7-day FVC because the week is a unit of time in social terms [1].

Compliance rates have been presented as the percentage of patients that completed the FVC at the end of the study period and vary from 57% to 100% [5-8]. High compliance rates were not achieved with intensive instructions or an encouraging fee [9;10]. Another study found no differences in compliance rates for FVCs kept for 2, 3, or 7-days by 162 patients with incontinence and LUTS [11]. However, the authors showed that the burden of an FVC increased with duration of the FVC.

Reliability is often presented as consistency of FVC data in terms of test-retest reproducibility or as internal correlations (split-half, day-to-day, or single-day to full FVC period)[6;9;12;13]. Locher et al calculated reliability on each day of a 14-day FVC and concluded that 5–7 days recording was required [14]. These findings were not taking into account any decrease in compliance. Schick et al compared 2- to 6- with 7-days- FVCs, and concluded 4-day FVCs were almost equivalent to 7-day FVCs [15]. Assuming decrease of compliance they plead against recording of 7-day FVCs. In two reviews it was concluded that no reports provided enough evidence to prove a significant relationship between compliance and FVC duration [7;16].

In establishing the optimal duration of the FVC, the key issue is how much information is gained or lost with every extra day that the FVC is kept.

The aims of the present study are to examine the day-to-day reliability of FVCs and to assess the optimal duration of the FVC related to compliance.

Subjects and methods

Design

The study was prospectively designed to collect 7-day FVCs from adult urologic patients visiting two outpatient clinics. To avoid selection of patients by invitation, it was decided to invite consecutive patients regardless of the reason for their visit, until a number of 500 willing patients was recruited. No records were kept of whom the forms were distributed to, neither of why some patients were unwilling to participate. Later, the records of all patients were reviewed, and each patient was assigned a categorized diagnosis, based on the clinical diagnostic code and/or started treatment.

Patients received oral and written information on the nature of the study and informed consent was achieved. The study was approved by the hospital's ethical committee.

Before recording the FVC, the patients were asked to record their height, weight, and daily activities and to complete a general questionnaire (self-estimated fluid intake, presence of urologic symptoms, history of operations of the lower urinary tract, diabetes, and use of

medication) as well as an International Prostate Symptom Score and a score to categorize bladder storage symptoms. Subsequently, the patients received a measuring cup, written and oral instructions, and forms on which to record the FVC, one for each day.
During 7 consecutive days, the patients had to record the day of the week, every voiding (time and volume, day, and night), and the times of waking up and going to sleep, in accordance with the ICS definition of FVC.17 When they were not able to record the volume and the exact time of a voiding episode, they had to record the missed measurement by providing a coded letter indicating the reason for the missing record. Purposely, no emphasis was given on any benefit of recording of the FVC with regard to a patient's diagnosis. Records of patients lacking essential data such as gender, birthday, and dates were excluded.

Compliance

Compliance is the agreement between the times or volumes recorded and the true frequency. The total numbers of voiding episodes and of voided volumes recorded per day as well as missed recordings were computed, resulting in completeness of time and volume. Compliance can be described in two ways. One way is by the day-by-day mean value of the completeness of each patient's recordings. This value can be interpreted as the overall compliance of the group and has confidence intervals. The other way is by the day-by-day number of patients that recorded voiding events above or equal to a certain level of completeness. The results are percentages of patients meeting that criterion and can be interpreted as the chance that an individual will completely record the FVC. Both methods can apply to time, to volume, or both.

If, for example, a patient voids 9 times in 24 hr and misses 1 volume recording, his compliance in time will be 100% but his compliance in volume will be 8 of 9, or 89%. For the group, if 8 of 10 patients record 100% of the events, 1 patient records 92%, and 1 patient records 88%, the first method will show mean compliance of 98%. The second method will show 80% of the patients being compliant for 100% of the events, 90% being compliant for 90% or more, and 100% being compliant for 80% or more. For example, in judging an individual's compliance one could decide an 80% level of completeness to be acceptable.

Reliability

The term reliability may be used in different ways: to indicate the extent to which the measured FVC parameters are representative of the voiding pattern or to which repeated measurements yield the same results (test-retest reliability or reproducibility). The first definition is appropriate for the present study because the aim is to study the optimal duration of the FVC.

Statistical Analysis

No formal power analysis was conducted but we aimed to include 400 patients because the standard error of the sample reliability would then be below 0.05. We stratified for five diagnostic groups: (1) benign prostatic hyperplasia (BPH); (2) urinary tract infection (UTI); (3) overactive bladder and urgency or stress incontinence (OAB/incont); (4) LUTS not due to BPH, UTI or OAB/incont (e.g., hematuria, pain, smelling urine); (5) a normal group without LUTS (e.g., urolithiasis, matters of sexual function and fertility, scrotal diseases, elevated PSA, requests for screening).
The reliability of a single measurement of FVC parameters per patient was quantified with the intraclass correlation coefficient (ICC) and its 95% confidence interval. The ICC was calculated from the repeated measurements of the FVC parameters on days 1 to 7 using a linear mixed-effects regression model assuming compound symmetry covariance structure. The ICC represents the reliability of the FVC parameters if they would be measured in patients on 1 day

only. The Spearman–Brown prediction formula has been developed to predict the reliability of a test after changing the test length. The reliability of the mean of k FVC measurements was calculated with the Spearman–Brown formula (k x ICC/(1+(k-1 x ICC))), where we varied k between 1 and 7 [17]. With time and with 100% compliance, reliability will increase to a limit, where eventually the whole spectrum of variability of a patient's FVC parameters is covered.
Compliance for time and volume was graphically and mathematically related to reliability. SPSS Statistics v.19.0 (IBM Corp., Armonk, NY) was used for data analysis. Statistical significance was defined as $p < 0.05$.

Results

Of all 500 distributed forms, 398 were returned, for a response rate of 79.6% in patients who had previously indicated to be willing to participate. Twenty FVCs lacked essential data and were excluded, leaving 378 FVCs (228 male, 150 female) for evaluation. Patient characteristics are summarized in Table 1. Between sexes, no differences were found in FVC parameters, but there was a significant difference in age: men 59.1 years (SD 14.2), women 48.8 years (SD 16.8) ($p < 0.001$).

Table 1. Patient Characteristics.

	n	mean	SD
Age, years	378	55.2	16.2
BMI	331	25.8	4.3
IPSS	335	13.8	7.9
24-h urine production, ml	358	1856	828
24-h voiding frequency	378	9.1	3.5

Grouped urologic diagnoses were recorded: UTI, 102 (27.0%); BPH, 77 (20.4%); OAB/incont, 48 (12.7%); other LUTS (no BPH, OAB, or incontinence), 63 (16.7%); no LUTS, 88 (23.3%). Mean compliance for time and volume recordings decreased from the 2nd day gradually with the FVC duration, from 96% to 83% and from 93% to 78%, respectively. The first day compliance was hampered due to patients starting recording at an arbitrary moment of the day, instead of at a first morning void.
We calculated the numbers of patients that recorded 100%, 90%, 80%, 70%, or 60% of the events (for both time and volume; for example, patients that were 80% compliant were those with at least 80% completeness for time recordings as well as for volume recordings): The percentage of fully compliant patients decreased from 71% and 78% on day 1 and 2, to 58% on day 7, it dropped below 70% after 4 days (Figure 1). The percentage of patients with nearly complete recordings (missing only one or two recordings in 24 hr) was nearly 90% at day 2.
The reliability of several FVC parameters is shown in Table 2. At day 5, all parameters achieve reliability of 90%. In Figure 1 compliance (3 levels of completeness) and reliability of 3 FVC parameters are plotted. Not shown levels of completeness were in between adjacent levels and would hamper clarity of the figure. Likewise other FVC parameters were not shown as they were resembling the ones shown. With increasing duration of the FVC, reliability increased, whereas compliance decreased. Because volume recordings are less frequently complete than time recordings, volume recordings will be the determining factor for reliability. The lowest reliability was found in recording nocturnal urine production (NUP). The relation between compliance (100% completeness) and reliability for NUP is presented in

Figure 2 (figures of other parameters are less illustrative and are therefore not shown). Details for reliability of NUP by diagnostic group are presented in Table 3. For all FVC parameters, no significant differences in reliability occurred between diagnostic groups nor between sexes.

Figure 1. The percentages of patients with different levels of completeness (60%, 80%, and 100%) versus the reliability of 24-hr frequency (freq24), 24-hr urine production (UP24), and nocturnal urine production (NUP), by duration of the FVC.

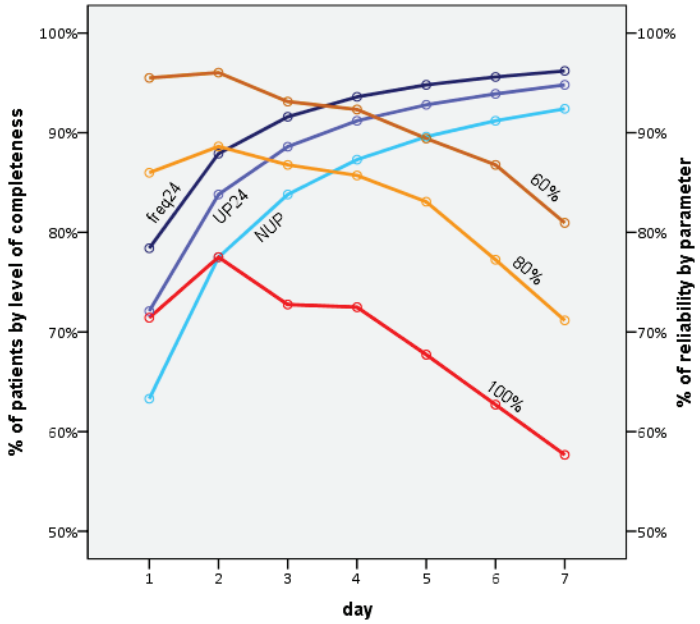


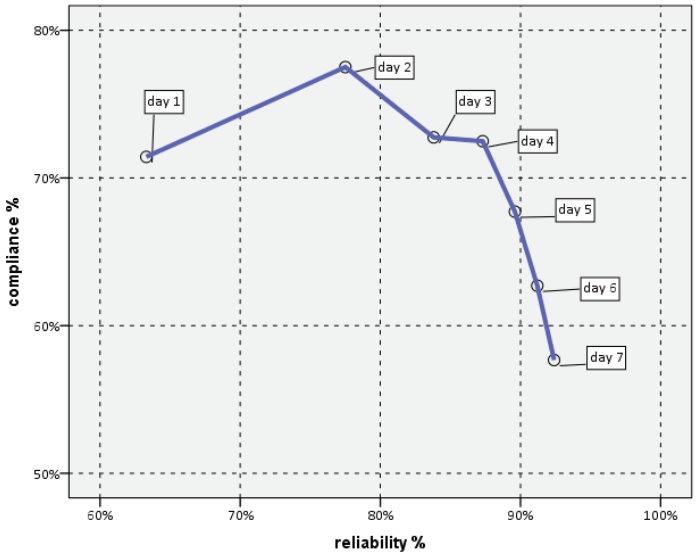
Table 2. Reliability of several FVC parameters by FVC duration.

			Reliability % at FVC duration (days)				
	ICC	95% CI ¥	1	2	3	5	7
24-h voiding frequency	0.78	0.75-0.81	78	88	92	95	96
24-h urine production	0.72	0.69-0.81	72	84	89	93	95
NUP ‡	0.63	0.58-0.68	63	78	84	90	92
Nocturia	0.66	0.61-0.70	66	79	85	91	93
Mean voided volume	0.80	0.77-0.83	80	89	92	95	96
Maximum voided volume	0.64	0.60-0.68	64	78	84	90	92

ICC = intraclass correlation coefficient
CI = confidence interval
NUP = nocturnal urine production

‡ NUP was measured over 6 nights, because the 7th night was incomplete in most cases due to missing records of the first morning void on the 8th day.
¥ CI of reliability on day 2 and up can be obtained by applying the Spearman-Brown formula on the lower and upper bound values of the first day ICC.

Figure 2. The relation between compliance (the percentage of patients with 100% complete recordings for both time and volume) and reliability for the nocturnal urine production.



Discussion

To the best of our knowledge, this study is the first in which documented compliance is related to the reliability of FVCs from day to day.

After 3 days, reliability for all FVC parameters is 80% or more and compliance is little above 70% (Figure 1). Although the rates of completeness generally drop below 70% after 4 days, the percentage of patients with nearly complete recordings (missing only one or two recordings in 24 hr) is above 80% at day 4. Lacking one or two records does not necessarily result in useless FVCs. We want to emphasize that the chosen levels of completeness are somewhat arbitrarily. Presentation of any percentile would be possible. We might just as well have chosen levels 100%, 75%, and 50%, or levels with steps of 5%. With a mean voiding

Table 3. Percentages of compliance vs. reliability of nocturnal urine production by diagnostic group.

	all		no LUTS		BPH		UTI		OAB & incont		other LUTS	
day	C	R	C	R	C	R	C	R	C	R	C	R
1	94	63	95	59	97	59	95	64	92	82	89	60
2	90	78	92	74	96	74	92	78	83	90	84	75
3	81	84	84	81	83	81	83	84	75	93	78	82
4	75	87	75	85	78	85	77	88	67	95	71	86
5	64	90	67	88	69	88	68	90	50	96	57	88
6	50	91	55	90	60	90	50	92	38	96	43	90
7	28	92	34	91	29	91	25	93	21	97	27	91

C = compliance, *R* = reliability.
The first two columns of the table are shown in figure 1, and in figure 2.

frequency of 9.1, loss of 10% of completeness reflects about one missed recording of a voiding event.
At day 5, reliability of more than 90% is achieved for all FVC parameters. Taking into account the large intraindividual variation of FVC parameters, recording of FVCs longer than 5 days does not seem useful.
These findings show that in general a 3-day FVC should be regarded as a reliable estimation of a patient's voiding pattern. However, the optimal duration of an FVC does not exist, because the aim of the FVC is the decisive factor. Longer recordings may be more informative but with a loss of compliance. In contrast, more emphasis on compliance will shorten the duration of the FVC. No rule states that the optimal duration must be at the intersection of the curves representing compliance and reliability; that optimal duration depends on the weight of each curve, and that weight will be assigned by the investigator.
For the individual patient, it will often be enough to get an initial impression of the voiding pattern. In that case, the completeness of the data seems more important than high reliability. When the results of a treatment or the natural course are of interest, more discerning details will be needed, implying higher reliability and thus a longer period of recording. For scientific studies, the present study provides clues for the proper planning of the needed number of patients, depending on the requirements of the data and the goals of the study.
Reports on compliance rates are remarkably different. In a study of 3-day FVCs in 188 BPH patients, 15% did not complete the first day [5]. Of the remaining 160 patients, 91 completed 3 days, resulting in 3-day compliance of 57% but overall compliance of 48%. In 14-day FVCs of 50 incontinent women, unlikely compliance of 100% was reported [6]. We have been able to identify only two studies calculating a day-to-day consistency of FVCs [14;15]. Locher et al showed that for 214 incontinent women recording 14-day FVCs, sufficient internal consistency (Cronbach's alpha>0.90) was achieved in 5 days for urgency incontinence and 7 days for stress incontinence [14]. Schick et al compared 7-days FVCs of 84 women [15]. They calculated that 4-day FVCs had nearly all its correlations above 0.95, and were almost equivalent to 7-day FVCs. Taking into account an assumed decrease of compliance they concluded that 4-day FVCs were preferable. The findings of these two studies are comparable with our study, although Locher et al. did not include compliance in judging FVCs.
Groutz et al used test-retest reliability of 1- to 3-day FVCs recorded in 2 weeks [12]. They found reliability of 0.83 for voiding frequency after a 3-day FVC. Although compliance decreased to 76% at day 3 for voided volumes, which is comparable to 73% in our study, they advocated that a 24-hr FVC was sufficient because on the 2nd and 3rd days the improvement in reliability was small compared to loss of compliance. Fitzgerald and Brubaker performed a test-retest reliability of 1-day FVCs in women without LUTS with an 8-months interval and found no significant differences using paired Mann–Whitney tests [9]. Mazurick and Landis correlated the first day with day 2 and 3 of a 3-day FVC, and concluded that a 3-day FVC was of no more benefit than a 1-day FVC [18]. Wyman et al performed a split-half reliability test of FVCs recorded by incontinent woman in two consecutive weeks [6]. Correlations varied between different FVC parameters, but it was concluded that 1-week was reliable in assessing urinary frequency. Nygaard and Holcomb studied incontinent women who recorded 7-day FVCs [13]. The first 3-days correlated well with the last 4-days and it was therefore concluded that 3-day FVC was sufficient. Gisolf et al found only small variations in the 24-hr mean voided volume in 3-day FVCs and concluded that a 24-hr FVC is sufficient and reliable [5]. Other reports, however, showed that the mean voided volume had the smallest variation of FVC parameters [19;20]. This finding is in agreement with the present study (Table 2). The reliability of FVCs

should be based on parameters with the lowest reliability, resulting from the highest variations, and not on those with small variations. In the present study we showed that NUP has the lowest reliability of all parameters including daytime voiding frequencies and voided volumes. In the present study, the differences between diagnostic groups were small. It should be noticed that the assignment of diagnostic categories did not comply with strict criteria, causing differences between groups to be exaggerated or ameliorated. Incontinent patients showed lower compliance, which can be explained from more missed volume recordings due to incontinence.

The assessment of compliance might limit the results of the study. The ''true frequency'' is still based on patient report, by recording coded letters. Mean urine production, however, is comparable with other studies [21-24]. Other types of voiding diaries that include urgency scales or fluid intake, might show different compliance rates.

Another limitation could be our recruitment strategy. No records were kept of patients that were not willing to participate. It was our general impression that these patients judged that it was of no benefit for them and too much hassle to join the study. A substantial number of patients who initially showed willingness to complete an FVC did not return the FVC. Some had second thoughts and were not motivated to participate, probably some did not want to confess their illiteracy, some forgot to return the FVC, and some patients did not return to the urologic outpatient clinic. We recorded no distribution list, so we can only speculate on the reasons. Both, the reluctance to record an FVC and the initially shown willingness to record which was not followed by actually returning an FVC, should be considered as a type of noncompliance. However, in general, compliance is addressing the degree of constancy and accuracy with which a patient follows a prescribed regimen, in this study the recording of an FVC. Moreover, reliability can only be assessed when the FVC is actually recorded. Therefore, such noncompliance has no influence on reliability and compliance of a patient who is keeping an FVC. Because we showed no important differences between diagnostic subgroups, we assume that the aforementioned group would not have altered the results.

The significant age difference between sexes is attributed to the groups OAB/incont and UTIs, the majority of which are women, whose diagnoses occur at younger ages than BPH in men. This difference between sexes has no influence on our results.

The number of patients with OAB/incont is lower than expected. Compliance for this group was lower than for other diagnostic groups (Table 3), so a larger number of these patients could have lowered the compliance rates. Further studies should clarify whether the results can be generalized across different populations of patients with various underlying disease processes.

Conclusion

A day-to-day analysis of 7-day FVCs showed a decrease in compliance and an increase in reliability. At day 3, reliability of 80% is achieved for all FVC parameters, but compliance drops to 73%. We advocate an FVC duration of 3 days, but the duration may be shortened or extended depending on the purpose or goal of the FVC.

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	الوقت	الحجم ب: مل
1	١ ساعة	١٠٧
2	١,٤٥ ساعة	١٠٠
3	٢,٢٥ ساعة	١٠٠
4	٢,٥٥	١٠٠
5	٣,٤٠	١٠٠
6	٤,٥٠	١٠٠
7	٦	١٤٠
8	٦,٢٥	١٨٠
9	٧,٠	١٤٠
10	١٠,١٠	١٥٠
11	١١,٤٠	١١٠
12	١٢,١٥	١٣٠
13	٢,٣٠	٩٠
14	٥,٤٥	١٥٠
15	٧,٤٥	٢٠٠

Chapter 7

The international prostate symptom score in relation to age and gender

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A cross-sectional study of the international prostate symptom scores related to age and gender in dutch adults reporting no voiding complaints

Abstract

Objective
To determine the IPSS in a selected population reporting no voiding complaints.

Subjects and methods
1143 adults without voiding complaints were included. They were divided over both sexes and all decades. All subjects filled out questionnaires including the IPSS. Statistical analysis was aimed at relating the IPSS to age and gender.

Results
The IPSS in both sexes shows a gradual significant increase in consecutive age groups. Men in the third age decade have a mean score of 2.8, while men older than 70 years of age have a score of 7.0. In women these scores are 4.0 and 5.6 respectively. The increase is about equally caused by storage and voiding scores. The items addressing weak stream in men and nocturia and urgency in men and women are the major factors causing the correlation with age. Nearly 17% of all subjects have moderate symptom scores and 1% has severe scores.

Conclusion
In both adult men and women reporting no voiding complaints the IPSS increases with age. This rise is more prominent in males.

Keywords: IPSS; LUTS; Asymptomatic; Cross-sectional study; Male; Female

Introduction

In 1992 Barry et al. reported the AUA-7 symptom index was a valid short questionnaire useful in the diagnostic work-up of voiding symptoms [1]. Subsequently it was adopted by the World Health Organization (WHO) and renamed the International Prostate Symptom Score (IPSS) after adding a disease-specific quality of life score [2]. Since then the IPSS has been widely used in the evaluation of lower urinary tract symptoms. After Abrams introduced the term LUTS replacing prostatism, the awareness broadened that voiding symptoms were not necessarily related to the prostate [3-6]. Many community-based studies have concluded that voiding problems are highly prevalent. Moreover, it has been recognized that LUTS are gender nor age-specific [7-11]. Although the IPSS has not been validated for women, they do have similar voiding symptoms or complaints. Differences between countries have been reported [12]. Most studies concerning the IPSS are community-based, i.e. including subjects with urinary symptoms, and address men over the age of 50 years [12-16]. Bosch et al. found in a population of 502 male subjects that 82% claimed to have no voiding complaints, while only 12% had an IPSS of 0 [13]. The objective of this study is to examine the IPSS and quality of life score in a population of men and women, selected on the absence of voiding complaints, equally distributed over age groups per decade above 20 years of age. In doing so we aim to define a frame of reference for patients with voiding complaints.

Subjects and methods

The study was part of an epidemiological survey on voiding habits. It was not population-based as subjects with voiding complaints were excluded, moreover initially mostly family members of patients and employees of the hospital and their relatives were approached. Each recruited individual was stimulated to invite other adults to participate. A positive answer to the questions ‘‘do you have voiding complaints now’’ and ‘‘are you being treated for voiding complaints now’’ would prohibit entry in the study. These questions were not previously validated. We aimed at including 100 men and women in each age decade. Volunteers were asked to fill out a questionnaire addressing voiding habits and urological symptoms, including the IPSS and the associated quality of life score. Other items addressed pelvic complaints and their treatment, general health, co-morbidity and medication. Dates and whether they were working days or leisure days were noted.

We collected data of 1749 volunteers. 480 subjects had to be excluded because one or more items of the IPSS or the quality of life question were missing. Another 126 subjects were excluded because of a positive answer to the initial questions ‘‘do you have voiding complaints now’’ and ‘‘are you being treated for voiding complaints now’’. This was obviously due to inappropriate instructions when distributing the questionnaires.

Available for analysis were complete data sets of 1143 volunteers, 556 men and 587 women, over 20 years of age. There was a slight over-representation of individuals from the 4th and 5th age decade, and a slight under-representation of the older age decades (Table 1).

The IPSS was subdivided into storage and voiding symptoms, previously named irritative and obstructive symptoms. The IPSS questions addressing incomplete emptying (item 1), intermittency (item 3), weak stream(item 5) and hesitancy (item6) contribute to the voiding score. The questions addressing frequency (item2), urgency (item 4) and nocturia (item 7) contribute to the storage score. The total score was divided into three groups with mild (IPSS <8), moderate (IPSS 8–19) and severe (IPSS >19) symptoms.

The relationship between the IPSS and age was modeled with linear regression analysis (LRA). For the non-linear relation between age and the quality of life score, as it is an ordinal variable, the Spearman's non-parametric test was used. Statistical significance was defined as a probability of less than 0.05.

Results

The results are summarized in Table 1. In men the mean IPSS increased from 2.8 in the third decade to 7.0 in men older than 70. In women the increase was less accentuated from 4.0 in the third decade to 5.6 in the oldest category. Although this increase with age is statistically significant, there is only a weak correlation between the IPSS and age (R2 0.11 and 0.02 in men and women, respectively, LRA $p < 0.001$; Figure 1).

Table 1. Characteristics of the IPSS per age decade and gender.

			mean (SD) IPSS			% of subjects with IPSS			
decade	sex	n	total	storage	voiding	0	≤ 7	8-19	≥ 20
20-29	M	85	2.8 (2.3)	1.9 (1.4)	0.9 (1.4)	4.8	86.2	8.5	5.3
	F	101	4.0 (3.5)	2.6 (2.0)	1.4 (2.2)	5.9	70.9	22.4	6.7
30-39	M	114	3.5 (3.8)	2.1 (1.9)	1.3 (2.4)	13.8	76.2	16.8	7.0
	F	127	3.7 (3.3)	2.6 (1.9)	1.1 (1.9)	7.9	81.7	16.3	2.0
40-49	M	128	3.8 (3.5)	2.1 (1.6)	1.7 (2.5)	10.2	75.3	20.7	4.0
	F	120	4.3 (3.3)	3.1 (2.0)	1.2 (2.2)	5.8	78.0	18.4	3.5
50-59	M	83	4.7 (4.0)	2.8 (2.4)	1.9 (2.3)	8.5	42.9	37.1	20.0
	F	94	5.0 (4.9)	3.4 (2.8)	1.6 (2.9)	8.5	70.6	21.8	7.6
60-69	M	67	5.9 (5.1)	3.5 (2.9)	2.4 (3.0)	7.6	33.1	46.9	20.0
	F	78	5.7 (4.7)	3.8 (2.6)	2.0 (3.2)	3.8	65.7	28.3	6.1
70 +	M	83	7.0 (5.2)	3.8 (2.7)	3.2 (3.5)	3.7	31.7	50.0	18.3
	F	67	5.6 (5.6)	3.9 (3.2)	1.7 (3.4)	7.5	56.0	38.0	6.0
All	M	556	4.4 (4.2)	2.6 (2.2)	1.8 (2.6)	8.6	81.1	18.2	0.7
	F	587	4.6 (4.2)	3.1 (2.4)	1.4 (2.6)	6.6	83.3	15.5	1.2

SD = standard deviation; M = male; F = female; n = number of subjects.

Relating the total score to severity revealed that 16.8% had moderate scores (IPSS 8–19), and 1% had even severe (IPSS >19) scores, with a similar distribution over the sexes.
On average, the storage score, representing 3 of the 7 IPSS items, has more weight than the voiding score, though in men this is less accentuated than in women. In both sexes the voiding and the storage scores about equally contribute to the increase of the total IPS-Score in consecutive age groups. Further analysis of the separate items of the IPSS show that in men in consecutive age groups the increase in voiding scores is mainly caused by the increase in the scoring of item 5 (weak stream). The increase in storage scores is predominantly due to an increase in the scoring of items 4 (urge) and 7 (nocturia). The contribution of the separate IPSS items to the total score is shown in Figure 2.
The mean score of nocturia (item 7) rises in consecutive age groups in men from 0.4 to 1.4 and in women from 0.7 to 1.5 (LRA $p < 0.001$ for both sexes; R2 men 0.146, women 0.104). The percentage of men with any nocturia increases from 31% in the youngest decade to 85% in the group over 70 years of age.
The question concerning the quality of life showed a consistent though not linear increase in men from 0.9 to 2.8 (mean values) in the oldest category (Figure 3). The graph suggests a

breakpoint at 50 years. In women this value increased with age from 1.8 to 2.3 (Spearman's correlation coefficient in men 0.413, in women 0.152, $p < 0.001$ for both sexes). Scores 0, 1 and 2 are the most prevalent. Scores of 3 or higher occur in both sexes in the age groups below

Figure 1. Scatter plot of the IPSS values by age and gender. Continuous lines are the regression lines, representing the mathematical formula in the upper left corner. Dotted lines are reference lines, indicating the subdivision in IPSS categories mild, moderate and severe.

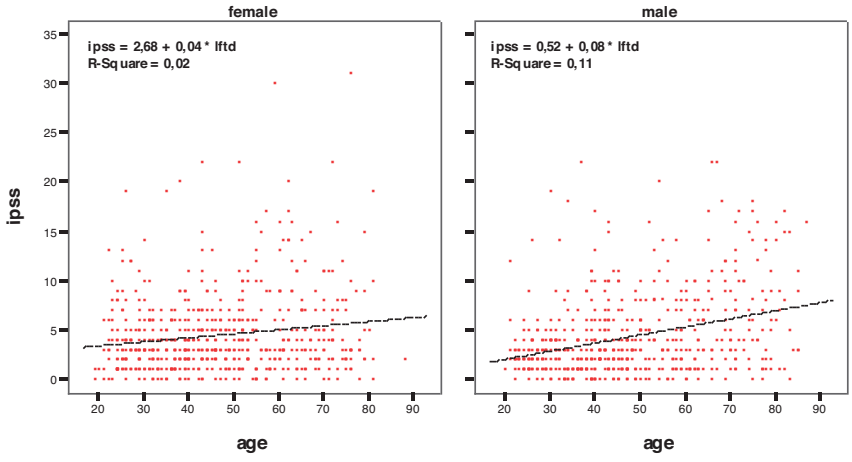
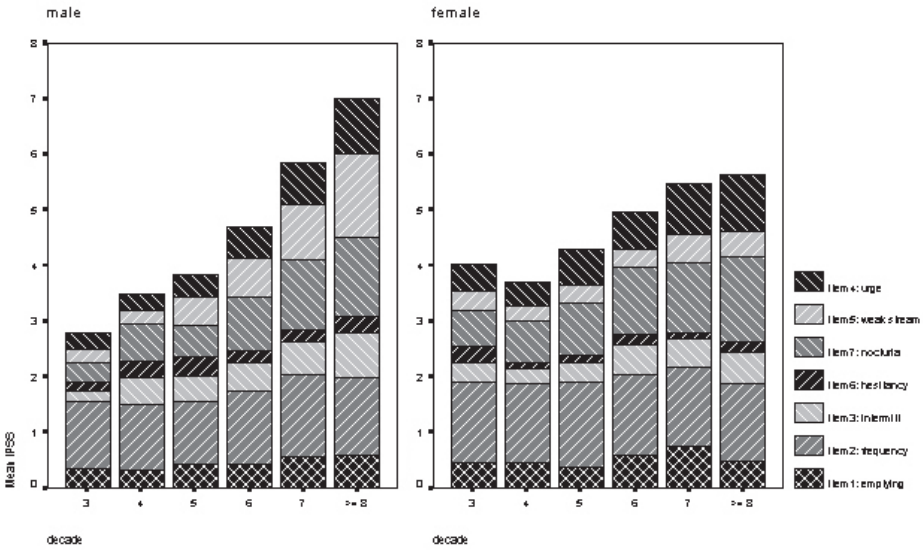


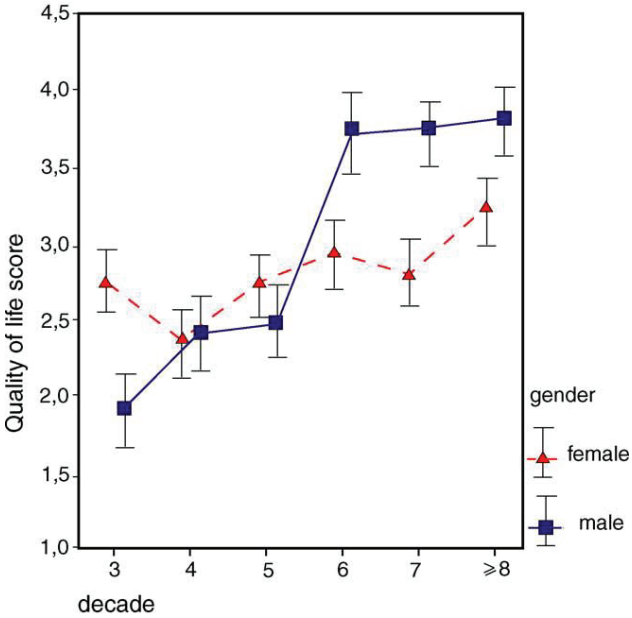
Figure 2. IPSS items stacked, per decade and per gender. Bars show mean values.



50 years in about 5%, and above 50 years in about 10%. In the older age groups the prevalence of the lower scores decreases. This trend is more prominent in men. The Spearman's correlation between the quality of life score and the IPSS in men and women was 0.58 and 0.53, respectively ($p < 0.001$). Multivariate regression analyses (stepwise method) shows a

positive significant correlation of the quality of life score with the IPSS and age (r^2 in men 0.40 and women 0.28; $p < 0.001$). There are significant though weak correlations with gender and with a history of pelvic surgery. The quality of life score is not correlated to the type of registration day, to the season or to the use of medication.

Figure 3. Quality of life score by gender and decade. Error bars show 95% confidence intervals of the means.



Discussion

The present study describes symptoms related to voiding in different age groups in a population of adult men and women without voiding complaints. The reported IPSS can be used as a frame of reference for subjects that do have LUTS. The non-existence of voiding complaints was based on two not validated questions. This group differs from a community-based population in which voiding complaints are not excluded. Moreover, community-based studies are likely to be biased by an overrepresentation of symptomatic subjects, as these seem to be more motivated to participate. However, we found no reports analyzing the non-respondents.

We compared different age groups, though we realize that a cross-sectional study could introduce some bias. Younger adults who will develop voiding complaints later are now included, while they would be excluded at older age. Since these individuals can not be identified, one can only speculate what influence they have on the scores of the younger age groups. If these individuals would have scores above average at younger age, omitting their data would result in lower scores in the lower decades, thereby only accentuating the increase of the IPSS with age. An assumption that their scores at a young age would be below average is not very obvious, but would diminish the slope of the IPSS increase. It is also possible that with time the perception of the complaints changes. Only a cohort study could answer these questions.

Most studies on LUTS have been confined to a male population over 50 years of age. Sommer et al. evaluated men between 20 and 79 years and found a significant increase in both voiding, storage and total symptom scores in the fifth and sixth decade [10]. Desgrandchamps et al. reported on an IPSS study in an unselected population of 161 women of all ages [17]. The present study showed that lower urinary tract symptoms are prevalent in all age categories above 20 years in men as well as in women. This sustains the concept of LUTS being not organ or disease specific, nor is it reserved to a certain gender or age [18-20]. As was noticed by Chute et al. these findings underline the possibility of having LUTS without having an actual complaint which might lead to consultation with a general practitioner or an urologist [14]. Araki et al. studied the IPSS in a population of men and women of 40 years or older [21]. In contrast to the present study, all subjects had a urological examination, and in those presenting with LUTS an urodynamic test was performed. In those in whom no urological related disorder was found the IPSS was analyzed. Although the selection criteria were stricter than in the present study, in general the same trends were reported.

The present study demonstrates in both genders a more or less gradual rise in the total IPSS with increasing age. As would be expected, age is only a minor contributing factor in the IPSS which is demonstrated by the wide variance in all age groups. Therefore the correlation is weak. This is consistent with the report of Bosch [13]. With every decade the IPSS increases in men by about one point and in women by a half point (Figure 1). It seems obvious that these findings are clinically not relevant in the individual patient. However, it is important to notice that adults without voiding complaints do have voiding symptoms, and that these are more prevalent at an older age. In order to clarify the nature of these findings, further analyses were performed as reported.

Until the age of sixty years these scores in men and women are not very different. After the age of 60 years the total score in men has a tendency to increase further while in women there is a diminished increase. In our study we made a distinction between storage and voiding scores corresponding with items in the IPSS. This distinction has been validated in earlier studies although the clinical usefulness has never been proven [10;22;23]. Women up to the age of 50 years have a higher storage symptom score (questions 2, 4 and 7), after which age the storage scores in men and women equalize. The explanation for the initial higher storage score in the female population in this study remains uncertain. Higher storage scores in women were also found by Araki et al., Desgrandchamps et al. and Madersbacher et al., and the authors suggest structural alterations of the ageing detrusor, endocrine disturbances effecting lower urinary tract function, and changes in the diurnal urine production as possible explanations [9;17;21]. The functional bladder capacity does not seem to be an explanatory factor, for results of our study using a voiding diary, reported recently, show a distribution of the maximal voided volume that does not resemble that of the storage scores [24]. The voiding scores (questions 1, 3, 5 and 6) are more or less alike for both genders until the age of 60 years. In men above this age there is a tendency, though not significant, to further increase compared with women, in whom the voiding scores seem to stabilize. The influence of BPH on the voiding score in elderly men in general can be assumed, although it is not proven by this study. Although we selected our participants by the absence of voiding complaints, the presence of BPH in our male population cannot be excluded. The existence of an enlarged prostate was not evaluated, nor was uroflowmetry performed.

The development of the score on the individual items and the total IPSS in men with increasing age in this study is comparable with the results in other studies. The development of the score concerning nocturia (question 7) in this study resembles the results of the study by Bosch et

al. using the IPSS in a community based Dutch male population [13]. We note an almost similar rise in nocturia in the different age groups of men and women.
In this study the quality of life score is correlated to the IPSS (r = 0.58 and 0.53 in men and women). However, the correlation is somewhat weaker than in other studies addressing men, reporting 0.71 [1] and 0.74 [13]. The lower correlation is probably a reflection of the subjects' claim to be without voiding symptoms. There is a remarkable, though low, number of subjects with high scores for the quality of life, which remains unexplained.

Conclusion

Voiding symptoms, as measured by the IPSS, are very common in both men and women who reported no voiding complaints. These data suggest that voiding symptoms, even in the moderate to severe range, are often not perceived as complaints, probably because they are thought to be part of a changing physical status. Furthermore this study confirms lower urinary tract symptoms as being neither gender nor age specific.
In this cross-sectional study of adult men and women the total IPSS increases in consecutive age groups. This increase is more pronounced in men. Nearly 17% of all subjects have moderate symptom scores and 1% has severe scores. The mean quality of life score rises as a reflection of the increase in total IPSS, but in this study seems not to be translated into complaints. The voiding score in men and women initially is comparable, but in men over 60 years of age this score rises to a higher value. Women in the younger age decades score higher on the storage items but in the higher age decade this score for men and women is about equal.

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Chapter 8

The international prostate symptom score overestimates nocturia assessed by frequency-volume charts

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The international prostate symptom score overestimates nocturia assessed by frequency-volume charts

Abstract

Objective

We analyzed differences in nocturia, as estimated by the International Prostate Symptom Score and 7-day frequency-volume charts.

Subjects and methods

A total of 398 forms were collected from 500 consecutive urological outpatients willing to record a 7-day frequency-volume chart. All patients completed a general questionnaire, an International Prostate Symptom Score, and a bladder symptom and bother score. Missed recordings were indicated by a coded letter. Patients who lacked essential data, bedtimes or an International Prostate Symptom Score, or who recorded the frequency-volume chart for less than 5 days were excluded from study.

Results

A total of 186 men and 115 women with a mean age of 56 years were evaluable. In 10.6% of patients no nocturia occurred. Of those with nocturia 70% and 34% experienced nocturia a mean of 1 or more and 2 or more times, respectively. In 43% of patients the International Prostate Symptom Score equaled calculated categorized nocturia while 50% had a higher International Prostate Symptom Score nocturia score than calculated nocturia. On univariate analysis the correlation of International Prostate Symptom Score question 7 with mean nocturia increased with frequency-volume chart duration (day 1 $r = 0.52$ to day 3 $r = 0.63$). On longer duration frequency-volume charts the correlation showed no further increase. Multivariate regression analysis revealed that the nocturia score was determined by mean nocturia in the frequency-volume chart, the nocturia bother score and patient age.

Conclusions

The International Prostate Symptom Score nocturia score overestimated nocturia in most patients, as derived from a 7-day frequency-volume chart. When scoring International Prostate Symptom Score nocturia question 7, patients included a degree of bother. The correlation of question 7 with mean nocturia increased with frequency-volume chart duration until day 3.

Key Words: urinary bladder; questionnaires; nocturia; urination disorders; quality of life

Introduction

The American Urological Association symptom index was established in 1992 as a validated 7-item scoring system for LUTS [1]. Subsequently a quality of life (QoL) question was added and this system became known as the International Prostate Symptom Score (IPSS). Currently the IPSS is one of the most frequently used scoring systems to assess patients with LUTS.
A significant proportion of patients with LUTS have nocturia as the most bothersome symptom [2]. Nocturia becomes a problem when it interferes with normal sleep, and the result is a serious impact on daily life [3;4].
Reports of nocturia differ in the data collection method, which can be based on questionnaires, interviews or frequency-volume charts (FVCs). A few groups noted relevant differences in questionnaire based estimates of nocturia and nocturia values derived from FVCs [5-7]. For LUTS and nocturia several guidelines recommend or suggest that the patient complete a FVC [8-10].
We compared nocturia, as estimated by the IPSS and a 7-day FVC, and analyzed dependent factors.

Subjects and methods

All adult patients who visited the outpatient urological clinic at 2 hospitals from June 2008 to January 2009 were requested to record a paper FVC for 7 days regardless of the reason for the urological visit (table 1). Those willing to do so were asked to record height, weight and daily activity, and complete a general questionnaire, the IPSS and the International Consultation on Incontinence Questionnaire-OAB Questionnaire (ICIQ-OABq). The latter is a score to categorize bladder storage symptoms [11]. The ICIQ-OABq scores 4 symptoms, including nocturia, and has an additional question on the bother of that symptom. Scores reflect the last 4 weeks. The nocturia question is, “During the night, how many times do you have to get up to urinate, on average?” The question can be answered none, or 1 to 4 or more. The next question is, “How much does this bother you?” This can be answered 0—not at all to 10—a great deal. IPSS question 7 on nocturia is, “In the last month, how many times did you most typically get up to urinate from the time you went to bed until the time you got up in the morning?” This can be answered none, or 1 to 5 or more.
Subsequently patients received a measuring can, written instructions and forms to record the FVC, including 1 for each day and the subsequent night. A total of 500 of forms and cans were distributed. No records were kept on which patients received the forms.
In accordance with International Continence Society instructions patients had to record the date, the time and volume of each daily void, and the times of rising in the morning and going to sleep at night. On day 8 only the time of rising was recorded but first void time and volume were not requested. When patients could not record a voiding moment or voided volume, the missed measurement was documented by a coded letter indicating the reason for the missing record.
The records of patients lacking essential data, such as gender, birthday and dates, were excluded from study and not entered in the database. Patients who recorded fewer than 5 nights or bedtimes and those missing the IPSS nocturia item were also excluded from analysis. The principles of the Helsinki Declaration were followed.
The records of all patients were reviewed and each patient was assigned a categorized diagnosis. For each patient nocturia was calculated for each recorded night. We subsequently

estimated the highest and lowest nocturia values, the difference between those 2 values and the mean of all nocturia values.
IPSS question 7 on nocturia assigns the highest score of 5 to 5 or more nocturia episodes per night. Thus, when comparing the IPSS nocturia score with FVC calculated nocturia, maximum and mean nocturia values that scored higher than 5 were considered 5. We also categorized mean calculated nocturia by rounding values to the nearest integer to correlate it with IPSS values.
SPSS® Statistics was used for data analysis. Groups were compared by ANOVA. The Pearson correlation coefficient r was used to test the relation of several parameters. Differences in correlations were analyzed using the Hotelling T statistic.
Multivariate linear regression analysis was done with backward exclusion of variables using an exclusion cut-off at $p < 0.10$. This was performed with IPSS question 7 as the dependent variable and with the independent variables of patient age, body mass index, FVC mean and maximum nocturia, mean and maximum nocturnal urine volume, maximum bladder capacity, the ICIQ-OABq nocturia bother score and the IPSS QoL question. The unstandardized coefficient B represents the increase of the slope of the regression line for each unit increment of the specified variable. Statistical significance was considered at $p < 0.05$.

Results

Patients

The forms of 398 patients were collected. Of the patients 97 were excluded from analysis, including 20 for lacking data on essential characteristics that were not entered in the database, 19 for lacking all nocturnal records, 45 for recording fewer than 5 nights and 13 for lacking IPSS question 7. Of the excluded 97 patients 77 were entered in the database and IPSS was recorded for 53, for whom mean IPSS was 15.1 ($p = 0.19$). Thus, 301 records were included, including those of 186 men and 115 women with a mean age of 56 years (60.0 and 49.1, respectively, range 19 to 87, $p < 0.001$). Table 1 shows the diagnostic groups.

Table 1. Groups of diagnosis.

	No. of men	No. of women	Total, *n*	%
No LUTS	16	13	29	9.6
LUTS not specified	37	16	53	17.6
BPH	64	0	64	21.3
Urinary tract infection	26	55	81	26.9
OAB	13	10	23	7.6
Stress incontinence	2	9	11	3.7
Urolithiasis	7	5	12	4.0
Malignancy	13	1	14	4.7
Pain	8	6	14	4.7
Totals	186	115	301	100.0

LUTS = lower urinary tract symptoms; BPH = benign prostatic hyperplasia; OAB = overactive bladder and urgency incontinence.

Nocturia

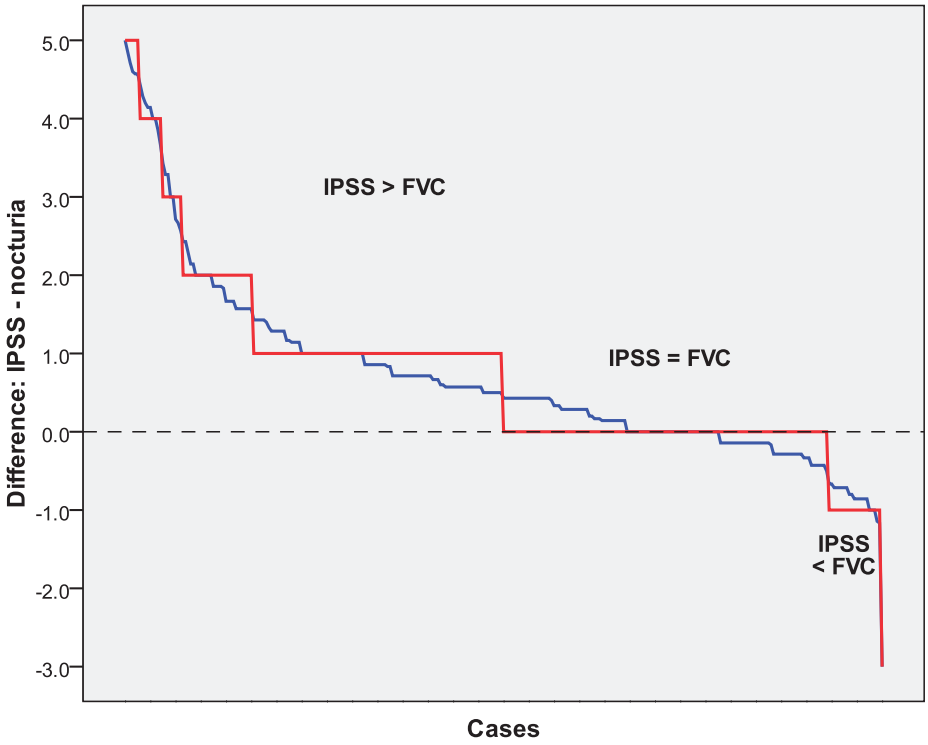
The 301 patients recorded a total of 2,022 nights (mean 6.72). The number of completely recorded nights was 7 in 231 patients (77%), 6 in 55 (18%) and 5 in 15 (5.0%). A total of 3,091

nocturnal voids (mean 1.5) were recorded. During the study period no nocturia occurred in 32 patients (10.6%). Of those with nocturia 70% had a mean of 1 episode or more and 34% had 2 or more.

Comparison with IPSS

There was no difference in mean IPSS between men and women (13.8, range 0 to 32 and 13.0, range 1 to 33, respectively, $p = 0.40$). However, IPSS nocturia question 7 differed in men vs women (2.4 vs 1.9, $p = 0.009$). Mean IPSS did not differ in patients younger than 60 vs 60 years or older (mean 13.2 vs 13.9, $p = 0.45$). However, IPSS question 7 differed (1.8 vs 2.7, $p < 0.001$). The mean IPSS question 7 score was 2.2 and mean FVC derived nocturia was 1.5 (paired sample t test $p < 0.001$). The difference between these parameters (question 7 minus calculated nocturia) showed wide variation from -3.0 to 5.0 (see figure 1). IPSS equaled calculated categorized nocturia in only 43% of cases. Of the patients 50% had a higher IPSS question 7 result than calculated nocturia and in 17% the difference was 2 or more points. Only 7% of patients had lower question 7 values. We found no difference in agreement between patients younger vs older than 60 years (40% vs 46%) or in men vs women (45% vs 39%, each $p = 0.3$). In patients with LUTS or overactive bladder (OAB) the mean question 7 score was 2.7 and the mean FVC derived nocturia score was 2.2 ($p < 0.001$). The distribution of differences revealed no relevant differences in the whole group.

Figure 1. Difference between IPSS question 7 (nocturia), and FVC mean (blue line) and categorized mean (red line) nocturia. Cases were sorted by difference.



Multivariate linear regression analysis showed that question 7 was determined by mean FVC nocturia, the nocturia bother score and patient age (table 2). The overall model fit was $r^2 = 0.487$. Subanalysis by gender did not influence these results.

Table 2. Results of linear regression analysis with the IPSS nocturia question as the independent variable.

Variable	Mean	SD	Univariate correlation coefficient	Unstandardized coefficient (B)	SE	*p*
Age (yr)	55.9	16.3	0.296	0.016	0.005	0.001
Body mass index (kg/m^2)	25.8	4.4	0.160			
IPSS quality of life	3.1	1.5	0.350			
Nocturia bother score	3.6	4.5	0.605	0.170	0.025	<0.001
Nocturia, mean	1.5	1.3	0.633	0.383	0.070	<0.001
Nocturia, maximum	2.7	2.0	0.598			
Nocturnal volume, mean	512	286	0.309			
Nocturnal volume, maximum	770	467	0.341			
Maximum bladder capacity	510	264	-0.089			

SD = standard deviation; SE = standard error.

Mean nocturia was calculated for the first 1 to 5 days and correlated to IPSS question 7 ($r = 0.52$, 0.58, 0.63, 0.64 and 0.64, respectively, each $p < 0.001$). Correlations were compared with the correlation of the 7-day FVC to IPSS question 7 ($r = 0.63$). One and 2-day FVCs showed lower correlations than the 7-day FVC ($p = 0.003$), in contrast to 3-day ($p = 0.42$) or longer FVCs. When we selected only men with BPH, the correlation of mean nocturia on the 7-day FVC with question 7 was only a little lower ($r = 0.60$).

8

Discussion

In our study fewer than half of the patients had an IPSS nocturia score that equaled the number of nocturnal voids (rounded to integers) derived from a 7-day FVC. Half of the patients overestimated nocturia on the IPSS. The IPSS nocturia score correlated modestly with actual nocturia ($r = 0.63$). The age related nocturia rate in our study agreed with previously reported rates [5;12;13].

Results show that mean nocturia on the FVC is the major determining factor for IPSS question 7. This is in accord with expectations since IPSS question 7 is designed to reflect the number of nocturnal voids. However, nocturia bother was another important determining factor. To our knowledge this finding is new and important.

Apart from nocturia and its bother our study reveals that patient age is an independent but small determinant of IPSS question 7. Although IPSS increases with age in each gender [14], there is no reason to expect older patients to score the same symptom higher than younger patients. We have no explanation for this age factor.

In a 1996 article stressing the value of FVCs Abrams and Klevmark noted, “Patients who are inconvenienced or disturbed by their symptoms might be expected to overemphasize (exaggerate) the frequency and severity of their complaints.”[15] Others agreed with that statement on nocturia since each found a modest correlation of IPSS question 7 and the

calculated nocturia with an overestimation of question 7 [7;16]. However, none found evidence of a role for symptom bother.
Blanker et al evaluated data on 1,211 males who kept a 3-day FVC [5]. At all ages the intraclass correlation of IPSS nocturia question responses with FVC data was 0.30. In older age categories the correlation was higher than in younger groups. The group found only minor agreement of the 3 methods to estimate nocturia without specifying the percent.
Gisolf et al evaluated the 1 to 3-day FVCs of 160 males [16]. The percent of agreement between IPSS and FVC nocturia was not reported but they found a modest correlation (r = 0.44). There was no relation between nocturia derived from the FVC with the QoL score [17].
Ku et al studied 164 patients using a 3-day FVC and noted agreement of nocturia using IPSS and FVCs in 32.3%, including 39.2% younger than 60 years and 22.4% 60 years or older (r = 0.609, p = 0.024)[6]. It was unclear from the results whether the IPSS was compared with FVC mean values or rounded means.
Yap et al studied 3-day FVCs of 140 men 40 years or older with uncomplicated LUTS and noted a correlation of 0.44 [7]. Predicted IPSS was estimated to increase by 0.3 for each unit increase in the IPSS QoL variable, suggesting that differences in QoL ratings explain some overestimation. Nonetheless, in our series the regression model explained only 49% of the variation in IPSS nocturnal voids among patients.
In contrast to previous studies, we included a bother score of storage symptoms, which enabled us to construct a more accurate model for IPSS question 7. Our study also differs from these previous studies in our use of a 7-day FVC. We found a higher correlation between nocturia and IPSS question 7 than previous groups using 1 to 3-day FVCs. This may have been the result of recording a whole week, which is a better reflection of the previous month than indicated by the IPSS time frame. However, compared with the mean nocturia correlation of the 7-day FVC with question 7 we found differences only in correlations of 1 and 2-day FVC durations, and not 3 or more days.
Although IPSS content validity and reproducibility have been proved, to our knowledge the IPSS construct validity of reflecting a period of 1 month has not been proved. Our results suggest that patient recall reflects a shorter period. Another explanation of the higher correlation might be that all patients may have indicated missed recordings, thus, improving FVC validity with respect to voiding frequency.
We found no indication that selecting patients other than elderly patients and men with BPH influenced the results since the correlation between the mean nocturia values of the 7-day FVC and IPSS question 7 was only a little less (r = 0.60 vs 0.63). The study population was of all adult ages and included each gender. Regression analysis revealed no major difference between the genders. When assessing symptoms, the final diagnosis should not influence the initial symptom score.
A perfect symptom score should reflect the measured symptom exactly as it is. However, due to the inevitable categorizing of scores a perfect match is not always achieved. Moreover, due to the wide inpatient variation of voiding patterns a single normal voiding pattern does not exist. As noted by others, it is likely that the IPSS reflects actual symptoms and bother. We found evidence of that.
The International Continence Society BPH study suggested that symptom occurrence alone does not necessarily reflect the degree to which patients are bothered by LUTS [18]. The exact agreement between bother and actual symptoms is less important. By incorporating a degree of bother IPSS question 7 seems to be a good indicator of the need to start or change nocturia

treatment. However, an FVC is obligatory to evaluate the nature of nocturia. As such, FVCs and the IPSS are complementary tools to analyze LUTS.

Conclusions

The IPSS nocturia score overestimated the nocturia derived from a 7-day FVC in most patients. When scoring the IPSS, patients included a degree of bother. The correlation of IPSS question 7 with mean nocturia increased with FVC duration until day 3. Longer duration FVCs did not improve this correlation. To analyze nocturia FVCs are obligatory but should be used to complement rather than verify the IPSS.

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مدة زمنية

	MiddAG	أدوات
3+	63-TOT9	
2+	9-TOT 11	
3+	11-TOT 30 44R	
3X	30TOT 5 44R	
1X	5-TOT 6	
2X	6-TOT 8	

Chapter 9

A cut-off value based on analysis of a reference population decreases overestimation of the prevalence of nocturnal polyuria

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A cut-off value based on analysis of a reference population decreases overestimation of the prevalence of nocturnal polyuria.

Abstract

Objective

We sought criteria for nocturnal polyuria in asymptomatic, nonurological adults of all ages by reporting reference values of the ratio of daytime and nighttime urine volumes, and finding nocturia predictors.

Subjects and methods

Data from a database of frequency-volume charts from a reference population of 894 nonurological, asymptomatic volunteers of all age groups were analyzed. The nocturnal polyuria index and the nocturia index were calculated and factors influencing these values were determined by multivariate analysis.

Results

The nocturnal polyuria index had wide variation but a normal distribution with a mean ± SD of 30% ± 12%. The 95th percentile of the values was 53%. Above this cut-off a patient had nocturnal polyuria. This value contrasts with the International Continence Society definition of 33% but agrees with several other reports. On multivariate regression analysis with the nocturnal polyuria index as the dependent variable sleeping time, maximum voided volume and age were the covariates. However, the increase in the nocturnal polyuria index by age was small. Excluding polyuria and nocturia from analysis did not alter the results in a relevant way. The nocturnal voiding frequency depended on sleeping time and maximum voided volume but most of all on the nocturia index.

Conclusions

The prevalence of nocturnal polyuria is overestimated. We suggest a new cut-off value for the nocturnal polyuria index, that is nocturnal polyuria exists when the nocturnal polyuria index exceeds 53%. The nocturia index is the best predictor of nocturia.

Key Words: urinary bladder; urination; nocturia; reference values; urination

Introduction

Nocturia is one of the most bothersome lower urinary tract symptoms. Several causative categories are recognized, including low maximum nocturnal voided volume, general polyuria and nocturnal polyuria (NP), including combinations of these causes in some cases, and sleep disorders. It is assumed that this classification is useful for understanding and treating the problem. The need to treat a patient is determined by the potential physical harm when the problem goes untreated and by the degree of bother that a patient experiences. When assessing patient status, a key step is to determine a cutoff or a reference value above or below which treatment initiation is appropriate. However, the first issue is which group should serve as the reference group, including those without complaints, those without symptoms, those without nocturia or polyuria, those who are elderly or maybe a combination.

Nocturia evaluation implies the use of frequency-volume charts (FVCs). Several nocturia indices (NIs) were introduced in 1998 and seem to have gained some acceptance [1]. The nocturnal polyuria index (NPi) is the ratio of nocturnal urine production (NUP) to total 24-hour urine production. The NI is calculated as NUP divided by FBC, where FBC is the largest single void in a typical 24-hour period.

A prerequisite when considering NP is normal 24-hour urine output [2;3]. The International Continence Society (ICS) defines general polyuria as a urine output of more than 40 ml/kg of body weight during a 24-hour period. Often definitions of volume only are used, varying from more than 1,800 ml for females and more than 2,200 ml for males [4] to more than 2,500 ml [1;5]. Studies of asymptomatic subjects showed that the 95% upper limit of the values was more than 3,000 ml [6-8]. With an assumed average body mass of 70 kg the ICS definition advises a cutoff of 2,800 ml.

An accurate, generally accepted definition of NP is a prerequisite for any meaningful discussion of clinical significance [3]. In older individuals NP is defined by the ICS as NUP exceeding 33% of total 24-hour urine output but a lower cutoff of 20% is suggested for younger individuals [2]. Subsequently the nocturia think tank at an International Consultation on Incontinence-Research Society meeting in 2010 noted that no group had assessed the validity of these cutoffs in clinical practice [9].

We sought criteria for NP in adults of all ages without urological complaints by reporting reference values of the ratio of daytime and nighttime urine volumes.

Subjects and methods

Data from a database of 1,152 FVCs were used. An analysis of the frequency and volume data of these FVCs was previously published [6]. Adult volunteers without a urological complaint or a urological history completed questionnaires and 24-hour FVCs. Volunteers were recruited from hospital staff and families, and patient families. The principles of the Helsinki Declaration were followed. All subjects were instructed not to change fluid intake habits.

Recording started with the first micturition after rising and finished with the first morning micturition the next day. During this period time in hours and minutes, the volume of each void, the time of rising on days 1 and 2, and the time of going to bed were recorded on a standard form. All subjects were provided with a water can capable of measuring 25 ml units. Dates and whether the dates indicated working or leisure days were noted. Day of the week and season were derived from the dates.

Volume and frequency were defined as described by the ICS [2]. Diurnal urine production was the sum of all voided volumes while the subject was awake and out of bed minus the first voided

volume, which was regarded as part of the preceding night. The NUP was calculated from all voided volumes during the night and the subsequent first voided volume the next morning. In those without nocturia the NUP was represented by the first morning void only.
The volume of the first morning void on day 2 was missing for 183 subjects, who were excluded from analysis. For some individuals a large interval occurred between the last daytime void and bedtime or between rising and the first morning void. We excluded another 75 subjects for whom these intervals exceeded 25% of sleeping time since we assumed that this might have a relevant influence on the NPI.
Subject body weight was not recorded. Thus, we defined general polyuria as a 24-hour urine output of more than 2,800 ml, in accordance with the ICS definition [2].
The actual recorded period was calculated as the time difference between the first morning void on days 1 and 2. Since recorded periods of 24 hours are often not exact due to differences in the time of rising and, subsequently, for the first morning void 24-hour and daytime volumes were adjusted to exactly 24 hours. Because the night was completely within this period, nocturnal volumes were not adjusted.
To identify NPI determinant factors we performed multivariate linear regression analysis with the NPI as the dependent variable. Univariate analysis was used to select variables. All relations were tested for linearity. Tested variables were gender, age, sleeping time, date (day of the week, month and season), urine production (24-hour and daytime) and maximum voided volume (24- hour and nighttime). Voiding frequency was not tested as a potential determinant of NPI since it is the result rather than the cause of the ratio of NUP to diurnal urine production. Regression analysis was done with backward exclusion of independent variables and an exclusion cutoff of $p < 0.10$. In the constructed model with each 1 unit increase in an independent variable the NPI increased by the value of the unstandardized coefficient β.
IBM® SPSS Statistics 19.0 was used for data analysis. The Pearson correlation coefficient r was used to test the relation of several parameters with statistical significance considered at $p < 0.05$.

Results

Data from the FVCs of 436 men and 458 women 19 years or older were available for analysis. Table 1 lists patient characteristics. Mean age was 47.7 years for men and 45.5 years for women ($p = 0.04$). Table 2 shows the distribution by 10-year age strata.
In 489 subjects (55%) no nocturia occurred. One, 2 and more than 2 nocturia episodes occurred in 286 (32%), 87 (10%) and 32 subjects (3%), respectively. NPI had a normal distribution (Figure 1). By decade the 95th percentile showed small variations, which increased to 57% in the seventh decade (Table 2). An NPI of more than 60% occurred in each decade. Of all subjects 66 had general polyuria, 105 had 2 episodes or more of nocturia and 14 had each condition. After excluding these 185 subjects mean ± SD NPI was 29% ± 10.6%. The 95th percentile was 48%.

Table 1. Characteristics of the studied population.

	mean	SD	range
Age (yr)	46.6	16.1	19 - 87
IPSS	4.4	4.1	0 - 30
Quality of Life score (IPSS)	1.2	1.1	0 - 6
Actual duration of the FVC (h:mm)	23:22	1:28	15:09 - 27:30
Time in bed (sleep time) (h:mm)	8:15	1:14	3:25 - 14:00
Interval last daytime void to bed time (h:mm)	0:17	0:26	0:00 - 2:30
Interval rising to first morning void (h:mm)	0:03	0:11	0:00 - 2:00
24-hour urine output (ml)	1810	761	322 - 6335
24-hour voiding frequency	7.2	2.5	2 - 19
Daytime urine output (ml)	1236	616	185 - 5460
Daytime voiding frequency	6.5	2.2	2 - 18
Nocturnal voiding frequency	0.6	0.9	0 - 0 – 7
Maximum voided volume (24-h)	467	179	80 - 1200
Maximum nocturnal voided volume	350	172	40 - 1000
Nocturnal urine output (ml/night)	526	291	10 - 2400
Nocturnal urine output (ml/h)	64	35	2 - 306
Nocturnal Polyuria index (%)	30.8	11.8	2 - 76
Nocturia index	1.19	0.61	0.03 6.18

Figure 1. NPI histogram. Curve represents normal distribution. Dashed line represents mean. Dotted line represents 95th percentile.

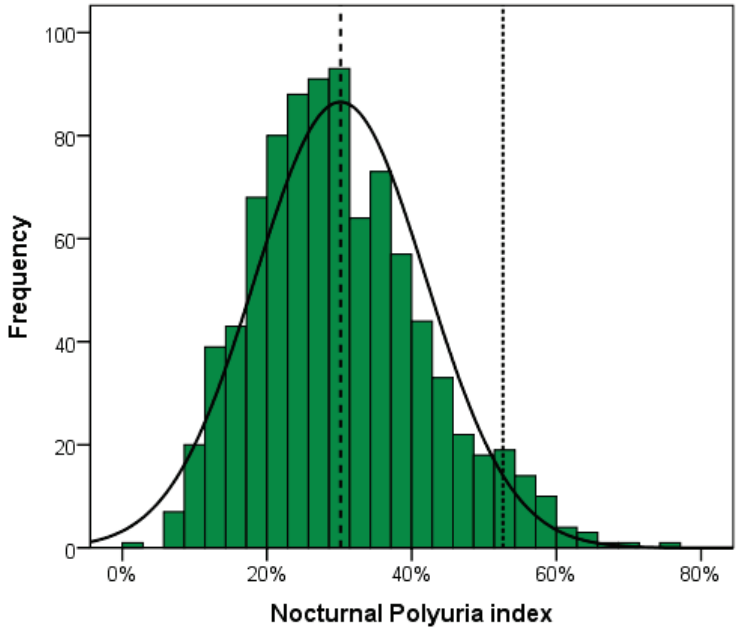
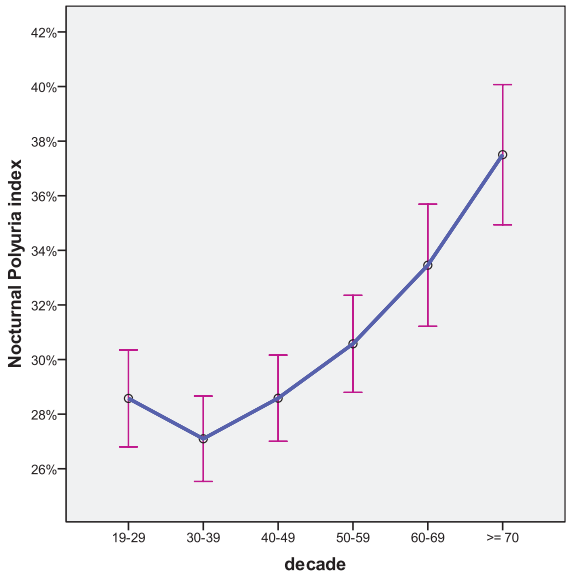


Table 2. Nocturnal Polyuria Index by 10 year age strata.

age	n	female	male	mean	SD	range	95th percentile
19-29	166	92	74	29.6	11.8	8 - 64	54.8
30-39	193	107	86	28.1	11.5	2 - 71	46.7
40-49	185	84	101	29.2	10.9	8 - 76	49.4
50-59	141	76	65	31.0	10.5	10 - 59	50.5
60-69	111	58	53	33.6	11.8	7 - 64	55.4
>= 70	98	41	57	37.4	12.5	9 - 66	57.6
all	894	458	436	30.8	11.8	2 - 76	53.1

With all 894 subjects included univariate analysis of FVC parameters revealed a moderate correlation of the NPI with nocturnal voiding frequency ($r = 0.51$). This was considered the result of the NPI rather than a causative factor and was not included on multivariate analysis. The NPI did not correlate with gender ($p = 0.77$), or the day of the week ($p = 0.24$) or season ($p = 0.15$) in which FVC recording started. Maximum voided volume ($r = 0.06$, $p = 0.06$) dropped out on multivariate analysis. Multivariate regression analysis with the NPI as the dependent factor demonstrated that age (β = 0.1 per year), maximum nocturnal voided volume (β = 1.0/ 100 ml), sleeping hours (β = 1.7 per hour), daytime urine production (β = –3.3/100 ml) and 24-hour urine production (β = 2.1/100 ml) were covariates (each $p \leq 0.001$). The model was quite good at explaining the NPI (overall model fit $r^2 = 0.735$).
The relationship between NPI and 10-year age strata showed wide variation while the mean demonstrated a mild increase by age stratum (ANOVA $p < 0.001$, Figure 2). A comparison of subjects younger than 50 years vs 50 years or older revealed only small differences with a mean of 28.9% and 33.6%, and a 95th percentile of 50.0% and 54.1%, respectively.

Figure 2. Mean NPI by age decade. Error bars indicate 95% CI of mean.



Nocturnal voiding frequency had good correlation with the NI (r = 0.85) and modest to low correlation with NUP (r = 0.58), NPI (r = 0.51), age (r = 0.34), sleep duration (r = 0.025) and maximum voided volume (r = –0.18; each p < 0.001). On multivariate analysis with nocturnal voiding frequency as the dependent variable NPI, NUP and age were not covariates while sleep duration, maximum voided volume and NI were covariates. The latter had a 10 to 18-fold higher β than the other variables.

Discussion

In our study of 894 volunteers without urological complaints we found a mean NPI of 30% with a 95th percentile of 53%. One nocturia episode per night is considered normal in many studies due of this occurrence in many subjects. Those with 2 or more nocturia episodes per night have higher urine output than those without nocturia [10]. The NPI increases with nocturnal voiding frequency [11]. Thus, the NPI was recalculated after excluding patients with nocturia and polyuria. In the subpopulation without nocturia or polyuria the mean was 29% with a 95th percentile of 48%. Thus, excluding nocturia and polyuria did not seem to have a major impact on the mean or on reference values.

To distinguish normal from high values it is common to establish the reference range by all observed values within the 95th percentile. In a normal distribution this corresponds to the mean plus 1.645 x SD. The upper limit of this reference range is the cutoff point to classify values as normal or not normal. Based on our results we advocate that an NPI of more than 53% should be classified as NP.

We identified a few original studies in which the NPI was reported or could be deduced. Straightforward data comparison is hampered not only by differences in the study populations or the FVC duration (1 to 7 days) but also by the data presentation. The NUP is shown as ml per night, ml per hour, ml/kg or ml per hour per kg. Moreover, night sometimes refers to a fixed time (23:00 or 24:00 to 7:00 or 8:00) but most often is defined as the time between going to bed and rising the next morning. Since publication of the ICS standardization report, several groups have used the ICS definition with 33% cutoff to present the percent of patients with or without NP [1;4;8;10;12-16]. Others reported actual NPI values as the mean or sometimes as the median while a minority provided an indication of the variation by presenting the range [17;18], SD [11;19], or percentile [20]. Of 14 studies including a total of 2,266 subjects, in which there is some overlap due to repeat use of data, we calculated a weighted mean NPI of 33% [11;17-27]. Mean values of more than 40% for the NPI were consistently reported in elderly populations including those with nocturia [20;21;27], healthy subjects [17] or urological patients [11]. A mean NPI of less than 25% was reported in Asian men with lower urinary tract symptoms [26] and in individuals without nocturia [22].

Our findings agree with those of Parsons et al, who studied 253 asymptomatic adults of all age groups and noted a mean NPI of 27% ± 10% [19], and with those of Bing et al, who found an NPI of 25% in 25 men and 26% in 50 women in an elderly control group with less than 1 nocturia episode [22].

The NP cutoffs adopted by the ICS seem to represent the mean NPI instead of the upper limit of a reference range. The ICS criterion for younger patients was based on a small study of 9 with enuresis and 9 controls for whom night was defined as 23:00 to 7:00 [28]. In a large population based study of elderly men Blanker et al suggested that the cutoff for NUP exceeding 54 ml per hour should be shifted to 90 ml per hour [29].

Considering that many studies refer to the ICS definition of the NPI, the impact of ICS standardization reports is high. The ICS definition of NP will lead to overestimating NP and consequently to underestimating other disorders.
Our study revealed through multivariate regression analysis that with the available variables our model for constructing the NPI has only moderate prospective value. The NPI increased by 3% per sleep hour and by 2% per age decade. For each 100 ml of maximum voided volume the NPI increased 2%. An adaptive mechanism of the bladder to larger volumes was previously suggested [6;7]. The NPI increased 0.6% with each 100 ml decrease in 24-hour urine output. Obviously lower 24-hour volume would lower daytime volume while nocturnal volume would remain unchanged or show a much smaller decrease than daytime volume.
With respect to the wide range of NPI values small influences may be due to selection of the study population. At the individual level these influences do not seem to be relevant, although they give us information about the complex NPI relations.
As reported previously and adopted subsequently by the ICS [2] the age dependence of the NPI exists but is much weaker, although the increase in the means seems graphically evident (Figure 1). The correlation between age and NPI is weak ($r = 0.25$).
The impact of the NPI depends on other conditions, such as maximum voided volume and sleeping time. High NPI becomes a problem only when it does not match maximum nocturnal voided volume, in other words when the NI is high.
Reported predictors of the number of nocturnal voids are NI [10], maximum voided volume, NUP and sleeping time [23;25]. Our results concur, except for NUP. NUP is a modest determinant of increased nocturnal voiding frequency [29].
These considerations make it clear that other factors have important roles in the symptom of nocturia. Disturbances in homeostasis, disorders in the circadian rhythm of hormones such as arginine vasopressin and atrial natriuretic peptide, and lifestyle factors have an influence [22]. Based on these considerations it is unlikely that a new NPI cutoff would deprive certain patient categories from potentially effective treatment.

Conclusions

The NP prevalence has been overestimated due to low cutoffs. We suggest that an NPI of more than 53% should be classified as NP. More importantly, a high NPI does not necessarily indicate a disorder since it should be related to nocturnal maximum voided volume. In the evaluation of nocturia a high NI, ie the combination of maximum voided volume and NUP, is more important than NP alone.

Editorial comment

This study raises the issue of how to define abnormal. The authors state that the NP incidence is overestimated and NP only exists when the proportion of urine produced at night is greater than 53%. This is counterintuitive since one would assume that we only produce a third of our urine in a third of the 24-hour period. In addition, it is believed that urine production at night is decreased by antidiuretic hormone. The authors draw this conclusion because they define NP as an NPI of greater than 2 SD from the mean, in other words the worst 5% of the study population. Does this method of defining NP help patients? If one used the analogy of obesity, since 35% of adults are defined as obese, this issue becomes clearer. If obesity was defined as

only being in the largest 5% in the population with no advice for the 30% who are also obese, this would be a considerable disservice to individuals and society. This argument also applies to NP because, if one had a 24-hour urine output of 2,000 mL and an NPI of 50%, by the author definition one would not have NP. However, the individual would probably get out of bed at least 3 times in the night, suffer a considerable reduction in quality of life and like some medical help. The value of this definition of NP is severely limited by making the definition too severe.

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Reply by author

The comment gives us the opportunity to clarify some important considerations concerning normality. Table 2 shows that for all ages the mean NPI was 30.8, which is approximately equivalent to a third. Thus, on average the assumption is true that two-thirds of the 24-hour urine production is produced during the day and a third is produced during the night. The value of 53% reflects only the upper limit of the reference range as defined by standard conventions. When tools such as NPI are used to understand a symptom, it is important to establish reference ranges. A reference range usually describes the variations of a measurement in healthy individuals. The SD of a reference range for a particular measurement is defined as the 95% CI of the reference group. Our study shows that NPI is not a determining factor of nocturia. In practice patients do not suffer from a high NPI but from high nocturnal frequency, ie nocturia. Our data reveal that nocturnal urine production should always be related to bladder capacity. NPI only serves as a parameter to understand the problem of nocturia. The fear that a new cutoff for NPI would deprive certain patient categories from potentially effective treatment could be translated into a fear of sensitivity that would be too low. The decision to deviate from the standard definition of a reference range, ie to lower the upper bound of 95% to 85% or perhaps 75%, should be based on calculations of sensitivity and specificity in a general or urological population. However, since the correlation between nocturia and NPI was only modest (r _ 0.51), it is our opinion that the NPI should not have too much focus. Concerning the analogy to obesity, the 1998 National Institutes of Health Clinical Guidelines on the Identification, Evaluation and Treatment of Overweight and Obesity in Adults stated that the definition of overweight that has been used to compare epidemiological surveys is statistical and corresponds to the 85th percentile of body mass index for men and women at ages 20 to 29 years. Obesity is clearly associated with increased morbidity and mortality. There is strong evidence that weight loss in overweight and obese individuals decreases risk factors for diabetes and cardiovascular disease. The body mass index is an indicator of obesity, although there is no perfect correlation between obesity and body mass index. Nocturia is a symptom and not a condition like obesity. In contrast to the body mass index with respect to obesity, the NPI is not a good indicator of nocturia, as we outlined.

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	Tijd	Volume in ml
1	0830	160 ml
2	0945	170 ml
3	1000	150 ml
4	1010	150 ml
5	1019	160 ml
6	10.25	140 ml
7	10.28	135 ml
8	10.33	165 ml
9	10.36	150 ml
10	10.41	135 ml
11	10.44	145 ml
12	1047	150 ml
13	1050	160 ml
14	11.01	150 ml
15	11.06	135 ml

Chapter 10

Summary

Summary

This thesis is an analysis of frequency-volume charts (FVCs) and International Prostate Symptom Scores (IPSS) and their relations, based on 2 large databases. The first database consists of a large sample of adult men and women without voiding complaints, representing a sample of the normal population. This database comprises 24-hour FVCs including IPSS. The second database comprises 7-day FVCs and symptom scores of a sample of urologic patients visiting 2 outpatient clinics.

1. Introduction

Chapter 1 is a short introduction, showing that in the analysis of voiding patterns, symptom scores and diaries are basic but important tools. Numerous terms for bladder diaries or FVCs are used, depending on the recorded parameters. Here, we prefer FVCs.

2. Review on FVCs

Chapter 2 focussed on FVCs, by a review of the literature on FVCs through the end of 2011. We showed that especially since 1995 there has been an increase in the number of publications on FVCs, although most of these articles discuss using FVCs to evaluate therapeutic interventions. The number of original articles addressing the value and content of FVC seems to have stabilised at approximately 20 per year. Several studies have outlined differences between populations, but from a diagnostic point of view, clear cut-off points are obviously lacking. Several authors have argued that as a result of the wide variability of FVC parameters, the large overlap between groups make the FVC unsuitable as a diagnostic tool. Due to this lack of diagnostic sensitivity, the use of FVCs by physicians seems to be limited. Nevertheless, several international guidelines on lower urinary tract symptoms (LUTS) or incontinence advocate the use of FVCs. We argued that despite disappointing results reported in some studies, future studies should aim at elucidating the potential (additional) diagnostic value of FVCs.
Our summary showed there is a tendency to advise a duration of FVCs for 3 days. Information on how FVC data are being processed is currently sparse. Digital processing of FVCs is likely to facilitate the assessment of FVC parameters. However, the way doctors will interpret FVC data remains unclear.

3. Scope of the thesis

At the end of the 1990s, when we started building our databases, little was known about normal ranges of FVC parameters. Then, it was clear that urologic science needed reference values. The goals of our research are outlined in Chapter 3. The first goal was to establish normal ranges of FVC parameters as well as of the IPSS and its correlations. Also, we wanted to establish normal ranges of nocturnal urine production and thereby assessing a cut-off point for nocturnal polyuria, and we wanted to compare the assessment of nocturia by IPSS vs FVC. Another goal was to contribute to the assessment of the optimal duration of FVCs, taking into account the reliability of FVC parameters as well as patient compliance.

4. Normal ranges for 24-hour frequency-volume charts

In Chapter 4 we used data of 24-hour FVCs of 1152 men and women older than 20 years representing all age groups and denying any voiding complaints to describe the FVC variables (e.g., voiding frequency, voided volumes, urine production) and their mutual relationships and differences between age groups and genders. We found a linear increase in mean 24-hour voiding frequency and nocturia in men, from 6.0 and 0.5 in the third decade to 8.5 and 1.6 in those older than 70 years. In contrast to men, in women the mean 24-hour frequency declined slightly in the older decades; it increased from 6.9 in the third to 8.2 in the sixth, declining to 7.8 in those older than 70 years. Nocturia in women increased linearly, although more slowly than in men, from 0.7 in the third decade to 1.4 in those older than 70 years. The mean volume/void decreased significantly in both genders, from 313 to 209 ml in men and from 274 to 240 ml in women. The mean 24-hour volume was 1718 and 1762 ml in men and women, respectively. For both genders we found a strong linear association between 24-hour urine production and voided volumes.

5. Compliance with 7-day frequency-volume charts

Urologic patients visiting an outpatient clinic were asked not only to record an FVC for 7 days but also to record missed recordings. This enabled us to analyse compliance to recording an FVC, as outlined in Chapter 5.
Of 500 consecutive urologic outpatients willing to complete a 7-day FVC, 378 forms of 228 men and 150 women were evaluable. Patients were instructed to indicate missed entries for time and/or volume with a coded letter. Compliance was defined as agreement between the times or volumes recorded and the true frequency (times or volumes recorded plus missed entries). The number of completely recorded days was calculated and the level of compliance by day was computed. The mean values were 55 years (standard deviation [SD]: 16 years) for age, 13.8 (SD: 8.9) for IPSS, and 1856 ml (SD: 828 ml) for 24-hour urine production. At day 7, 28% of the patients had not missed a single entry for time and volume. For all patients, group compliance with recording time alone decreased from 96% to 81% (mean: 91%); compliance with recording volume alone decreased from 93% to 78% (mean: 88%). No significant relationship between compliance (times or volumes) and any of the FVC parameters was found. From day 2, compliance decreased significantly with each day. For the first 5 days, the level of completion was above 80% in most patients. We concluded that for the whole group, a 7-day FVC has high compliance rates with means of 91% and 88% by time and volume, respectively.

6. Optimal duration of frequency-volume charts

In Chapter 6 we combined these compliance data with calculated reliability of 7-day FVCs to assess the yield of additional recorded days and the ideal duration of recording. FVCs of 228 men and 150 women were evaluated. Mean age was 55.2 years (SD: 16.2 years), and mean 24-hour urine production was 1856 ml (SD: 828 ml). During 7 consecutive days, every voiding time and volume was recorded. Missed entries were indicated with a coded letter, thereby assessing the true frequency and compliance. The percentage of patients with complete FVCs decreased from 78% on day 2 to 58% on day 7, and it dropped below 70% after 4 days. Reliability is the agreement of the day-to-day FVC parameters with the 7-day FVC pattern. Single-day reliability was assessed using in the Spearman-Brown formula. Single-day reliability was $r = 0.63$ for nocturnal urine production, $r = 0.72$ for 24-hour urine production, and $r = 0.80$

for mean voided volume. At 5 days, reliability of 90% was achieved for all parameters. We concluded that with each additional day, FVCs showed a decrease in compliance and an increase in reliability. At day 3, reliability of 80% was achieved for all FVC parameters, but compliance dropped to 73%. Beyond 5 days, the yield of additional recorded days was limited. We advocate an FVC duration of 3 days, but the length of time may be shortened or extended depending on the goal of the FVC.

7. International Prostate Symptom Score in a population-based sample

In 1992, a 7-item validated questionnaire to categorise LUTS was adopted by the American Urological Association. Adding a disease-specific quality-of-life score, it was popularised as the IPSS. Unfortunately, this term reflects a too prostate-centric concept of LUTS.
In Chapter 7 we showed in a population of 1143 adults without voiding complaints and divided over both sexes and all decades that the IPSS shows a significant increase in consecutive age groups. Men in the third decade had a mean score of 2.8; men older than 70 years had a score of 7.0. In women these scores were 4.0 and 5.6, respectively. Thus in both adult men and women reporting no voiding complaints, the IPSS increased with age. This rise was more prominent in men. The increase was about equally caused by storage and voiding scores. The items addressing weak stream in men and nocturia and urgency in men and women were the major factors causing the correlation with age. Although all subjects stated they had no voiding complaints, nearly 17% had moderate symptom scores, and 1% had severe scores.

8. Nocturia by International Prostate Symptom Score and frequency-volume chart

In Chapter 8 we analysed differences in nocturia, as estimated by the IPSS and 7-day FVCs. A total of 398 forms were collected from 500 consecutive urologic outpatients willing to record a 7-day FVC. All patients completed a general questionnaire, an IPSS, and a bladder symptom and bother score. Missed recordings were indicated by a coded letter. Patients who lacked essential data, bedtimes, or an IPSS, or who recorded the FVC for less than 5 days were excluded from the study. FVCs from 186 men and 115 women with a mean age of 56 years were evaluable. In 10.6% of patients, no nocturia occurred. Of those with nocturia, 70% and 34% experienced mean nocturia frequency of 1 or more and 2 or more, respectively. In 43% of patients the IPSS equalled calculated categorised nocturia; 50% had a higher IPSS nocturia score than calculated nocturia. On univariate analysis the correlation of IPSS question 7 with mean nocturia initially increased with FVC duration (day 1 $r = 0.52$ to day 3 $r = 0.63$). On longer duration of FVCs, the correlation showed no further increase. Multivariate regression analysis revealed that the nocturia score was determined by mean nocturia in the FVC, the nocturia bother score, and patient age. We concluded that the IPSS nocturia score overestimates nocturia in most patients, compared with that derived from a 7-day FVC. When scoring IPSS nocturia question 7, patients seem to have included a degree of bother. The correlation of question 7 with mean nocturia increased with FVC duration until day 3.

9. Nocturnal polyuria

The nocturnal polyuria index is the ratio of nocturnal urine production to total 24-hour urine production. Based on 2 small studies, the International Continence Society (ICS) defined nocturnal polyuria as a nocturnal polyuria index above 33%. During the analysis of the data of

the population addressed in Chapter 2, we noticed that the occurrence of nocturnal polyuria, as defined by the ICS, was high.

In Chapter 9 we sought criteria for nocturnal polyuria in asymptomatic nonurologic adults of all ages by reporting reference values of the nocturnal polyuria index and finding nocturia predictors. Data from a database of FVCs from a reference population of 894 nonurologic asymptomatic volunteers of all age groups were analysed.

The nocturnal polyuria index had wide variation but a normal distribution with a mean ± SD of 30% ± 12%. The 95th percentile of the values was 53%. Above this cut-off a subject had nocturnal polyuria. This value contrasts with the ICS definition of 33% but agrees with several other reports. On multivariate regression analysis with the nocturnal polyuria index as the dependent variable, sleeping time, maximum voided volume, and age were the covariates. However, the increase in the nocturnal polyuria index by age was small. Excluding polyuria and nocturia from the analysis did not alter the results in a relevant way. The nocturnal voiding frequency depended on sleeping time and maximum voided volume but most of all on the nocturia index, which is the nocturnal urine production divided by functional bladder capacity. We concluded that the prevalence of nocturnal polyuria is overestimated. We suggested a new cut-off value for the nocturnal polyuria index; that is, nocturnal polyuria exists when the nocturnal polyuria index exceeds 53%. The nocturia index is the best predictor of nocturia.

	Tijd	Volume in ml	Verlies (x)
1	5 keer		
2	—		
3	Nee		
4	Ja		
5	Nee		
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			

Chapter 11

General discussion and future perspectives

General discussion and future perspectives

Normal ranges for 24-hour frequency-volume charts

We were one of the first to publish a large population-based study on voiding parameters derived from frequency-volume charts (FVCs). We showed that voiding frequencies were higher in older age groups and the mean voided volumes were lower, which was more explicit in men. The 24-hour urine production has a parabolic curve with the highest volumes found in middle-age groups. Our findings were confirmed in a British study [1]. We also showed that for both genders there was a strong linear association between 24-hour urine production and voided volumes. This remarkable finding was confirmed by others [1-3]. In reverse, a purposely increased fluid intake was shown to increase bladder capacity, suggesting an adaptive mechanism of the bladder to an increased volume load [4]. The filling velocity or the concentration of urinary substances might influence bladder sensitivity or contractility. Future research should clarify the physiology behind this phenomenon.
We showed that the International Prostate Symptom Score (IPSS) in both adult men and women reporting no voiding complaints increased significantly in consecutive age groups. This emphasised that, unlike its name, lower urinary tract symptoms (LUTS) are neither prostate nor gender specific.

Literature review

In the literature review, we showed the increasing number of articles addressing FVCs over the years, especially since 1995. From 2011 until now, this increase has continued and has reached 100 articles per year, although the number of articles addressing the value and content of FVC has not increased. Less than half of all physicians, mostly general practitioners or gynaecologists, use FVCs.

Nocturia

Nocturia is the most bothersome factor in LUTS and may have a serious impact on quality of life and well-being. The proper analysis of nocturia is of utmost importance. There is broad agreement on the utility of FVCs in the analysis of nocturia. We showed that an initial assessment of nocturia by IPSS may be influenced by the level of bother that a patient has experienced. This is once more a plea for using FVCs.
In 2002, the International Continence Society (ICS) defined nocturnal polyuria as an increased ratio of nocturnal to 24-hour urine production of more than 20% in the young and more than 33% in the elderly, with the value for middle age probably falling in between these values [5;6]. In general, this is referred to as 33%. This definition was based on 2 rather small studies with only 9 and 45 patients, respectively [7;8].
We showed that this cut-off for nocturnal polyuria seems to represent the mean ratio of the nocturnal urine production to the 24-hour urine production, instead of the upper limit of a reference range. This upper limit in our study was 53%, which is much higher than the 33% according to the ICS definition. We also showed, in agreement with other reports, that not nocturnal polyuria but rather the ratio of nocturnal urine production to functional bladder capacity—the nocturia index—is the most important factor in the aetiology of nocturia. ICS definitions are important and often used. We recommend that the ICS update the definition of nocturnal polyuria.

Frequency-volume chart: content and duration

The discussion on the optimal duration of FVCs has continued, but there is a tendency to advise a duration of 3 days. Statements on the optimal duration are most often based on the reliability of FVC parameters that are calculated with several statistical techniques. It has been acknowledged that compliance with recording of an FVC decreases with time. Some studies reported compliance rates by the end of the recorded period. We have contributed to this discussion with a study calculating day-to-day levels of completeness of recordings, as outlined in Chapter 4. Compliance in general is good and indeed decreases with time. We found little differences among the various diagnostic groups, but in incontinent patients compliance was lower. This finding was probably due to their inability to record volumes of involuntarily lost urine. However, a shortcoming was that these groups were relative small and that we used no solid diagnostic criteria for them. Furthermore, we made clear that FVCs that are less than 100% complete do not necessarily have to be categorised as "noncompliance" and therefore may be useful recordings to some extent. Thus certain levels of completeness may still be very informative.

These findings were combined with the day-to-day reliability of several FVC parameters in Chapter 5. We showed that beyond an FVC duration of 4 days, the yield of extra days of recording of the FVC is very limited because reliability no longer increases. This enabled us to clarify that the optimal duration of FVCs is nonexistent. An optimum duration will depend on the goal of recording an FVC. To get just an objective impression of a patient's voiding pattern, a shorter duration of an FVC is often sufficient. In patients with urinary urgency incontinence or overactive bladder, a higher frequency will not be missed due to 1 or 2 missed recordings, and most likely the mean value of voided volumes will not be changed. In patients predominantly complaining of nocturia, a high compliance is necessary to establish nocturia indexes and ratios of volumes produced during the day or night. However, the variability of symptoms does require good reliability, for which a recording of at least 3 days and nights is needed. In studies evaluating therapies or epidemiology, a longer duration of FVCs will yield a higher reliability and thus more discerning details. One will have to take into account the loss of data due to a decreased compliance, implicating the need of a higher number of patients to record the FVC.

Little attention has been paid to the content and layout of FVCs. A study was performed recently hoping to provide a starting point for the development and validation of a generic urinary diary, based on patients' and clinicians' views of importance. It was appreciated that the diary was unlikely to be a one-size-fits-all tool with the potential to replace all other diaries, and that the final urinary diary may only be recommended for use in certain circumstances [9]. A diary duration of 3 to 4 days was preferred. The unlikeliness of one standard format as well as the preferred duration agrees with our findings.

Several authors have been rather sceptical or negative about the diagnostic potential of FVCs because of the wide variability and as a result the low discriminative value of FVC parameters. Despite the discouraging findings of several studies, it is conceivable that certain parameters will show better diagnostic properties than others [10]. For example, the median voided volume was reported as the most constant parameter [11-13]. Combining data of FVCs with other examinations (e.g., symptom scores, uroflowmetry, and ultrasonography) for measurements of postvoid residual volume or bladder wall thickness might add to the diagnostic abilities of FVCs, as suggested in several studies of patients with LUTS [14-18]. More recently, it was suggested that a single-day maximum voided volume excluding the first

morning void of less than 250 ml was useful in screening for bladder oversensitivity [19]. This study used receiver-operating curve and predictive values.
Reported results often focus too much on small or clinical insignificant differences of mean values of a parameter. Despite small mean differences, predictive values and odds ratios may add to the diagnostic process. Physicians make decisions based on the likelihood that a supposed condition will be present. Somehow the results of several tests and symptoms are given a certain weight, together attributing to a diagnosis. Clinicians prefer easy diagnostic noninvasive tools that tell them whether or not a disorder is present. However, in the diagnostic process of LUTS, no such tools exist. FVCs do not provide this either. Interpretation of FVCs requires simple calculations of FVC parameters such as means, maximum and total voided volumes and frequencies, or parameter ratios. However, even simple calculations may be too elaborate in daily clinical practice. There is still a need to explore predictive values of FVC parameters and to compare these between diagnostic groups.
Despite these shortcomings of FVCs, several international guidelines on LUTS or incontinence have recommended using FVCs for many years. Although we endorse their importance, guidelines should indicate more precisely which kind and duration of FVC or diary is advocated, which parameters are most important, and how the generated data should be used.
Digital processing of FVCs is likely to facilitate the assessment of FVC parameters, as was shown recently [20]. In that study, electronic vs paper diaries of 22 patients and its analysis by 22 urologists were compared. Overall, 82% of the patients preferred electronic diaries. More importantly, analysis of the paper diary took 66% more time and was less accurate with 58% vs 100% in favour of the electronic diary. However, the way doctors will interpret the FVC data remains unclear.
With the currently increasing use of digital devices, computerised collection and processing of FVC data seems to be a promising development. This will facilitate the challenges just described. Integration in electronic patient files will add to its potential value. Smart combination of data from FVCs and other noninvasive basic evaluations such as symptom scores, uroflowmetry, and ultrasonography for the measurement of postvoid residual urine or bladder wall thickness will probably yield important diagnostic and therapeutic tools.

Summary

At present, it has become clear that the content and structure of FVCs will probably depend on symptoms and the aims of a patient's evaluation. Scientific reports, not in the least due to our findings, and clinical experiences suggest that 3-day FVCs are generally sufficient.
More important, despite disappointing results reported in some studies, future studies should aim at further elucidating the potential (additional) diagnostic value of FVCs. Using receiver operator curves and odds ratios, such studies should be able to provide diagnostic cut-offs. The use of digital recording and processing of data will most certainly contribute to the diagnostic value of FVCs.

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家中

上床睡覺

第二天起床

出生日期 Geboortedatum:	25 -
量小便日期 Datum:	22 -
起床時間 Tijdstip opstaan:	Zzz van 2
時間 Tijdstip naar bed gaan:	Van 21:0
Tijdstip opstaan volgende dag: 時間	Elke dag

ij't opstaan
moet ik altijd
elijk plassen.
laarna is't
meestal om
t uur een
keer naar
: toilet.

尿量(毫升)

	Tijd 時間	Volume in ml
1	1 : 20	150, 100
2	6,	150, 100
3	6,	100, 100
4	6,	100, 100
5	~~6, 20~~ 6	100, 100
6	6, 9	100, 100
7	6, 9	100, 100
8	6 9	100, 100
9	6, 9	100, 100
10	6, 9,	100, 100
11	6.	100,
12		

27,15
28.
29
30
31

Chapter 12

Nederlandse samenvatting

Nederlandse samenvatting

Dit proefschrift is een analyse van plasdagboeken en de Internationale Prostaat Symptoom Scores (IPSS) en hun onderlinge relaties, gebaseerd op 2 grote databases. De eerste database bevat een gegevens van een groot aantal mannen en vrouwen zonder plasklachten, die samen een normale populatie vertegenwoordigen. Deze database bevat 24-uurs plasdagboeken alsook IPSS. De tweede database bevat 7-daagse plasdagboeken en symptoom scores van urologische patiënten die 2 urologische poliklinieken bezochten.

1. Introductie

Hoofdstuk 1 is een korte introductie, waarin wordt uitgelegd dat analyse van plaspatronen symptoom scores en plasdagboeken basale tools zijn. In de literatuur worden vele termen gebruikt voor plasdagboek, deels afhankelijk van de bijgehouden parameters. De essentie is het aantal keren en de hoeveelheid per keer dat geplast wordt. In dit proefschrift gaat daarom de voorkeur uit naar de Engelse term *frequency-volume charts* (FVCs).

2. Review van literatuur over FVCs

Hoofdstuk 2 richt zich op FVCs, door middel van een review van de literatuur over FVCs tot eind 2011. Daarin werd getoond dat er vooral sinds 1995 een toename is van het aantal publicaties over FVCs, hoewel het merendeel van deze artikelen FVCs gebruiken om therapeutische interventies te evalueren. Het aantal originele artikelen dat zich richt op de waarde en de inhoud van FVCs lijkt zich te hebben gestabiliseerd rond de 20 per jaar. Enkele studies hebben verschillen tussen populaties beschreven, maar vanuit een diagnostisch oogpunt ontbreken duidelijke afkappunten. Meerdere auteurs hebben beargumenteerd dat als gevolg van de brede variatie in de FVC-parameters, de brede overlap tussen groepen de FVC ongeschikt maakt als diagnostisch instrument. Als gevolg van dit gebrek aan diagnostische sensitiviteit lijken artsen FVCs weinig te gebruiken. Desalniettemin adviseren meerdere internationale richtlijnen m.b.t. lage urinewegsymptomen of incontinentie om FVCs te gebruiken. Wij stelden dat ondanks teleurstellende resultaten in enkele studies, toekomstige studies zich moeten richten op de potentiële (toegevoegde) diagnostische waarde van FVCs.
In onze samenvatting lieten we zien dat er een trend is om een duur van 3 dagen voor FVCs te adviseren. Informatie over hoe data worden verwerkt is op dit moment schaars. Digitale verwerking van FVCs zal waarschijnlijk het vaststellen van FVC parameters vergemakkelijken. De wijze waarop artsen FVC gegevens interpreteren is vooralsnog echter niet duidelijk.

3. Reikwijdte van dit proefschrift

Aan het eind van de jaren negentig, toen wij begonnen aan de bouw van onze databases, was weinig bekend van de spreiding van FVC parameters. Het was toen duidelijk dat de urologische wetenschap behoefte had aan referentiewaarden. De doelstellingen van ons onderzoek zijn uiteengezet in Hoofdstuk 3. Het eerste doel was om normaalwaarden vast te stellen van FVC parameters alsook van de IPSS en hun onderlinge relaties. Voorts wilden we normaalwaarden voor de nachtelijke urineproductie en daarmee de grenswaarden voor nachtelijke polyurie vaststellen, en de vergelijking maken tussen nycturie vastgesteld d.m.v. IPSS versus FVC. Een ander doel was om bij te dragen in de discussie over de optimale duur van FVCs, waarbij zowel

de betrouwbaarheid (*reliability*) als de nauwgezetheid van patiënten in het vastleggen (*compliance*) van FVC parameters zou worden meegewogen.

4. Normaalwaarden voor 24-uurs *frequency-volume charts*

In Hoofdstuk 4 gebruikten we gegevens van 24-uurs FVCs van 1152 mannen en vrouwen van 20 jaar en ouder uit alle leeftijdsgroepen en zonder plasklachten om een beschrijving te geven van de FVC variabelen (zoals plasfrequentie, geplaste volumina, urine productie) en de relaties tussen leeftijdsgroepen en geslachten.
Wij vonden een lineaire toename in de gemiddelde 24-uurs plasfrequentie en nycturie bij mannen van 6,0 respectievelijke 0,5 in de 3^{e} decade naar 8,5 respectievelijk 1,6 in de groep van 70 jaar of ouder. In tegenstelling tot mannen, nam bij vrouwen de gemiddelde 24-uurs urineproductie lichtelijk af in de oudere 10-jaars leeftijdsgroepen; van 6,9 in de 3^{e} decade nam het toe naar 8,2 in de 6^{e} decade, om vervolgens weer af te nemen naar 7,8 in de groep van 70 jaar of ouder. Nycturie nam ook bij vrouwen lineair toe, maar langzamer dan bij mannen, van 0,7 in de 3^{e} decade naar 1,4 in de groep van 70 jaar of ouder.
Het gemiddelde volume per mictie nam duidelijk af in beide geslachten, van 313 naar 209 ml bij mannen en van 274 naar 240 ml bij vrouwen. Het gemiddelde 24-uurs volume was 1718 en 1762 ml bij respectievelijke mannen en vrouwen. In beide geslachten vonden we een sterke lineaire associatie tussen de 24-uurs urineproductie en de per portie geplaste volumina.

5. Nauwgezetheid in vastlegging van 7-daagse *frequency-volume charts*

Urologische poliklinische patiënten werden verzocht om een 7-daagse FVC bij te houden, en daarbij notitie te maken van momenten of metingen die zij gemist hadden. Dit stelde ons in staat om de nauwgezetheid van patiënten in het vastleggen (*compliance*) van FVCs te analyseren, zoals is beschreven in Hoofdstuk 5.
Van 500 achtereenvolgende poliklinische urologische patiënten die bereid waren om een 7-daags FVC bij te houden, waren 378 formulieren van 228 mannen en 150 vrouwen evalueerbaar. De patiënten waren geïnstrueerd om gemiste registraties van tijd en/of geplast volume aan te duiden met een gecodeerde letter.
Compliance hebben wij gedefinieerd als de overeenkomst tussen de geregistreerde tijden en volumina en de werkelijke frequentie (geregistreerde tijden en volumina plus de gemiste waarden). Het aantal van volledig geregistreerde dagen en gecategoriseerd niveau van *compliance* werden berekend.
De gemiddelde waarden waren voor leeftijd 55 jaar (standaard deviatie [SD]: 16 jaar), voor IPSS 13,8 (SD: 8,9), en voor 24-uurs urine productie 1856 ml (SD: 828 ml).
Op dag 7 had 28% van de patiënten geen enkele registratie voor tijd of volume gemist. Gemeten over alle patiënten nam de compliance van de groep voor de registratie van alleen de tijd af van 96% naar 81% (gemiddeld: 91%); compliance van de groep voor de registratie van alleen het volume nam af van 93% naar 78% (gemiddeld: 88%). Er werd geen significante relatie gevonden tussen de compliance (tijd of volume) en enige FVC parameter. Vanaf dag 2 nam met de dag de compliance significant af. Over de eerste 5 dagen lag de compliance bij de meeste patiënten boven de 80%.
Wij concludeerden dat voor de totale groep een 7-daagse FVC een hoge compliance heeft met gemiddelde percentages van 91% voor tijd en 88% voor volume.

6. De optimale duur van *frequency-volume charts*

In Hoofdstuk 6 combineerden we de gegevens over de compliance met de berekende betrouwbaarheid (*reliability*) van 7-daagse FVCs om de meerwaarde te bepalen die elke dag langer meten zou hebben, waaruit de optimale duur voortvloeit. FVC van 228 mannen en 150 vrouwen werden geëvalueerd. De gemiddelde leeftijd was 55,2 jaar (SD: 16,2 jaar), en de gemiddelde 24-uurs urine productie was 1856 ml (SD: 828 ml). Gedurende 7 achtereenvolgende dagen werd van elk plasmoment de tijd en het volume genoteerd. Gemiste metingen werden aangeduid met een gecodeerde letter, waarmee de ware frequentie en daarmee de compliance werden vastgesteld. Het percentage patiënten met complete FVCs nam af van 78% op dag 2 tot 58% op dag 7, en zakte naar minder dan 70% na 4 dagen. *Reliability* is de overeenkomst van de per dag gemeten FVC parameters met het patroon van de 7-daagse FVCs. *Reliability* op een enkele dag werd bepaald door gebruik te maken van de Spearman-Brown formule. Deze enkele-dag *reliability* was r = 0.63 voor de nachtelijke urine productie, r = 0.72 voor de 24-uurs urine productie, en r = 0.80 voor het gemiddelde geplaste volume. Op dag 5 was voor alle parameters een *reliability* van 90% bereikt. We concludeerden dat met elke extra dag, FVCs een afname in compliance en een toename in *reliability* geven. Op dag 3 was een *reliability* van 80% bereikt voor alle FVC parameters, maar compliance zakte naar 73%. Na 5 dagen is de meerwaarde van extra gemeten dagen beperkt. Wij adviseren een FVC-duur van 3 dagen, hoewel de lengte korter of langer kan zijn afhankelijk van het doel van de FVC.

7. Internationale Prostaat Symptoom Score in een populatiesteekproef

In 1992 werd een gevalideerde vragenlijst van 7 items, die ten doel had plasklachten te categoriseren, door de *American Urological Association*_omarmd. Na toevoeging van een ziekte-specifieke kwaliteit van leven score, werd deze vragenlijst populair onder de naam IPSS. Ongelukkigerwijs geeft deze term teveel een prostaat-georiënteerd concept van plasklachten weer.
In Hoofdstuk 7 lieten we zien dat in een populatie van 1143 volwassenen zonder plasklachten, verdeeld over beide geslachten en alle leeftijdsgroepen in decaden, de IPSS significant hoger ligt in opeenvolgende leeftijdsgroepen. Mannen in de 3^{e} decade hadden een gemiddelde score van 2,8; mannen ouder dan 70 hadden een score van 7,0. Bij vrouwen waren deze scores respectievelijk 4,0 and 5,6. Dus in zowel mannen als vrouwen zonder plasklachten neemt de IPSS toe met de leeftijd. Deze stijging was meer uitgesproken in mannen. De toename was ongeveer gelijk verdeeld over de scores betreffende de blaasvulling als de scores betreffende het plassen. De factoren die het meest bijdroegen in de correlatie met de leeftijd waren bij mannen de zwakke straal en bij zowel mannen als vrouwen de nycturie en de aandrangsklachten. Hoewel dus alle personen stelden geen plasklachten te hebben, had 17% middelmatige symptoom scores, en had zelfs 1% ernstige scores.

8. Nycturie afgeleid uit de Internationale Prostaat Symptoom Score en uit de *frequency-volume chart*

In Hoofdstuk 8 analyseerden we verschillen in nycturie zoals die was vastgesteld d.m.v. de IPSS en 7-daagse FVCs. In totaal werden 398 formulieren verzameld van 500 achtereenvolgende urologische poliklinische patiënten die bereid waren om gedurende 7 dagen een FVC bij te houden. Alle patiënten vulden een algemene vragenlijst in, een IPSS, en

een blaas-symptoom- en -hinderscore. Gemiste metingen werden aangegeven met een gecodeerde letter. Patiënten van wie essentiële gegevens, bedtijden of de IPSS ontbrak, of die hun FVC minder dan 5 dagen bijhielden, werden uitgesloten van de studie.
FVCs van 186 mannen en 115 v rouwen met een gemiddelde leeftijd van 56 jaar waren evalueerbaar. Bij 10,6% vd patiënten trad geen nycturie op. Van de patiënten met nycturie had 70% een gemiddelde nycturie van 1 of meer, en 34% had een gemiddelde nycturie van 2 of meer. Bij 43% van de patiënten kwam de IPSS overeen met de gecategoriseerde nycturie; 50% had een hogere IPSS nycturie score dan de berekende nycturie. In univariate analyse nam de correlatie van IPSS nycturie score met de gemiddelde berekende nycturie aanvankelijk toe met de duur van de FVC (dag 1 r = 0,52 tot dag 3 r = 0,63). Bij een langere registratieduur van FVCs nam de correlatie niet verder toe. Multivariate regressie analyse liet zien dat de nycturie score werd bepaald door de gemiddelde nycturie in de FVC, de nycturie hinderscore en de leeftijd van de patiënt. We concludeerden dat de IPSS nycturie score de nycturie in de meeste patiënten overschat vergeleken met de nycturie afgeleid uit een 7-daagse FVC. Bij het scoren van IPSS nycturie vraag 7 lijken patiënten de mate van hinder mee te wegen. De correlatie van de nycturie score met de gemiddelde nycturie nam tot dag 3 toe met de duur van de FVC.

9. Nachtelijke polyurie

De nachtelijke polyurie index is de ratio van de nachtelijke urine productie en de totale 24-uurs urine productie. Op basis van twee kleine studies heeft de *International Continence Society* (ICS) nachtelijke polyurie gedefinieerd als hebbende een nachtelijke polyurie index van boven de 33%. Tijdens de analyse van de data van de populatie beschreven in Hoofdstuk 2, viel het ons op dat het voorkomen van nachtelijke polyurie zoals gedefinieerd door de ICS hoog was.
In Hoofdstuk 9 zochten we criteria voor nachtelijke polyurie in asymptomatische, niet-urologische volwassenen van alle leeftijden, door het vaststellen van referentiewaarden voor de nachtelijke polyurie index en voorspellers van nycturie te vinden. Data van een database van FVCs uit een referentie populatie van 894 niet-urologische, asymptomatische vrijwilligers uit alle leeftijdsgroepen werden geanalyseerd.
De nachtelijke polyurie index had een brede spreiding maar een normale verdeling met een gemiddelde ± SD van 30% ± 12%. Het 95e percentiel van de waarden was 53%. Boven dit afkappunt had iemand nachtelijke polyurie. Deze waarde staat in scherp contrast met de ICS definitie van 33% maar komt overeen met diverse andere rapportages. In multivariate regressie analyse met de nachtelijke polyurie index als de onafhankelijke variabele, waren slaaptijd, maximum geplaste volume, en leeftijd de covariaten. De toename in de nachtelijke polyurie index met de leeftijd was echter klein. Exclusie van personen met polyurie en nycturie vd analyse veranderde de resultaten niet relevant. De nachtelijke mictiefrequentie was afhankelijk vd slaaptijd en het maximum geplaste volume, maar bovenal vd nycturie index, dat is de nachtelijke urine productie gedeeld door de functionele blaascapaciteit.
We concludeerden dat het voorkomen van nachtelijke polyurie wordt overschat. We suggereerden een nieuwe afkapwaarde voor de nachtelijke polyurie index: er is sprake van nachtelijke polyurie indien de nachtelijke polyurie index groter is dan 53%. De nycturie index is de beste voorspeller van nycturie.

tijd	ml urine	bijzonderheden
1 °C	1 °C	
1 °C	1 °C	
1 °C	1 °C	
1 °C	1 °C	
1 °C	1 °C	
1 °C	1 °C	
1 °C	1 °C	
1 °C	1 °C	
1 °C	1 °C	
1 °C	1 °C	
1 °C	1 °C	
1 °C	1 °C	

Epilogue

Abbreviations

Co-authors

Curriculum vitae

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Abbreviations

AUA	American Urological Association
BPH	benign prostatic hyperplasia
FVC	frequency-volume chart
ICIQ-OABq	International Consultation on Incontinence Questionnaire - OAB Questionnaire
ICS	International Continence Society
IPSS	International Prostate Symptom Score
LUTS	lower urinary tract symptoms
NI	nocturia index
NP	nocturnal polyuria
NPI	nocturnal polyuria index
NUP	nocturnal urine production
OAB	overactive bladder
QoL	quality of life
SD	standard deviation
SE	standard error
UTI	urinary tract infection

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Curriculum vitae

Ernst van Haarst was born on april 1963 in Berkel en Rodenrijs in the Netherlands. He grew up in and around the city of Deventer, where he went to school at the Alexander Hegius Scholengemeenschap. He studied medicine at the State University Groningen, where he graduated in 1989 as a medical doctor. After his military service he was a resident in surgery and urology in several hospitals and started his urological training in 1994. He completed his two years of general surgery in the Sint Antonius Hospital in Nieuwegein, then VU Medical Centre in Amsterdam (supervision prof D. Newling), followed by Onze Lieve Vrouwe Gasthuis in Amsterdam (supervision dr. P. Karthaus). He succeeded dr Karthaus at his retirement in June 2000 and joined the partnership urology in the Sint Lucas Andreas Ziekenhuis, where he has been working since then.
He was member of national guideline committees on urinary tract infections (SWAB: 2006, 2013, and NVU: 2009, chairman) and on urinary stone disease (NVU: 2013).
He married Brenda Mark and they have one daughter Biene.

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