Prediction of Nocturia Severity in Men
Nocturnal Urine Overproduction vs Race or Metabolic Risk Factors

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IMPORTANCE Nocturia is one of the most common and bothersome of lower urinary tract symptoms.

OBJECTIVE To examine the effect of race and metabolic risk factors on nocturia severity in men as measured by the number of nightly voids.

DESIGN, SETTING, AND PARTICIPANTS A retrospective review from 2011 to 2013 was performed at a Veterans Affairs-based urology clinic in Brooklyn, New York, among 104 adult men 18 years or older who completed a 24-hour frequency and volume chart. Metabolic risk factors included race and a history of diabetes mellitus, hypertension, and obstructive sleep apnea. The 24-hour frequency and volume chart data included the nocturia index (nocturnal urine volume divided by maximal voided volume), the nocturnal polyuria index (nocturnal urine volume divided by 24-hour volume), and nocturnal urine production (nocturnal urine volume per hours slept). A nocturia index of less than 2 vs 2 or higher, a nocturnal polyuria index of less than 33% vs 33% or higher, and nocturnal urine production of less than 90 vs 90 mL/h or higher were chosen as clinically relevant cutoff points for nocturia severity. Nocturia severity was compared by race, the aforementioned variables, and the presence or absence of diabetes mellitus, hypertension, and obstructive sleep apnea.

MAIN OUTCOMES AND MEASURES The number of nightly voids.

RESULTS One hundred four adult men (mean age, 64 years; age range, 24-92 years) completed a 24-hour frequency and volume chart (mean number of nightly voids, 2.93; range, 0-15). The number of nightly voids was not statistically different for white vs black race (3.00 vs 2.93, \(P = .86\)) or for the presence vs the absence of diabetes mellitus (3.00 vs 2.88, \(P = .85\)), hypertension (2.94 vs 2.80, \(P = .75\)), and obstructive sleep apnea (2.93 vs 2.83, \(P = .50\)). However, nocturia severity was significantly different based on a nocturia index of less than 2 vs 2 or higher (1.39 vs 3.60), a nocturnal polyuria index of less than 33% vs 33% or higher (1.83 vs 3.65), and nocturnal urine production of less than 90 vs 90 mL/h or higher (2.27 vs 3.77) \((P < .001\) for all).

CONCLUSIONS AND RELEVANCE Neither race nor metabolic risk factors affect nocturia severity. In contrast, variables that denote nocturnal urine overproduction sharply discriminate the risk of nocturia severity and suggest that variable data may provide useful clinical correlation.

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nocuturia is one of the most bothersome of lower urinary tract symptoms for adult men and women. It is also remarkably prevalent, with approximately 60% of elderly individuals reporting severe nocturia in the form of 2 or more voids per night. Perhaps most important, nocturia contributes to morbidity via an increased risk of nocturnal falls and bone fractures in older persons.

The evaluation of nocturia takes into account multiple risk factors, including medical history, physical examination, and a voiding diary analysis. Studies have demonstrated an association between a diabetes mellitus (DM) diagnosis and nocturia. The results of similar studies have suggested an association between black race and nocturia as well as between hypertension and nocturia. Obstructive sleep apnea (OSA) has also been cited as a cause of nocturia secondary to nocturnal polyuria. However, few data correlate the presence or absence of the aforementioned risk factors with the degree of nocturia severity. The objective of this study was to examine the effect of race and a history of metabolic risk factors on nocturia severity (number of nightly voids) in a Veterans Affairs–based male population.

Methods
Veterans Affairs New York Harbor Healthcare System Institutional Review Board approval was obtained before initiation of the study. A retrospective review from 2011 to 2013 was performed. One hundred four men with lower urinary tract symptoms completed a 24-hour frequency and volume chart (FVC) at an equal-access Veterans Affairs–based urology clinic. Inclusion criteria were age 18 years or older, male sex, and report of lower urinary tract symptoms. Those with an incomplete or incorrectly recorded FVC were excluded. Possible risk factors were recorded, including race (white vs black) and a history of DM, hypertension, and OSA. All patients were identified as having DM or hypertension based on their current medications. However, not all patients with OSA were compliant with continuous positive airway pressure despite sleep study–based diagnosis. The 24-hour FVC-derived variables were analyzed, including the nocturia index (nocturnal urine volume [NUV] divided by maximal voided volume), the nocturnal polyuria index (NUV divided by 24-hour volume), and nocturnal urine production (NUP) (NUV per hours slept). A nocturia index of less than 2 vs 2 or higher, a nocturnal polyuria index of less than 33% vs 33% or higher, and NUP of less than 90 vs 90 mL/h or higher were chosen as clinically relevant cutoff points for nocturia severity. A test was used to compare nocturia severity as distinguished by race, the aforementioned FVC-derived variables, and the presence or absence of DM, hypertension, and OSA. Statistical significance was set at $P < .05$.

Results
Of 104 adult men who completed a 24-hour FVC, 50 were of white race, and 54 were of black race. The mean age of all men who completed a 24-hour FVC was 64 years (age range, 24-92 years). The mean age was older for white men than for black men (73 vs 64 years). The mean number of nightly voids among all men was 2.93 (range, 0-15). No significant difference in the number of nightly voids was observed for white vs black race (3.00 vs 2.93, $P = .86$).

Twenty-five men (24.0%) had DM. No significant difference in the number of nightly voids was observed between men with vs without DM (3.00 vs 2.88, $P = .85$). Similarly, no significant differences in the number of nightly voids were noted between men with (n = 78) vs without (n = 26) hypertension (2.94 vs 2.80, $P = .75$) or between men with (n = 21) vs without (n = 83) OSA (3.29 vs 2.83, $P = .50$). These results are summarized in Table 1.

Comparing white men with DM vs black men with DM, no significant difference in the number of nightly voids was observed (2.36 vs 4.00, $P = .25$). Similarly, no statistical difference was found in men with hypertension (2.91 vs 3.00, $P = .85$) or OSA (2.60 vs 3.91, $P = .30$).

We noted a significant association between the number of nightly voids and various FVC variables. Seventy-three men (70.2%) recorded a nocturia index of 2 or higher, indicating that NUV is at least 2 times greater than maximal voided volume, as well as that nocturnal urine overproduction occurs and results in nocturnal voids in relation to bladder capacity. This finding suggests that men with nocturia may be producing excess urine when sleeping, which cannot be comfortably stored based on their maximal voided volume (a proxy for maximal bladder capacity). These men reported significantly more nightly voids than men who recorded a nocturia index of less than 2 (3.60 vs 1.39, $P < .001$). Similarly, 64 men (61.5%) recorded a nocturnal polyuria index of 23% or higher, indicating nocturnal polyuria. These men had significantly more nightly voids than men who reported a nocturnal polyuria index of less than 33% (3.65 vs 1.83, $P < .001$). Men with NUP of 90 mL/h or higher (45.2%) also reported significantly more nightly voids than men with NUP of less than 90 mL/h (3.77 vs 2.27, $P < .001$). These results are summarized in Table 2.
Prediction of Nocturia Severity in Men

Discussion

The American Urological Association \(^1\) recommends a 24-hour FVC for all patients with lower urinary tract symptoms. The FVC aids in determining the pathophysiological cause of nocturia, which can then help in management. Five major etiological classifications of nocturia are global polyuria, nocturnal polyuria, decreased functional bladder capacity, primary sleep disorders, and combinations (also known as mixed nocturia etiology). \(^18\)

Global polyuria is defined as greater than 40 mL/kg of urine produced within 24 hours. \(^19\) Diabetes mellitus, diabetes insipidus, and primary polydipsia represent a few disease states associated with global polyuria. \(^20\) In contrast, nocturnal polyuria is defined as an excessive volume of urine produced during sleep despite a 24-hour output of less than 40 mL/kg. Increased urine production when asleep may be related to changes in circadian release of antidiuretic hormone, mobilization of peripheral fluid, or increased nocturnal release of atrial natriuretic peptide. \(^20\) Nocturnal polyuria is common and a leading cause of nocturia in adults. \(^21,22\)

Another benefit of the FVC in the evaluation of nocturia includes assessment of nocturnal bladder capacity to determine whether the bladder can accommodate NUV. Decreased functional bladder capacity may be secondary to structural or functional lower urinary tract abnormalities, specifically bladder outlet obstruction, overactive bladder, neurogenic bladder, calculi, or cancer. Finally, primary sleep disorders, such as insomnia or arousal disorders; neurologic conditions; psychiatric conditions; or drug or alcohol abuse may result in nighttime voiding secondary to simply awakening with subsequent elective voiding. \(^18\)

Our analysis showed a significant association between nocturia severity as defined by the number of nightly voids and nocturnal urine overproduction as a function of bladder capacity, 24-hour urine production, and time via the FVC variables (the nocturia index, the nocturnal polyuria index, and NUP, respectively). Therefore, our findings bolster the growing body of evidence suggesting that nocturnal polyuria and reduced bladder capacity may function as major contributors to the clinical symptom of nocturia. \(^23,26\)

Despite the evidence suggesting an association between DM or hypertension and nocturia, \(^4,12,14,15\) our analysis failed to demonstrate a significant difference in nocturia severity based on DM or hypertension status. However, those investigators who have demonstrated an association between nocturia and DM or hypertension must consider elderly status as a potential confounding factor. Widespread literature supports aging as the most pertinent risk factor for nocturia. \(^1,6,11,27-29\) The mean age of 64 years among the study group herein is not considered elderly, who are usually classified as 70 years or older. We acknowledge that failure to control for age was a limitation of our study. Therefore, age-related sources of nocturnal urine overproduction may have a role in our results.

Our study had other limitations as well. Data were captured based on a single FVC, and it is unclear whether this is a true baseline for the included patients. Three diaries would have been ideal for our study; however, our patient population was poorly compliant with multiple-day diaries. The few diaries collected may also have influenced our statistical significance, and it is possible that significance may have been achieved with more patients. In addition, we did not have a control group of patients who completed FVCs, which we also relate to a poorly compliant patient population. Furthermore, we limited our database and subsequent analysis to men, and it is unclear whether the results can be applied to women. However, this is largely a function of the overwhelming presence of men within the Veterans Affairs population.

Conclusions

We found no significant association between nocturia severity and race, DM, hypertension, or OSA. However, a significant association was observed between nocturia severity and nocturnal urine overproduction as a function of bladder capacity, urine volume, and time. The FVC remains a vital and important tool in the analysis of nocturia and its etiology.

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**Table 2. Correlation Between Nocturia Severity and 24-Hour Frequency and Volume Chart–Based Nocturia Variables**

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Nightly Voids, Mean</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nocturia index</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2 (n = 31)</td>
<td>1.39</td>
<td></td>
</tr>
<tr>
<td>≥2 (n = 73)</td>
<td>3.60</td>
<td></td>
</tr>
<tr>
<td>Nocturnal polyuria index</td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>&lt;33% (n = 40)</td>
<td>1.83</td>
<td></td>
</tr>
<tr>
<td>≥33% (n = 64)</td>
<td>3.65</td>
<td></td>
</tr>
<tr>
<td>Nocturnal urine production, mL/h</td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>&lt;90 (n = 57)</td>
<td>2.27</td>
<td></td>
</tr>
<tr>
<td>≥90 (n = 47)</td>
<td>3.77</td>
<td></td>
</tr>
</tbody>
</table>

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**ARTICLE INFORMATION**

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Study concept and design: Nassau, Weiss, Blaivas.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Nassau, Avulova, Friedman.

Critical revision of the manuscript for important intellectual content: Nassau, Friedman, Weiss, Blaivas.

Statistical analysis: Blaivas.

Administrative, technical, or material support: Avulova, Weiss.

Study supervision: Friedman, Weiss, Blaivas.

Conflict of Interest Disclosures: Dr. Weiss reported being a consultant for Ferring, Pfizer, Allergan, Astellas, Lilly, and Vantia and reported serving as a board member for Symptelligence. Dr Blaivas reported having equity interests in Endogun/IIB and Augmentrix and reported being an owner of Symptelligence and Klypit. No other disclosures were reported.

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REFERENCES