

## Comparison of Nocturia Severity with Interquartile Range of Voided Volumes and Bladder Compliance in Men

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**Aims:** Patients with low bladder compliance [BC] often void at fixed volumes. We aim to explore the relationship between actual number of nightly voids [ANV], interquartile range of voided volume [IRVV], and BC to determine whether ANV is related to BC and whether IRVV may serve as a surrogate for BC.

**Methods:** We performed a retrospective analysis of male patients who underwent urodynamic studies [UDS] and completed a 24-hour voiding diary. BC was determined from UDS. Subjects were grouped by BC. ANV was compared between groups. Student's t-test assessed significance. In a subgroup analysis of patients with ANV $\geq$ 3, the IRVV was determined from voiding diaries. ANV and IRVV were compared to BC using Spearman's rank correlation coefficient [SRCC].

**Results:** 102 men participated. 1082 voided volumes [VV] were recorded. ANV ranged from 0-11 (mean 2.8, standard deviation [SD] 1.7). BC ranged from 10-450 mL/cm H<sub>2</sub>O (mean 66, SD 61). Differences in average ANV between all three BC groups was significant. Subgroup analysis included 52 men (700 VV). ANV ranged from 3-11 (mean 2.5, SD 1.86); IRVV ranged from 5-350mL (mean 95, SD 61). BC ranged from 17-392 mL/cm H<sub>2</sub>O (mean 86, SD 68). ANV $\geq$ 3 correlated with BC (SRCC = -0.451, p = 0.027). IRVV in men with ANV $\geq$ 3 correlated with BC (SRCC = 0.415, p = 0.044).

**Conclusions:** IRVV may serve as a surrogate for BC in patients with ANV $\geq$ 3. Additionally, the significant inverse correlation between ANV $\geq$ 3 and BC suggests that BC may serve as a therapeutic target in men with nocturia.

**Keywords:** Nocturia; Lower Urinary Tract Symptoms; Quality Of Life; Bladder Compliance; Voiding Diary

### Abbreviations

ICS: The International Continence Society;

FVC: Frequency Volume Chart;

24UV: 24-hour Urine Volume;

ANV: Actual Number of Nightly Voids;

NUV: Nocturnal Urine Volume;

MVV: Maximum Voided Volume;

IRVV: Interquartile Range Of Voided Volume [IRVV];

NI: Nocturia Index;

NPI: Nocturnal polyuria index;

BC: Bladder Compliance;

QoL: Quality of Life [QoL];

UDS: Urodynamic Studies;

SD: Standard Deviation;

SRCC: Spearman's Rank Correlation Coefficient;

BTT-A: Botulinum toxin type A

## Introduction

The International Continence Society [ICS] defines nocturia as the complaint that an individual has to wake at night one or more times to void, with each void being preceded and followed by sleep [1]. The Frequency Volume Chart [FVC] is a non-invasive tool that assists in determining the underlying mechanism of a patient's nocturia. A patient is asked to record the time and volume of daytime and nighttime voids. From this data, the physician can calculate several parameters to aid in diagnosis including 24-hour urine volume [24UV], actual number of nightly voids [ANV], nocturnal urine volume [NUV, urine produced from the time of retiring through the first void upon rising], maximum voided volume [MVV], interquartile range of voided volume [IRVV], nocturia index [Ni, (NUV/MVV)], and nocturnal polyuria index [NPI, (NUV/24UV)] [2]. Bladder compliance [BC] can be determined by dividing the change in volume by the change in detrusor pressure at bladder capacity as determined by pressure-flow tracings. Wyndaele et al. reported that BC can give information relevant for clinical management if correctly measured and interpreted [3]. Although BC is a useful diagnostic parameter, urodynamic pressure-flow studies have been associated with complications including urinary tract infection, as well as high subjective morbidity, especially in men [4]. Therefore, a method for determining BC from FVCs would be beneficial. Our clinical experience has been that patients with low BC often void at fixed volumes, both diurnally and nocturnally. This observation is supported by studies that demonstrated that patients with interstitial cystitis have both lower bladder compliance and less variance in their voided volumes than patients with overactive bladder [5,6]. As such, we hypothesize that IRVV correlates with BC.

The purpose of our study was to determine whether IRVV correlates with BC and can be used as a non-invasive surrogate for measuring BC. Furthermore, given the correlation between ANV and quality of life [QoL] [7-11], we seek to determine the relationship between BC and ANV as the nature of such a relationship may suggest a therapeutic target for the treatment of bothersome nocturia.

## Materials and Methods

We performed a retrospective analysis of male patients seen at a single center from 2009-2011 with lower urinary tract symptoms. All selected patients underwent urodynamic studies [UDS]. Patients completed a 24-hour FVC within 1 month of their UDS. The procedure used for the UDS was as follows: First, a urine sample was taken for a urine analysis and urine culture. 30 minutes prior to the procedure, patients were treated with prophylactic antibiotics depending upon urine culture data. A 7-French urethral catheter and a 14-French rectal catheter were inserted, EMG patches were attached to the buttocks and another EMG patch was attached to the left thigh.

After the catheters were connected to the UDS system, the patient sat up and the fluoroscope was positioned to take images of bladder and urethra during filling and voiding. Volume was noted at the patient's first sensation, the patient's first desire to urinate, the patient's first strong desire to urinate, and once the patient desperately needed to void and could no longer hold his urine.

ANV was determined for each voiding diary. BC was determined from the pressure-flow tracing by dividing the change in volume by the change in detrusor pressure at bladder capacity (prior to detrusor contraction). The population was separated based upon cutoff values of 20, 40, and 60 mL/cm H<sub>2</sub>O for BC. Average ANV for each group above and below each cutoff value were compared to one another. Student's t-test was used to determine whether differences in the average ANV for each group were significantly different using SPSS® software.

Additionally, a subgroup analysis of men with ANV  $\geq 3$  was performed in which IRVV was determined from the voiding diaries using the QUARTILE.INC function (Microsoft Excel®). Both nocturia severity (as determined by ANV) and IRVV were compared to BC using Spearman's rank correlation coefficient using SPSS® software.

## Results

Our study included 102 men with a mean age of 68 years (age range 27-89, standard deviation [SD] 11). A total of 1082 voided volumes were recorded ranging from 10-800mL (mean 174, SD 115). ANV ranged from 0-11 (mean 2.8, SD 1.7). BC ranged from 10-450 mL/cm H<sub>2</sub>O (mean 66, SD 61). At all three cutoff values, the differences in average ANV between those above and those below the cutoff value were found to be statistically significant (Table I). Specifically, men with more compliant bladders had less nocturia than their counterparts with stiff bladders.

Our subgroup analysis of men with ANV  $\geq 3$  included 52 men with a mean age of 66 years (SD 14.6, age range 16-88). A total of 700 voided volumes were recorded ranging from 10-800mL (mean 174, SD 116). ANV ranged from 3-11 (mean 2.5, SD 1.86); IRVV ranged from 5-350mL (mean 95, SD 61). BC ranged from 17-392 mL/cm H<sub>2</sub>O (mean 86, SD 68). ANV  $\geq 3$  (Table II) was moderately inversely correlated with BC (Spearman's rank coefficient = -0.451, p = 0.027). IRVV in men with ANV  $\geq 3$  moderately correlated with BC (Spearman's rank coefficient = 0.415, p = 0.044). In other words, in men with ANV  $\geq 3$ , 17% (.415 x .415=0.17) of the variation in IRVV is determined by the variation in bladder compliance. That is, patients with stiffer bladders tend to have less variability in voided volumes and vice-versa.

Cohort Based on Bladder Compliance (number of patients)	Average ANV	SD	p-value	Confidence interval
Bladder Compliance $\leq 20$ ml/cmH <sub>2</sub> O (15)	3.6	1.24	0.0456	0.019-1.894
Bladder Compliance $> 20$ ml/cmH <sub>2</sub> O (87)	2.6	1.75		
Bladder Compliance $\leq 40$ ml/cmH <sub>2</sub> O (38)	3.5	1.64	0.0015	0.433-1.764
Bladder Compliance $> 40$ ml/cmH <sub>2</sub> O (64)	2.4	1.64		
Bladder Compliance $\leq 60$ ml/cmH <sub>2</sub> O (63)	3.3	1.76	0.0002	0.619-1.919
Bladder Compliance $> 60$ ml/cmH <sub>2</sub> O (39)	2	1.32		

**Table I:** Average ANV stratified by bladder compliance.

Bladder compliance vs.	Spearman's rho	p-value
ANV (all)	-0.287	0.039
ANV $\leq 2$	0.140	0.477
ANV $\geq 3$	-0.451	0.027
IRVV (all ANV)	0.264	0.059
IRVV (ANV $\leq 2$ )	-0.002	0.991
IRVV (ANV $\geq 3$ )	0.415	0.044

**Table II:** Bladder compliance compared to ANV and IRVV.

## Discussion

Nocturia has been associated with increased mortality, decreased QoL, and decreased economic production [7-15]. Studies have found that QoL significantly decreases when a patient experiences two or more episodes of voiding, and that QoL continues to decrease as number of voids increases [7-11]. Therefore, by decreasing ANV we may be able to improve QoL for those experiencing nocturia. Our study found ANV to be significantly correlated BC suggesting a possible therapeutic target. As an example, botulinum toxin type A [BTT-A] has been shown to improve BC and improve urinary symptoms in patients with spinal cord lesions [16]. Additionally, several studies have shown antimuscarinic medications to improve urinary symptoms and increase BC in patients with neurogenic overactive bladder [17-19]. Hence, BTT-A and antimuscarinic medications could be of therapeutic use in selected patients with decreased BC and severe nocturia.

Given the multifactorial nature of nocturia, several diagnostic tools, including FVCs and (where indicated based on clinical evaluation) urodynamic testing, can assist in the management of a patient experiencing nocturia. Urodynamic testing is invasive and has been associated with complications including urinary tract infection, as well as high subjective morbidity, especially in men [4]. However, urodynamic testing can be used to determine BC, a variable that has been reported to be useful in the clinical management of nocturia [3]. Our study suggests that in certain populations, IRVV, which can be calculated from the FVC, can be used as a correlate for BC. Specifically we found

that men with ANV  $\geq 3$  had an IRVV that moderately correlated with BC.

Our study was limited by several factors. We had a sample size of 102 and the subgroup analysis was limited to 52 of the patients. Diversity was limited in that all of our patients were men, and they were all patients at a single center. Though all of the patients completed a bladder diary within one month of UDS, we did not make note of exactly how many days after the UDS each patient completed the bladder diary. Analysis of such data may reveal a pattern of bias (i.e. hypothetically patients with a smaller latency period between UDS and completion of a bladder diary may self-select for the group with the most severe nocturia). Future investigation could involve a larger sample size and more diverse population including patients of both genders from multiple centers. Such a study may make the conclusions more applicable to the general population. The vast majority of our patients had an ANV  $\leq 3$  (72/102, 71%). As such, analysis comparing daytime IRVV to nighttime IRVV would be of little statistical significance. By expanding our sample-size, we can increase the sample of patients with large ANVs (ANV  $\geq 4$ ) and perform a more meaningful analysis on how daytime IRVV compares to nighttime IRVV.

## Conclusion

Bladder compliance was found to be inversely correlated to nocturia severity. This inverse relationship between nocturia severity and BC suggests an avenue for research in nocturia therapy through means to improve BC. The correlation between IRVV and BC demonstrated herein suggests that IRVV may be used as a surrogate for BC in patients with severe nocturia (ANV  $\geq 3$ ). Further study with a larger and more diverse population of both genders may improve the generality of these conclusions.

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