



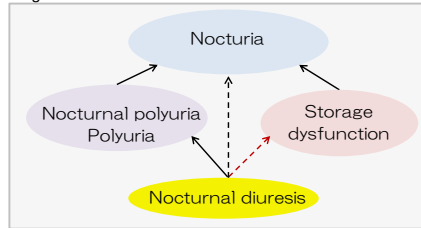
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## Introduction

Nocturia has two major causes. One problem is with the nocturnal urine volume, and the other is a problem with bladder capacity during the night. Since multiple factors affect nocturia, what affects it most has not been well investigated. We have been studying a bladder homeostatic system called "vesical adaptation response to diuresis (VARD)", which keeps micturition interval constant by increasing the bladder capacity during the diuretic phase.<sup>1)</sup> Impaired VARD results in storage dysfunction specific to the diuretic phase. Therefore, We hypothesized that **nocturnal diuresis** could affect **not only nocturnal polyuria but also bladder storage function**, causing nocturia.



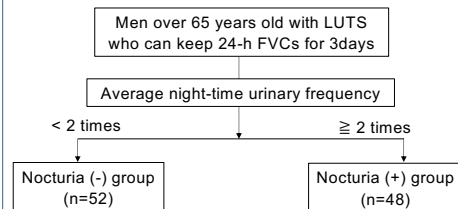
### Aim of Study

This study aimed to identify what factors are most associated with nocturia and investigate how strongly nocturnal diuresis affects bladder storage dysfunction as a factor related to nocturia.

## Methods and Materials

### Study design

Male patients with LUTS who were able to keep 24-h frequency-volume charts (FVCs) for 3 days were included in this study. Exclusion criteria were apparent neurogenic lower urinary tract symptoms, clean intermittent catheterization, and acute urinary tract infection. Uroflowmetry, ultrasonography to measure prostate volume, Overactive Bladder Symptom Score (OABSS) and 24-h FVCs were evaluated. OABSS evaluated OAB as a total score >3 and an urgency score >2. Nocturnal polyuria (NP) was diagnosed using the NP index (NPI) >0.33 definition (nocturnal urine volume >33% of total 24-hour urine volume). Patients who marked an average of two or more times per night on 3-days 24h-FVCs were defined as the nocturia (+) group, and those who marked less than two times were defined as the nocturia (-) group. Age, prostate volume, with and without NP and OAB, and parameters of 24-h FVCs were compared between groups.



### Statistical analysis

Mann-Whitney U-test was used to compare differences between groups. Correlations between categorical variables were investigated by simple regression analysis using the square of Pearson's correlation coefficient. Multivariable analyses were performed using multiple linear regression. P values < 0.05 were taken to indicate statistical significance.

## Results

### Result 1. Patient characteristics

Patients with nocturia was significantly older, had a smaller prostate volume and developed OAB than that without nocturia. All patients with nocturnal polyuria (NP) had nocturia.

Table 1. Patient characteristics with and without nocturia

|                        | Nocturia (-) | Nocturia (+) | P value |
|------------------------|--------------|--------------|---------|
| Age, years             | 74.1 ± 7.2   | 77.9 ± 5.4   | < 0.01  |
| BMI, kg/m <sup>2</sup> | 23.7 ± 3.2   | 22.8 ± 3.2   | 0.44    |
| HT, n (%)              | 30 (41.1)    | 38 (55.9)    | 0.18    |
| DM, n (%)              | 10 (45.5)    | 12 (54.5)    | 0.49    |
| SAS, n (%)             | 4 (8.0)      | 1 (2.0)      | 0.16    |
| NP, n (%)              | 0 (0.0)      | 37 (71.2)    | < 0.01  |
| OAB, n (%)             | 16 (36.4)    | 28 (63.6)    | 0.02    |
| Prostate volume (mL)   | 40.3 ± 20.3  | 30.5 ± 17.0  | 0.02    |

Values are mean ± SEM

HT: hypertension, DM: Diabetes mellitus, SAS: Sleep apnea syndrome, NP: Nocturnal polyuria (NPI >0.33)

### Result 2. Lower urinary tract function

Variables included in the 3-day 24-h FVCs including nocturnal diuresis rate were compared between groups. Mean nocturnal voided volume was significantly lower, and mean night-time urinary frequency and nocturnal diuresis rate was significantly higher in the Nocturia (+) group than in the Nocturia (-) group. Maximum flow rate and Post-void residual urine did not differ significantly between groups.

Table 2. Parameters of FVCs and uroflowmetry

|                                    | Nocturia (-) | Nocturia (+) | P value |
|------------------------------------|--------------|--------------|---------|
| Total voided volume, L/day         | 1.55 ± 0.45  | 1.79 ± 0.51  | 0.05    |
| Mean voided volume, mL             | 186.2 ± 67.9 | 174.6 ± 49.2 | 0.44    |
| Day-time voided volume, mL         | 173.0 ± 74.1 | 146.2 ± 40.1 | 0.18    |
| Nocturnal voided volume, mL        | 250.1 ± 80.6 | 213.1 ± 65.4 | 0.02    |
| Night-time urinary frequency, /day | 0.82 ± 0.60  | 3.2 ± 0.96   | < 0.01  |
| Nocturnal diuresis rate, mL/min    | 54.0 ± 28.9  | 91.1 ± 51.8  | < 0.01  |
| Maximum flow rate, mL/s            | 9.7 ± 5.1    | 9.6 ± 4.3    | 0.68    |
| Post-void residual urine, mL       | 40.4 ± 42.2  | 40.2 ± 47.6  | 0.60    |

Values are mean ± SEM

### Result 3. Multivariate analysis to find factors besides NP associated with nocturia

Since all patients with nocturnal polyuria had nocturia, patients with nocturnal polyuria were excluded from the analysis. Even when limited to patients without NP, increased nocturnal diuresis rate and decreased nocturnal voided volume were significantly related to nocturia in male LUTS patients.

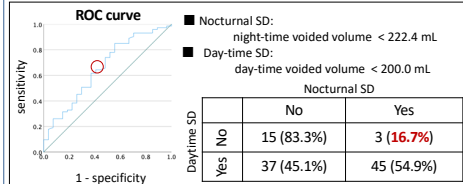
Table 3. Summary of multivariate analysis finding factors (n=51)

|                         | OR   | 95% CI        | P value |
|-------------------------|------|---------------|---------|
| Age                     | 0.95 | 0.945 – 1.074 | 0.43    |
| Nocturnal voided volume | 0.98 | 0.968 – 0.996 | 0.01    |
| Nocturnal diuresis rate | 1.04 | 1.009 – 1.061 | 0.01    |

### Result 4. Characteristics of patients with nocturia due to decreased night-time voided volume

Since bladder storage volume increases during the night, nocturnal storage dysfunction (SD) were defined as a night-time voided volume of 222.4 ml or less based on the ROC curve (AUC 0.66, sensitivity 62.5%, specificity 42.3%). Daytime SD was defined as less than 200 ml. Then, 16.7% of patients without daytime SD showed bladder storage dysfunction **only at night**.

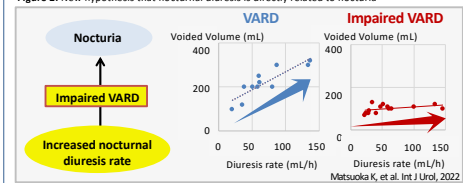
Figure 1. Estimation of nocturnal storage dysfunction



## Discussion

- This study showed that **all patients with NP had nocturia**. NP is thought to be a major contributor to nocturia in the elderly, but the number of patients in this study was probably insufficient.
- In the patients without NP, increased nocturnal diuresis rate and decreased nocturnal voided volume** were also independent risk factors for nocturia. Even if nocturnal polyuria was not diagnosed, it was possible that nocturnal diuresis itself could contribute to nocturia via a nocturnal SD including impaired VARD.

Figure 2. New hypothesis that nocturnal diuresis is directly related to nocturia



## Conclusions

Strategies focusing on nocturnal bladder storage dysfunction associated with increased nocturnal diuresis rate may be necessary for treating nocturia in elderly patients.

## References

- Matsuoka K, Akaihata H, Hata J, et al. Insight into the development of a new index, vesical adaptation response to diuresis, for understanding lower urinary tract dysfunction. Int J Urol. Apr;29(4):297-303, 2021

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