Diagnosing the Pathophysiologic Mechanisms of Nocturnal Polyuria

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Abstract

Background: Diagnosis of nocturnal polyuria (NP) is based on a bladder diary. Addition of a renal function profile (RFP) for analysis of concentrating and solute-conserving capacity allows differentiation of NP pathophysiology and could facilitate individualized treatment.

Objective: To map circadian rhythms of water and solute diuresis by comparing participants with and without NP.

Design, setting, and participants: This prospective observational study was carried out in Ghent University Hospital between 2011 and 2013. Participants with and without NP completed a 72-h bladder dairy. RFP, free water clearance (FWC), and creatinine, solute, sodium, and urea clearance were measured for all participants.

Results: The study participants were divided into those with (n = 77) and those without (n = 35) NP. The mean age was 57 yr (SD 16 yr) and 41% of the participants were female. Compared to participants without NP, the NP group exhibited a higher diuresis rate throughout the night (p = 0.015); higher FWC (p = 0.013) and lower osmolality (p = 0.030) at the start of the night; and persistently higher sodium clearance during the night (p < 0.001). The pathophysiologic mechanism of NP was identified as water diuresis alone in 22%, sodium diuresis alone in 19%, and a combination of water and sodium diuresis in 47% of the NP group.

Conclusion: RFP measurement in first-line NP screening to discriminate between water and solute diuresis as pathophysiologic mechanisms complements the bladder diary and could facilitate optimal individualized treatment of patients with NP.

Patient summary: We evaluated eight urine samples collected over 24 h to detect the underlying problem in NP. We found that NP can be attributed to water or sodium diuresis or a combination of both. This urinalysis can be used to adapt treatment according to the underlying mechanism in patients with bothersome consequences of NP, such as nocturia and urinary incontinence.

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1. Introduction

Nocturnal polyuria (NP) is an important cause of nocturia in adults and nocturnal enuresis (NE) in children [1]. Results of extensive investigations into the pathophysiology of NE in children have led to individualized treatments with higher efficacy rates and lower side effects [2,3]. In adults, NP is diagnosed based on a bladder diary, and treatment is more often based on trial and error than on evidence-based findings [4]. Extrapolation of pediatric data suggests that...
measurement of a 24-h concentration or renal function profile (RFP) for analysis of the nocturnal diuresis rate, concentrating capacity, and solute-conserving capacity could allow differentiation of NP pathophysiology as a guide to individualized treatment of adult patients with NP, as in children with NE [5].

In studies with limited participants, water diuresis and/or solute diuresis were identified as pathophysiologic mechanisms that play a role in adult NP [5]. Water diuresis is associated with impairment of vasopressin action, whereas solute diuresis can be due to increased atrial natriuretic peptide secretion, as seen in patients with obstructive sleep apnea and patients with heart failure [6]. Impaired circadian rhythms for these hormones also affect the circadian rhythms for renal clearance of free water and solutes. Healthy children exhibit marked circadian rhythms for hormones involved in urine production [7]. It is believed that a loss of these circadian rhythms in older patients is a physiologic aging effect. However, the consequences can be pathologic, for example when NP leads to bothersome nocturia affecting general health and sleep quality [8,9]. In younger adults, circadian rhythms are assumed to be somewhere in between those of children and older individuals, but evidence is limited.

The aims of this study were:

1. To map circadian rhythms for water and solute diuresis in populations with and without NP to establish a reference for normal circadian rhythms in an adult population;
2. To evaluate the use of RFPs in the diagnostic approach to NP; and
3. To evaluate the distribution of different pathophysiologic mechanisms of NP among patients.

2. Patients and methods

2.1. Patient selection and data collection

A prospective observational study was designed and carried out in Ghent University Hospital, Belgium, between October 2011 and May 2013. Participants were recruited via posters, brochures, and consultations. There were no specific inclusion criteria. Exclusion criteria were neurogenic bladder and/or bladder/urethra surgery. On the basis of There were no specific inclusion criteria. Exclusion criteria were 24-h polyuria and patients with heart failure [6]. Impaired circadian rhythms for these hormones also affect the circadian rhythms for renal clearance of free water and solutes. Healthy children exhibit marked circadian rhythms for hormones involved in urine production [7]. It is believed that a loss of these circadian rhythms in older patients is a physiologic aging effect. However, the consequences can be pathologic, for example when NP leads to bothersome nocturia affecting general health and sleep quality [8,9]. In younger adults, circadian rhythms are assumed to be somewhere in between those of children and older individuals, but evidence is limited.

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2.2. Statistical analysis

Statistical analysis was performed using SPSS v.21 for Windows (IBM Corp, Armonk, NY, USA). The median, interquartile range, and frequency were recorded as descriptive statistical parameters. Differences between groups were assessed using the chi-square test for dichotomous variables and the Mann-Whitney U test for nonparametric variables. Comparisons within groups were performed using the Wilcoxon signed rank test for two related samples, and the Kruskall-Wallis test for more than two related samples. Linear regression analysis and receiver operating characteristic (ROC) curves were used to determine cutoff values. A p value <0.05 was considered statistically significant.

3. Results

The results for 112 subjects were eligible for analysis; 77 with NP and 35 without NP. The mean age was 57 yr (SD 16 yr) and 41% of the participants were female. Significantly higher nocturnal voided volume (NVV; p < 0.001) and nighttime frequency (p < 0.006) were observed in the NP group (Table 1).

3.1. Reference population

Table 2 shows data for daytime and nighttime diuresis rates, free water clearance (FWC), osmolality, and creatinine, solute, sodium, and urea clearance for participants without NP. The nighttime diuresis rate was significantly lower than the daytime rate (p = 0.005). Solute (p < 0.002) and sodium (p = 0.025) clearance rates and the sodium excretion rate (p = 0.031) were significantly lower at night. Urea clearance was also lower at night (p < 0.001). FWC and creatinine clearance did not differ significantly between day and night.

Figure 1 shows a more detailed representation of the circadian rhythms. The diuresis rate during the daytime was relatively stable (p = 0.245) and then decreased at night (U6–U8, p = 0.043). No significant daytime variation was seen.
for FWC, osmolality, solute, sodium or urea clearance. There were significant nocturnal decreases in solute ($p < 0.001$), sodium ($p = 0.006$) and urea clearance ($p = 0.013$). A 24-h variation (U1–U8) was seen for the diuresis rate and for solute, sodium, and urea clearance.

### 3.2. NP population

Reversed day-night rhythms for concentrations were observed in participants with NP (Table 2). Comparison of nighttime with daytime values revealed no significant decrease in the diuresis rate ($p = 0.433$), a significant increase in FWC ($p = 0.021$), and a significant decrease in osmolality ($p < 0.001$). Creatinine clearance was lower at nighttime compared to daytime ($p = 0.036$). Whereas solute clearance was significantly lower at night ($p = 0.023$), sodium clearance remained at the same levels as during the day ($p = 0.592$), and sodium excretion increased at night ($p = 0.012$). Compared to the reference population without NP, significant differences were observed for the nighttime diuresis rate ($p = 0.019$) and sodium excretion ($p = 0.007$).

Variations during daytime and nighttime (Fig. 1) revealed a stable diuresis rate during both daytime and nighttime for participants with NP. FWC and osmolality showed no significant variation during daytime; at night, FWC decreased from the initial peak ($p < 0.001$) and osmolality increased from the initial drop ($p < 0.001$). The reverse was seen for solute, sodium, and urea clearance, with significant increases during the daytime ($p < 0.001$, $p = 0.021$, respectively), but no variation during the nighttime. All parameters exhibited significant 24-h variation.

### 3.3. Reference versus NP participants

Comparison of the reference and NP participants revealed significant differences during the night (Fig. 1). At the start

| Table 1 – Characteristics of participants with and without nocturnal polyuria (NP) |
|---------------------------------|-----------------|-------|
| Age (yr)                        | No NP ($n = 35$) | NP ($n = 77$) | $p$ value |
|                                | 57 (49–66)       | 61 (50–68)   | 0.775    |
| Gender, male/female (% female)  | 18/17 (49)       | 49/30 (38)   | 0.279    |
| Body mass index (kg/m²)         | 24 (22–27)       | 25 (23–27)   | 0.514    |
| Peak flow rate (ml/s)           | 18 (8–59)        | 16 (5–70)    | 0.143    |
| Post-voiding residual volume, % | 34; 36 (15–157)  | 38; 40 (11–209) | 0.354    |
| Female lower urinary tract symptoms (women only) | | |
| Storage symptoms (max 15)       | 3 (0–7)          | 4 (0–10)     | 0.493    |
| Voiding symptoms (max 12)       | 0 (0–6)          | 1 (0–6)      | 0.115    |
| Incontinence symptoms (max 20)  | 2 (0–7)          | 1 (0–14)     | 0.134    |
| Male lower urinary tract symptoms (men only) | | |
| Voiding symptoms (max 20)       | 5 (0–12)         | 8 (0–16)     | 0.214    |
| Incontinence symptoms (max 24)  | 3 (0–9)          | 5 (0–19)     | 0.707    |
| Drinking volume (ml)            | 1794 (1498–2072) | 1710 (1333–2107) | 0.462    |
| 24-h urine volume (ml)          | 1610 (1390–2048) | 1773 (1388–2210) | 0.376    |
| Nocturnal voided volume (ml)    | 313 (233–456)    | 643 (449–865) | 0.001    |
| Mean 24-h functional bladder capacity (ml) | 212 (171–267) | 196 (150–285) | 0.557    |
| Maximum voided volume (ml)      | 353 (277–407)    | 350 (267–480) | 0.613    |
| Voiding frequency daytime       | 7 (6–9)          | 7 (6–9)      | 0.472    |
| Voiding frequency nighttime      | 0 (0–2)          | 1 (0–3)      | 0.006*   |

Data are presented as median (interquartile range) unless indicated otherwise.

* $p < 0.05$, Mann-Whitney U test.

| Table 2 – Daytime and nighttime parameters for participants with and without nocturnal polyuria (NP) |
|---------------------------------|-----------------|-------|
| Diuresis rate (ml)              | No NP ($n = 35$) | NP ($n = 77$) | $p$ value |
|                                | 1.2 (0.9–1.8)   | 1.0 (0.8–1.3) | 0.005 |
|                                | 1.3 (0.9–1.7)   | 1.4 (0.9–1.8) | 0.433 |
| Free water clearance (ml/min)   | 0.8 (–1.4 to 0.4) | 0.8 (–1.2 to 0.5) | 0.291 |
|                                | 1.0 (–1.6 to 0.5) | 0.7 (–1.3 to 0.3) | 0.021 |
| Osmolality (mosm/kg)            | 550 (422–787)   | 626 (444–782)  | 0.176 |
|                                | 594 (481–729)   | 498 (396–656)  | 0.001 |
| Creatinine clearance (ml/min)   | 118 (98–156)    | 108 (87–54)    | 0.156 |
|                                | 128 (96–149)    | 115 (84–147)   | 0.036 |
| Solute clearance (ml/min)       | 2.4 (2.0–2.9)   | 2.0 (1.6–2.4)  | 0.002 |
|                                | 2.5 (1.8–3.0)   | 2.3 (1.7–2.8)  | 0.023 |
| Sodium clearance (ml/min)       | 0.9 (0.7–1.1)   | 0.7 (0.5–1.1)  | 0.025 |
|                                | 1.0 (0.7–1.2)   | 1.0 (0.7–1.2)  | 0.592 |
| Sodium excretion (mmol/l)/(mg/dl creatine) | 6.6 (6.0–7.5) | 5.8 (4.6–6.4) | 0.031 |
|                                | 6.3 (5.4–7.3)   | 6.5 (5.2–7.3)  | 0.012 |
| Urea clearance (ml/min)         | 57 (41–71)      | 18 (13–25)     | 0.001* |
|                                | 53 (37–67)      | 19 (14–25)     | 0.001* |

Data are presented as median (interquartile range).

* $p < 0.05$, within-group Wilcoxon test.

* $p < 0.05$, between-group Mann-Whitney U test.
of the night (U6), higher FWC \( (p = 0.013) \) and lower osmolality \( (p = 0.030) \) were observed in the NP group. In the middle of the night (U7), the diuresis rate remained high in the NP group, whereas it decreased in the reference group \( (p = 0.049); \) this trend continued until the end of the night \( (U8, p = 0.015). \) A difference in sodium clearance between the groups started at U7 \( (p < 0.001) \) and continued at U8 \( (p = 0.002). \) Solute clearance was higher in participants with NP compared to those without at U7 \( (p = 0.013); \) urea clearance did not differ at any point between the groups.

### 3.4. Pathophysiologic mechanisms of NP

ROC analysis to discriminate between the NP and reference groups revealed an area under the curve (AUC) of 65\% \( (p = 0.013) \) for nocturnal FWC (U6), with a cutoff value of \(-0.85\) ml/min corresponding to sensitivity of 66\% and specificity of 60\%. For nocturnal sodium clearance (U7) the AUC was 72\% \( (p < 0.001) \), with 0.65 ml/min corresponding to sensitivity of 69\% and specificity of 63\%.

Figure 2A shows the distribution of high FWC and/or high sodium clearance rates in participants with and without NP using the cutoff values with the highest sensitivity and specificity according to ROC analysis. None of the pathophysiologic mechanisms applied to 43\% of the reference group compared to 12\% of the NP group \( (p < 0.001); \) no significant difference was found for high FWC alone or high sodium clearance alone. The combination of both was significantly higher in participants with NP (47\%) than in the reference group (20\%; \( p = 0.022). \)

Using the NUP definition of NP of \( >90\) ml/h, ROC analysis revealed 76 subjects without NP and 36 with NP. For nocturnal FWC (U6) the AUC was 64\%, with highest sensitivity (71\%) and specificity (62\%) for a cutoff value of \(-0.65\) ml/min. For nocturnal sodium clearance (U7) the AUC was 67\%; a cutoff value of 0.77 ml/min resulted in sensitivity and specificity of 60\%.

According to these cutoff values, NP was attributed to high FWC alone in 34\%, high sodium clearance alone in 23\%, and a combination in 37\% of the NP group.

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**Fig. 1** – Circadian rhythms for (A) diuresis rate, (B) free water clearance, (C) osmolality, (D) solute clearance, (E) sodium clearance, and (F) urea clearance for participants with and without nocturnal polyuria (NP) according to eight urine samples collected over 24 h. Daytime urine samples were taken at 9–11 AM (U1), 12–2 PM (U2), 3–5 PM (U3), 6–8 PM (U4), and 9–11 PM (U5). Nighttime urine samples were taken at 12–2 AM (U6), 3–5 AM (U7), and 6–8 AM (U8). The table above each plot shows values for the within-group Kruskall-Wallis test; values in italics are significant. Reversed rhythms are evident for all variables except urea clearance for the NP group compared to the reference group \( (p < 0.05). \)

*p < 0.05 for NP versus the reference (no NP) group (Mann-Whitney U test).

**Fig. 2** – Distribution of the pathophysiologic mechanisms underlying nocturnal polyuria (NP) according to two different definitions: (A) NP index \( >20–33\% \) and (B) nocturnal urine production \( >90\) ml/h. FWC = free water clearance.
4. Discussion

NP can be considered a normal part of the aging process; it is known that loss of circadian rhythms for diuresis-regulating hormones and renal concentrating and sodium-conserving capacity occurs with advancing age [12,13]. However, the NP population in the present study did not consist of only older people (age range 18–85 yr), indicating that this process had already started at a younger age in a considerable proportion of the study population.

Healthy children exhibit a pronounced circadian rhythm, with a nocturnal decrease in the diuresis rate and excretion of solutes, and a nocturnal increase in urinary osmolality [14]. Although less pronounced, the adult population without NP exhibits a similar pattern for the diuresis rate and solute, sodium, and urea clearance, with a stable level during the day and a decrease during the night. FWC and osmolality, however, showed no significant circadian rhythm at all. Findings in our reference population suggest that the circadian rhythm for diuresis progressively disappears and NP starts from the age of 20–30 yr.

This study confirms that NP is a heterogeneous condition, in which water diuresis, solute diuresis, or a combination of both is the underlying cause. Water diuresis is represented by high FWC and low osmolality at night. For solute diuresis, the driving force seems to be increased sodium clearance during the night. Herek et al. [5] conducted a similar study to evaluate daytime and nighttime parameters for 24-h urine samples collected from 29 female patients with NP (mean age 74 yr) and described these three pathophysiologic subgroups of NP. This encourages categorization of NP to optimize the required treatment. A great advantage of the approach used in our study, with eight urine samples collected over 24 h, is that we can differentiate the timing of the pathophysiologic mechanisms involved. An increase in FWC and a decrease in osmolality were found only at the start of the night (U6), whereas sodium clearance in NP remained high throughout the night (U7 and U8).

Treatment with a V2 agonist is useful in NP patients with excessive water diuresis who have positive nocturnal FWC and/or low nocturnal osmolality, which is an indication of suppressed vasopressin. The time window in which a high V2 agonist response is expected is at the start of the night, which coincides with high FWC and low osmolality between 12 and 2 AM. Vasopressin can be suppressed by excessive fluid intake, so polydipsia has to be ruled out before starting V2 agonist treatment because of the risk of hyponatremia [15]. In the case of nocturnal sodium diuresis, treatment to restore a normal sodium clearance pattern could be indicated. By taking diuretics during the day, the body’s sodium load is handled during the day, leading to lower sodium excretion at night and thus lower NUP [16]. In the case of combined water and sodium diuresis, a combination of diuretics in the morning and antidiuretics in the evening might result in the desired decrease in NUP [17,18]. Treatment of NP with diuretics has only been studied in small samples in children with enuresis and in elderly individuals with nocturia. Nevertheless, these studies provide enough evidence to warrant large case-control trials to confirm the beneficial effect of diuretics on increased nocturnal sodium and water diuresis.

To evaluate the proportion of the study sample that qualifies for antidiuretic or diuretic treatment or both, ROC analysis was applied to the most representative samples for FWC and sodium clearance, U6 and U7, respectively. Using cutoff values with the best balance of sensitivity and specificity, almost half of the NP patients have combined water and solute diuresis and could benefit from a combination therapy, approximately 20% qualify for antidiuretic treatment, and another 20% qualify for diuretic treatment alone.

However, since the relevance of the ICS definition for NP is under discussion, ROC analysis was also applied for the NUP definition of >90 ml/h [19]. This resulted in higher cutoff values for FWC and sodium clearance. With these cutoff values, the distribution was approximately 30% for each of the subgroups, with no pathophysiologic mechanism identified for only 6% of the NP group. The most remarkable difference was a significantly lower proportion of the sample diagnosed with NP compared to the NPI > 20–33% definition (31% vs 69%, respectively).

These cutoff values are not intended to be extrapolated to a general NP population; rather, they serve as an indication of the distribution of the pathophysiologic mechanisms of NP.

4.1. Study limitations

Limitations of our study include the limited number of participants and the fact that comorbidities such as diabetes and arterial hypertension were not taken into account. Although the study population represents the population seen in clinical practice, we recommend larger studies in well-defined subgroups of NP patients to evaluate RFP differences and usable cutoff values.

5. Conclusion

NP is more than just an increase in overnight diuresis; it is a heterogeneous condition with two different underlying mechanisms: water diuresis and sodium diuresis. A large percentage of patients exhibit variable degrees of both characteristics.

RFP involving collection of eight urine samples over 24 h allows differentiation of the pathophysiologic mechanisms underlying NP and of the timing of high FWC or high sodium clearance during the night. Use of this test complements a bladder diary in diagnosing the characteristics of NP.

Author contributions: An-Sofie Goessaert had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Vande Walle, Everaert, Goessaert.

Acquisition of data: Goessaert, Everaert, Krott.

Analysis and interpretation of data: Goessaert, Vande Walle, Everaert, Krott.

Drafting of the manuscript: Goessaert, Everaert, Vande Walle.
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