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RESEARCH PAPER

Phenotyping nocturnal polyuria: circadian and age-related variations in diuresis rate, free water clearance and sodium clearance

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Abstract

Background: this study compares diuresis rate, sodium clearance and free water clearance (FWC) by age and time of day (nighttime vs. daytime) in subjects with and without nocturnal polyuria (NP) to determine whether these variables affect the phenotype of NP.
Methods: post hoc analysis of two prospective observational studies. Eight urine samples collected at 3-h intervals and a single blood sample were used to calculate daytime (10a/1p/4p/7p/10p) and nighttime (1a/4a/7a) diuresis rates, sodium clearance and FWC. Three mixed linear models were constructed for diuresis rate, sodium clearance and FWC using four predictor variables: NP status (present [nocturnal urine production >90 ml/h] vs. absent [≤90 ml/h]), time of day, age and study identification.
Results: subjects with NP experienced higher nighttime versus daytime diuresis rates, sodium clearance and FWC. Regardless of NP status, increased age was accompanied by an increase in the ratio of nighttime/daytime diuresis rate, nighttime sodium clearance and daytime sodium clearance. FWC showed a complex age effect, which was independent of time of day or NP status.
Conclusions: age-related increases in nighttime/daytime diuresis rate, 24-h sodium clearance and 24-h FWC are not specific to subjects with NP. The age-related surge in either nocturnal sodium clearance or nocturnal FWC may represent the relevant substrate for behavioural or pharmacologic interventions targeting sodium diuresis or free water diuresis, respectively. Increases in FWC in older age groups may reflect impaired circadian rhythmicity of endogenous AVP or changes in responsiveness of the aged nephron to water clearance.

Keywords: *urological*, *renal*, *nocturia*, *older people*

Key points

- Nocturnal urine overproduction, or 'nocturnal polyuria,' is the most common cause of nocturnal voiding in older adults.
- Nocturnal polyuria may be driven by excess sodium and/or excess free water leaving your kidneys.
- In our study, irrespective of nocturnal polyuria status, older age was accompanied by an increase in night-time sodium clearance.
- Free water clearance showed a complex effect with age, which was independent of time of day or nocturnal polyuria status.
- This age-related increase in nocturnal sodium and/or free water clearance may benefit from behavioural or pharmacologic therapy.

Introduction

Nocturia, defined as waking to void during the hours of intended sleep, is amongst the most common and bothersome lower urinary tract symptoms (LUTS) in the general population [1–4]. Although nocturia is common across patient populations, older individuals are particularly affected, with up to 60% of community-dwelling older males and females experiencing nocturia of two or more voids per night [5]. Nocturia is associated with significant morbidity and decreased quality of life, shown to have a direct adverse effect on sleep architecture and increase the risk of falls and hip fractures in older patients [6–9].

Nocturnal polyuria (NP)—alongside global polyuria, reduced bladder capacity (functional or extrinsic), and primary/secondary sleep disturbances—is one of the four major aetiologies which may underlie a patient's nocturia [10]. Age-related impairment in the circadian rhythm of hormones involved in the handling of both free water (i.e. arginine vasopressin [AVP]) and solutes (i.e. renin-angiotensin-aldosterone and natriuretic peptides) provides a foundation for the onset of NP [11–14]. However, it remains unclear whether circadian variations in water and sodium handling are consistent across different NP patient subpopulations by age.

Recent research suggests that various phenotypes can be assigned to patients with NP, whereby patients may have free water, sodium or mixed water/sodium diuresis [12, 15]. Treatment with AVP replacement therapy may be warranted if endogenous AVP is suppressed (as reflected by an increased free water clearance [FWC] and nighttime water diuresis) [15, 16]. Conversely, patients with an increased nighttime sodium diuresis (as reflected by high nighttime sodium clearance) may instead benefit from daytime administration of diuretics, which is thought to promote increased daytime sodium clearance and restore circadian sodium homeostasis [17]. Recent research has also demonstrated that dietary sodium restriction significantly reduces nocturnal voiding frequency and the proportion of urine produced at night ('Nocturnal Polyuria index') in patients with nocturia and high dietary sodium intake at baseline [18].

Past research comparing circadian rhythms of water and sodium diuresis in subjects with and without NP demonstrated that NP is a heterogeneous condition, in which a large proportion of participants with NP exhibit variable degrees of both nocturnal water and sodium diuresis [15]. However, the influence of age on circadian variations in water and sodium handling remains poorly understood. Accordingly, this study aims to compare circadian variations in diuresis rates, sodium clearance and FWC in subjects with and without NP across different age levels.

Methods

Study protocol

The present study is a post hoc analysis of data collected during two prospective observational protocols involving subjects at Ghent University Hospital from 2011 to 2016. The first protocol enrolled individuals ($n = 135$) recruited by the urology ambulatory care unit [15]. The second protocol ($n = 95$) recruited subjects $\geq$65 years who consulted the continence clinic [19]. The methods of both protocols have previously been described elsewhere in detail [15, 19].

For both protocols, participants completed a 24–72-h frequency-volume chart (FVC). Participants then collected urine samples at 3-h intervals for 24-h, wherein they were instructed to void at fixed 3-h intervals and record voided volumes, such that a total of 5 daytime (10 am/1 pm/4 pm/7 pm/10 pm) and 3 nighttime (1 am/4 am/7 am) samples were obtained. Precise times of data collection were not recorded by participants but, given a generally high rate of adherence with the study protocol (missing data ranged from 0.4 to 4.2% of samples across the 1840 samples), we were reasonably confident that the timing of study samples occurred close to pre-specified data collection intervals. For incontinent patients, detailed written and verbal instructions were provided for home measurements of incontinence weight on a home, kitchen-type household scale, which were added to FVC/3-h urine sampling volume totals. A total of 70 patients included at least one diaper weighing in their totals.

Upon completion of the FVC and 3-h urine sampling, patients provided a blood sample, which was used in along with the osmolality and sodium values of all eight urine samples to calculate solute clearance ($\text{urine}_{\text{osmolality}} \times \text{urine flow}/\text{plasma}_{\text{osmolality}}$), FWC (urine flow − solute

clearance) and sodium clearance ($urine_{sodium}$ × urine flow/$plasma_{sodium}$). NP was defined as a nocturnal urine production (voided volume + incontinence weight) >90 ml/h (NUP90) during the 24-h urine collection [20].

Ethical approval was obtained from the Ghent University Hospital ethics committee (EC/2011/565; EC/2013/950), and all subjects provided written informed consent in accordance with the Declaration of Helsinki.

Statistical analysis

Three separate mixed linear models were constructed for the three dependent variables (diuresis rate, sodium clearance and FWC). Four predictor variables were used in these models: NP status (present vs. absent), phase (nighttime vs. daytime), age (as a continuous measure) and study protocol (delineating the two studies merged for this investigation). For every regression performed, a quadratic age term (age squared) was incorporated into the model to determine whether a potential association with age was best described as linear or quadratic, as would be seen in a parabolic function. When the quadratic term was non-significant, it was removed from the model. Intra-subject covariance structure was modelled as unstructured. Given large differences in sample sizes across the different age groups [15,19], we employed Kenward–Rogers adjustments to standard errors and denominator degrees of freedom [21]. Dependent variables were transformed as needed to improve normality of residuals; a very small number of outlying observations were excluded as necessary.

Two-way, three-way, and four-way interactions (if applicable) were tested for significance. For all significant interactions, predictor variable stratification was performed in order to more clearly demonstrate the nature of the associations.

Model-generated means are reported with 95% confidence intervals (CIs). Demographic data are presented as median (interquartile range) and frequency (%) for continuous and categorical variables, respectively. SAS (SAS Institute, Cary, NC, USA) 9.4 software (PROC GLIMMIX) was used for analysis.

Results

Demographic data and results of FVCs

A total of 230 subjects were included: 103 (45%) with NP and 127 (55%) without NP. An overview of subject demographics and FVC outcomes is provided in Table 1.

Circadian rhythms of renal functions

Diuresis rate

A total of 1833 observations from 230 subjects were included. No main effect or interaction involving protocol was statistically significant.

Table 1. Demographic data and frequency-volume chart results by age and nocturnal polyuria status

	<40 years, $n = 28$		41–50 years, $n = 13$		51–60 years, $n = 30$		61–70 years, $n = 72$		71–80 years, $n = 67$		>80 years, $n = 20$	
	NP, $n = 8$	No NP, $n = 20$	NP, $n = 4$	No NP, $n = 9$	NP, $n = 8$	No NP, $n = 22$	NP, $n = 39$	No NP, $n = 33$	NP, $n = 35$	No NP, $n = 32$	NP, $n = 9$	No NP, $n = 11$
Demographics												
Age (years)	24 (22–33)	27 (23–36)	46 (43–49)	48 (46–49)	58 (56–59)	55 (51–57)	67 (65–68)	66 (65–69)	75 (73–77)	75 (72–77)	82 (81–84)	84 (83–85)
Sex (♂/♀; %♀)	3/5 (63)	3/17 (85)	2/2 (50)	3/6 (67)	5/3 (38)	11/11 (50)	17/22 (56)	13/20 (61)	13/22 (63)	8/24 (75)	3/6 (67)	1/10 (91)
BMI (kg/m^2)	23 (22–23)	22 (19–24)	26 (23–31)	22 (21–24)	25 (24–27)	25 (23–25)	26 (24–30)	24 (23–27)	28 (25–31)	26 (23–28)	27 (24–29)	23 (21–24)
Frequency-volume chart												
Number of daytime voids	7 (4–10)	7 (6–9)	9 (7–9)	6 (6–7)	9 (7–10)	6 (6–9)	8 (6–9)	7 (6–9)	7 (6–8)	7 (6–8)	7 (6–7)	8 (6–8)
Number of nighttime voids	0 (0–1)	1 (0–1)	1 (0–3)	0 (0–1)	2 (2–2)	1 (0–2)	2 (1–3)	1 (1–2)	2 (1–2)	2 (1–2)	1 (1–2)	2 (1–3)
Maximum voided volume (ml)	628 (460–774)	404 (282–522)	542 (437–660)	310(267–342)	365 (272–518)	371 (283–455)	380 (309–485)	325 (260–450)	467 (350–623)	321 (238–402)	400 (277–540)	280 (210–410)
Mean voided volume (ml)	392 (288–556)	225 (142–330)	302 (197–409)	186 (145–226)	226 (163–289)	220 (168–278)	219 (181–276)	186 (163–249)	273 (193–331)	170 (129–209)	188 (153–260)	180 (150–262)
Nocturia ≥ 1	2 (25)	12 (60)	2 (50)	2 (22)	8 (100)	13 (59)	33 (85)	25 (76)	33 (94)	27 (84)	9 (100)	11 (100)
Nocturia ≥ 2	2 (25)	5 (25)	1 (25)	1 (11)	6 (75)	7 (32)	22 (56)	16 (49)	18 (51)	16 (50)	4 (44)	6 (55)

Note. Data are presented as median (interquartile range) and frequency (%) for continuous and categorical variables, respectively. Abbreviations: BMI: body mass index.

Table 2. Nocturnal polyuria status (present vs. absent) by time of day (daytime vs. nighttime) for diuresis rate, sodium clearance and free water clearance

NP status	Time of day	Adjusted mean diuresis rate (ml/min)	Adjusted mean sodium clearance (ml/min)	Adjusted mean FWC (ml/min)
No NP	Daytime	1.06 (0.98–1.14)	0.64 (0.56–0.72)	−0.86 (−0.98— −0.75)
NP	Daytime	1.44 (1.33–1.55)	0.74 (0.65–0.82)	−0.71 (−0.85— −0.58)
No NP	Nighttime	0.94 (0.89–0.99)	0.59 (0.52–0.67)	−0.80 (−0.92— −0.69)
NP	Nighttime	1.89 (1.80–1.00)	0.91 (0.82–1.01)	−0.38 (−0.51— −0.25)

Note. Model-generated adjusted means are reported along with 95% CIs. Diuresis rate: Significant time of day effect amongst both subjects with NP ($P < 0.001$) and without NP ($P = 0.004$); significant difference in subjects with NP versus without NP at both day ($P < 0.001$) and night ($P < 0.001$). Sodium clearance: Significant time of day effect for subjects with NP ($P < 0.001$) but for subjects without NP ($P = 0.120$); significant difference in subjects with NP versus without NP at night ($P < 0.001$) and in the day ($P = 0.026$). FWC: Significant time of day effect for subjects with NP ($P < 0.001$) but not subjects without NP ($P = 0.268$); significant difference in subjects with NP versus without NP at night ($P < 0.001$) but not in the day ($P = 0.097$).

There was, however, a significant NP status by phase interaction ($P < 0.001$) (Table 2). Compared to subjects without NP, those with NP demonstrated higher nighttime (1.89 vs. 0.94 ml/min, $P < 0.001$) and daytime (1.44 vs. 1.06 ml/min, $P < 0.001$) diuresis rates. Analysis within groups showed a significant nighttime versus daytime phase effect amongst both subjects with NP (1.89 vs. 1.44 ml/min, $P < 0.001$) and participants without NP (0.94 vs. 1.06 ml/min, $P = 0.004$). The interaction indicates that the direction of the phase effect amongst subjects with NP is opposite to that amongst subjects without NP.

There was also a significant NP status by age interaction ($P = 0.019$). Table 3a shows mean diuresis rate by NP status estimated separately for participants aged 50, 60, 70 and 80 years. There were significant differences in participants with versus without NP across ages ($P < 0.001$ at all 4 age levels), but the interaction indicates that the extent of difference between subjects with and without NP diminishes with increased age.

A significant age by phase interaction was also identified ($P < 0.001$). Table 3b shows mean diuresis rate by phase estimated separately for participants aged 50, 60, 70 and 80 years. Statistically significant nighttime versus daytime phase differences occurred at ages 70 ($P < 0.001$) and 80 ($P < 0.001$), but not at ages 50 ($P = 0.157$) or 60 ($P = 0.064$).

There were no statistically significant 3-way or 4-way interactions amongst predictors of diuresis rate.

Sodium clearance

A total of 1803 observations from 230 subjects were included. There was a significant protocol main effect, with higher values in the ambulatory care protocol compared to the continence clinic protocol (0.94 vs. 0.78 ml/min, $P = 0.025$) and marginally significant protocol by age effect ($P = 0.069$); these terms were retained in the final model. Additionally, there was no significant age by NP status effect ($P = 0.248$).

There was, however, a significant NP status by phase interaction ($P < 0.001$) (Table 2). Compared to subjects without NP, those with NP demonstrated higher nighttime (0.91 vs. 0.59 ml/min, $P < 0.001$) and daytime (0.74 vs. 0.64 ml/min, $P = 0.026$) sodium clearance. Analysis within groups demonstrated significantly higher nighttime versus daytime sodium clearance amongst participants with NP (0.91 vs. 0.74 ml/min, $P < 0.001$) but not in those without NP (0.59 vs. 0.64 ml/min, $P = 0.120$).

There was also a significant age by phase interaction ($P < 0.001$). Table 3c demonstrates mean sodium clearance by phase estimated for participants aged 50, 60, 70 and 80 years. Examination of these mean values demonstrates significant phase differences in rates at ages 70 ($P < 0.001$) and 80 ($P < 0.001$), but not at ages 50 ($P = 0.109$) or 60 ($P = 0.101$). The interaction indicates that, regardless of NP status, the extent of the phase effect increases with age.

There were no significant 3- or 4-way interactions amongst predictors of sodium clearance.

Free water clearance

FWC is expressed in ml/min and may either be positive (when $\text{urine}_{\text{osmolality}} < \text{plasma}_{\text{osmolality}}$) or negative (when $\text{urine}_{\text{osmolality}} > \text{plasma}_{\text{osmolality}}$). Thus, 'higher' FWC is used to denote values that are relatively less negative.

A total of 1762 observations from 230 subjects were included. No main effect or interactions involving protocol were statistically significant.

There was, however, a significant NP status by phase interaction (Table 2). Mean values demonstrated significantly higher FWC (i.e. less negative value) at night versus day for participants with NP (−0.38 vs. −0.71 ml/min, $P < 0.001$) but not for those without NP (−0.80 vs. −0.86 ml/min, $P = 0.268$) and a significantly higher FWC rate for those with NP versus those without NP at night (−0.38 vs. −0.80 ml/min, $P < 0.001$), but not during the day (−0.71 vs. −0.86 ml/min, $P = 0.097$).

Importantly, unlike diuresis rate and sodium clearance, FWC showed a significant quadratic main effect of age ($P = 0.039$), independent of phase ($P = 0.574$) or NP status ($P = 0.279$). The quadratic function can be described algebraically as an association between two variables (in this case, age and FWC) that approximates a U-shaped curve. The effect is demonstrated in Figure S1, which shows graphically the relatively higher FWC values seen on both ends of the age spectrum, although considerable variance was noted amongst those in the youngest group (≤40 years old).

Table 3. Significant interactions in diuresis rate and sodium clearance by age

(a) Nocturnal polyuria status (present vs. absent) by age for diuresis rate (ml/min)

NP status	Age	Adjusted mean diuresis rate (ml/min)
No NP	50	0.98 (0.92–1.04)
NP	50	1.73 (1.60–1.86)
No NP	60	0.99 (0.94–1.05)
NP	60	1.67 (1.58–1.76)
No NP	70	1.01 (0.96–1.07)
NP	70	1.62 (1.53–1.71)
No NP	80	1.03 (0.95–1.11)
NP	80	1.56 (1.46–1.67)

(b) Time of day (nighttime vs. daytime) by age for diuresis rate (ml/min)

Time of day	Age	Adjusted mean diuresis rate (ml/min)
Daytime	50	1.35 (1.26–1.45)
Nighttime	50	1.28 (1.21–1.34)
Daytime	60	1.26 (1.20–1.34)
Nighttime	60	1.34 (1.29–1.39)
Daytime	70	1.19 (1.12–1.26)
Nighttime	70	1.40 (1.34–1.45)
Daytime	80	1.11 (1.02–1.20)
Nighttime	80	1.46 (1.38–1.53)

(c) Time of day (nighttime vs. daytime) by age for sodium clearance (ml/min)

Time of day	Age	Adjusted mean sodium clearance rate (ml/min)
Daytime	50	0.67 (0.55–0.80)
Nighttime	50	0.63 (0.51–0.75)
Daytime	60	0.68 (0.60–0.77)
Nighttime	60	0.72 (0.63–0.80)
Daytime	70	0.69 (0.64–0.75)
Nighttime	70	0.81 (0.76–0.87)
Daytime	80	0.71 (0.64–0.78)
Nighttime	80	0.92 (0.85–0.99)

Note. Model-generated adjusted means are reported along with 95% CIs. (a) Significant difference in subjects with NP versus without NP across ages ($P < 0.001$ at all 4 age levels). (b) Significant time of day effect at age 70 ($P < 0.001$) and at age 80 ($P < 0.001$), but not at 50 ($P = 0.157$) or 60 ($P = 0.064$). (c) Significant time of day effect for 70- ($P < 0.001$) and 80-year-olds ($P < 0.001$), but not for 50 ($P = 0.109$) or 60-year-olds ($P = 0.101$).

There was no significant 3-way or 4-way interaction amongst remaining predictors of FWC.

Discussion

The principal finding in this study is that healthy older kidneys lose their circadian rhythm of water and salt handling and is likely the main cause for the increasing prevalence of nocturia with advancing age. Several physiologic changes in water and solute handling occur as part of the normal ageing process, including impairment in renal concentrating capacity, decreased nocturnal AVP secretion, partial resistance to AVP action, impaired sodium conservation, decreased active plasma renin and aldosterone and increased secretion of natriuretic peptides [13, 22–26]. Any or all of these factors could play a role in the results that we have presented here. Our study is limited to the extent we examined only three parameters associated with the body's fluid homeostasis (total volume and rates of sodium and free water clearance), and we did not measure plasma AVP levels, nor did we examine in detail changes in kidney structure or function. Despite these limitations, our data imply differential impact of these various physiologic changes, particularly as they may be relevant to age.

For both diuresis rate and rate of sodium excretion, the effects of age occurred in the context of daytime versus nighttime differences and/or NP status. Loss of the normal circadian variation in diuresis appears to be a physiological phenomenon related to ageing that should be understood in the clinical evaluation and management of nocturia. This impairment has important implications for patients with nocturia who do not have NP; even in patients with small bladder capacity and no NP, nocturia has been demonstrated to improve through a reduction in nocturnal urine volume rather than a change in bladder capacity [27, 28].

In terms of sodium clearance, for both subjects with and without NP, the age-related increase was more prominent during the night (+0.29 ml/min from age 50 to age 80) than the day (+0.04 ml/min from age 50 to age 80), such that increasing age was accompanied by a significant increase in the proportion of the total 24-h sodium clearance occurring during the nighttime period. The extent to which relevant measures of comorbidities (e.g. ventricular dysfunction, non-dipping of BP and sleep apnoea) may play a role in the age-related nocturnal sodium diuresis that we have observed

remains unknown as we did not have routine assessments of such physiologic parameters in this study.

In our time of day analysis of FWC in subjects with and without NP, we noted significantly higher nighttime, relative to daytime, rates. Although technically constituting a quadratic trend, these higher FWC rates at night, particularly prominent amongst our older groups, are compatible with either lower rates of AVP release and/or inability of the aged nephron tubules to concentrate urine [29]. Experimental evidence has shown that, relative to younger persons, plasma osmolality in older persons appears more dependent on fluid volume [30]. The clinical implications of this for treatment remain unclear, although it is certainly possible that older patients may see a particular benefit from interventions directed at reducing nocturnal free water diuresis.

Additional limitations of the present study include the small sample size (particularly in some age groups) and inability to control for medication use, dietary salt intake, fluid intake and comorbidities associated with NP. Data on medications impacting urine production, such as the dose and timing of diuretics, and comorbid diseases, including diabetes and obstructive sleep apnoea, which may have a differential effect and/or distribution with age, were not obtained for the present analysis, nor did we assess factors such as atrial natriuretic peptide or brain natriuretic peptide, which may impact urine production. Moreover, a record of fluid/nutritional intake was not part of either protocol. Although instructions for measuring incontinence weight were standardised, this process relied on patients' own home scales, which is another potential source of variability in these data. Future research is needed to define reference values for nighttime FWC and sodium clearance according to age and sex, to define new criteria for NP that account for the presence of LUTS, medications and comorbidities, as well as potential differences in dietary intake and continence status, and to better understand the implications for treatment.

Conclusions

Regardless of NP status, increased age was accompanied by an increase in the ratio of nighttime/daytime diuresis rate, nighttime sodium clearance and daytime sodium clearance. FWC showed a complex age effect, which was independent of time of day or differences by NP status. In older persons, surge in either nocturnal sodium clearance and/or nocturnal FWC may represent the relevant substrate for behavioural or pharmacologic interventions targeting NP. Future research to elucidate the specific physiologic mechanisms underlying these age-related changes will be needed to facilitate more individualised treatment strategies for older patients with nocturia.

Supplementary data: Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

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