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Nighttime Blood Pressure and Nocturnal Dipping Are Associated With Daytime Urinary Sodium Excretion in African Subjects

Lise Bankir, Murielle Bochud, Marc Maillard, Pascal Bovet, Anne Gabriel, Michel Burnier

Abstract—Blood pressure (BP) follows a circadian rhythm, with 10% to 15% lower values during nighttime than during daytime. The absence of a nocturnal BP decrease (dipping) is associated with target organ damage, but the determinants of dipping are poorly understood. We assessed whether the nighttime BP and the dipping are associated with the circadian pattern of sodium excretion. Ambulatory BP and daytime and nighttime urinary electrolyte excretion were measured simultaneously in 325 individuals of African descent from 73 families. When divided into sex-specific tertiles of day:night ratios of urinary sodium excretion rate, subjects in tertile 1 (with the lowest ratio) were 6.5 years older and had a 9.8-mm Hg higher nighttime systolic BP (SBP) and a 23% lower SBP dipping (expressed in percentage of day value) compared with subjects in tertile 3 (P for trend <0.01). After adjustment for age, the SBP difference across tertiles decreased to 5.4 mm Hg ($P=0.002$), and the SBP dipping difference decreased to 17% ($P=0.05$). A similar trend across tertiles was found with diastolic BP. In multivariate analyses, daytime urinary sodium and potassium concentrations were independently associated with nighttime SBP and SBP dipping ($P<0.05$ for each). These data, based on a large number of subjects, suggest that the capacity to excrete sodium during daytime is a significant determinant of nocturnal BP and dipping. This observation may help us to understand the pathophysiology and clinical consequences of nighttime BP and to develop therapeutic strategies to normalize the dipping profile in hypertensive patients. (*Hypertension*. 2008;51:1-8.)

Key Words: circadian rhythm ■ glomerular filtration rate ■ potassium ■ humans ■ families

Blood pressure (BP) is known to follow a circadian rhythm with 10% to 15% lower values during the night than during the day. In hypertensive patients, the absence of a nocturnal BP dipping has been associated with the development of target organ damage, such as left-ventricular hypertrophy¹ and microalbuminuria,² and the occurrence of cerebrovascular^{3,4} and cardiovascular events.⁵⁻⁷ In some studies, nighttime BP has been found to be a better predictor of cardiovascular risk and mortality than daytime BP,^{8,9} but this observation has not been confirmed in all of the studies.¹⁰

The main determinant of the circadian variations of BP appears to be the activity of the sympathetic nervous system. However, several other neurohormonal systems regulating BP have been shown to follow a circadian rhythm and may contribute to the circadian variations in BP.^{11,12} Some studies have suggested that the reduction or even the inversion of the usual nocturnal dipping in some subjects is associated with high sodium intake and salt sensitivity¹³⁻¹⁷. Recently, Fukuda et al¹⁸ proposed a hypothesis according to which the nondipping pattern of BP at night is because of an impaired capacity to excrete sodium during daytime. Hence, to maintain 24-

hour sodium balance, BP increases at night to promote sodium excretion. The impaired capacity to excrete sodium may be due either to a reduced renal function as seen in subjects with a low glomerular filtration rate or to an increased tubular sodium reabsorption as observed, eg, in primary aldosteronism.¹⁹

The hypothesis linking the dipping pattern to the capacity to excrete sodium is supported essentially by several small studies in selected salt-sensitive and salt-resistant patients.^{14,16,20} To our knowledge, this concept has not been tested in a large group of unselected subjects from the population. Therefore, the aim of the present analysis was to assess whether the circadian pattern of sodium excretion is indeed associated with nighttime BP and is a significant determinant of the magnitude of the nocturnal BP dipping. To this purpose, we analyzed the data of a large sample of subjects of African descent, including both normotensive and hypertensive subjects, in whom 24-hour BP recordings, as well as renal function and separated daytime and nighttime urine collections, were available. Clinical investigations in healthy subjects have shown that an increase in urine con-

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Table 1. Participants' Characteristics Overall and by Tertiles of Day:Night Ratio of the Urinary Sodium Excretion Rate

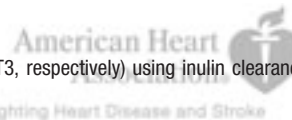
Variable	All	Tertile 1	Tertile 2	Tertile 3	P (Trend)
No.	325	109	108	108	
D/N U_{NaV} *	0.85 (0.59)	0.36 (0.12)	0.73 (0.13)	1.46 (0.63)	<0.001
Sex, % women	55	55	56	56	0.94
Age, y	46.4 (11.5)	49.9 (11.9)	46.0 (10.7)	43.4 (11.1)	<0.001
Height, cm	166 (9)	165 (9)	166 (8)	166 (8)	0.63
Weight, kg	74.8 (15.7)	76.5 (15.6)	74.8 (14.6)	73.2 (16.8)	0.09
BMI, kg/m ²	27.1 (5.1)	27.9 (5.0)	27.1 (5.1)	26.4 (5.0)	0.024
24-h SBP, mm Hg	127.3 (16.3)	131.2 (14.8)	126.6 (17.9)	123.9 (15.5)	<0.001
24-h DBP, mm Hg	81.9 (10.8)	83.7 (10.3)	81.4 (11.8)	80.6 (10.3)	0.026
P Na, mmol/L	140.3 (4.0)	139.9 (3.7)	140.4 (3.6)	140.7 (4.6)	0.15
P K, mmol/L	3.7 (0.3)	3.7 (0.3)	3.8 (0.3)	3.7 (0.3)	0.21
P creatinine, μ mol/L	76 (16)	80 (18)	74 (17)	75 (14)	0.06
FBG, mmol/L	4.9 (2.2)	5.2 (2.6)	5.1 (2.3)	4.5 (1.5)	0.043
24 h V, mL/min	1.38 (0.75)	1.47 (0.87)	1.41 (0.76)	1.26 (0.61)	0.043
24 h C_{creat} , mL/min†	110 (44)	106 (55)	112 (43)	114 (42)	0.008
C_{inulin} , mL/min†‡	111 (42)	112 (47)	112 (42)	110 (39)	0.67
MDRD, mL/min†	110 (36)	109 (37)	116 (29)	108 (40)	0.18
Na excretion, mmol/24 h	103 (53)	99 (51)	106 (55)	104 (52)	0.65
K excretion, mmol/24 h	43 (18)	41 (20)	45 (16)	43 (18)	0.50

Results are means (SD) unless otherwise specified. D/N U_{NaV} indicates day/night ratio of urinary sodium excretion rate; P, plasma concentration; FBG, fasting blood glucose; MDRD, simplified Modification of Diet in Renal Disease equation.

*This day:night ratio was used to divide the 325 subjects into 3 sex-specific tertiles. Urinary sodium excretion rates in micromoles per minute were used to calculate this ratio.

†Data are medians (interquartile range).

‡GFR was evaluated in a large subset of subjects (n=89, 84, and 84 in T1, T2, and T3, respectively) using inulin clearance on the morning following the 24-hour urine collection.



centration may reduce the capacity of the kidney to excrete NaCl.^{21,22} For this reason, special attention was given to the concentration of sodium in the urine, in addition to its excretion rate. Our results confirm that sodium excretion during daytime and even more so, sodium concentration in the urine, are significant determinants of nighttime BP and of the nocturnal dipping.

Materials and Methods

The study took place in the Seychelles islands, which are populated predominantly by individuals of East African descent. Participants were recruited between August 1999 and January 2002. The study was approved by the ethical committees of the Ministry of Health in the Seychelles and of the University of Lausanne Faculty of Medicine. All of the participants provided written informed consent. The selection process for families has been described previously.²³ The study originally aimed at examining genetic determinants of hypertension in families including ≥ 2 hypertensive siblings. Subjects <18 years of age or with an acute medical condition (eg, acute stroke or myocardial infarction within the past 6 months) were excluded from the study. A total of 350 individuals from 76 families had data available for this analysis. We excluded 25 individuals on the basis of a urinary creatinine excretion >0.4 mmol/kg per 24 hours (n=4) and/or a day:night ratio of creatinine excretion rate >2 (n=15) or <0.3 (n=8), as this suggested excessive or incomplete urine collection of either daytime or nighttime. The present analyses are, therefore, based on 325 individuals from 73 families of mean \pm SD size 5.6 ± 2.4 (with 1 or 2 generations).

Antihypertensive therapy, if any, was stopped for 2 weeks before conducting ambulatory BP monitoring (ABPM) and urine collection.

Ambulatory BP was measured for 24 hours using Diasys Integra devices (Novacor SA, Rueil-Malmaison) every 20 minutes during the day and every 30 minutes at night. Additional methodological criteria have been described previously.²³ For the analyses, we used the average of 10 daytime and 10 nighttime randomly selected measures to have the same number of measures for each participant and each period. Sensitivity analyses conducted using all of the available daytime and nighttime BP measures led to very similar results and did not alter our conclusions. In a subgroup of subjects (n=55), a second off-treatment ABPM was performed after 6 weeks to calculate the reproducibility of the dipping pattern in this population using the Pearson's correlation coefficient.

Participants were investigated under their usual diet. Twenty-four-hour urine was collected on the same day as ABPM. Urine was collected separately for day and night. As for BP, day and night were defined according to each participant's self-reported bedtime and wake-up time. The average \pm SD durations of the daytime and nighttime urine collections were, respectively, 14.1 ± 1.9 and 9.2 ± 1.6 hours. Blood was drawn under fasting conditions between 7:30 AM and 10:00 AM, just after completion of the ABPM recording and urine collection.

Plasma and urinary sodium and potassium concentrations (P_{Na} , P_K , U_{Na} , and U_K , respectively) were measured by flame photometry (IL-943, Instrumentation Laboratory). Creatinine concentration was measured by the picric acid method (Cobas-Mira, Riche) and creatinine clearance (C_{creat}), often used as an approximation of the glomerular filtration rate (GFR), was calculated for daytime and nighttime separately. We also used the abbreviated Modification of Diet in Renal Disease equation to estimate GFR.²⁴ In 257 participants (n=89, 84, and 84 in T1, T2, and T3, respectively), GFR was measured as described previously²³ using inulin clearance under fasting conditions in the morning after 24-hour urine collection and

ABPM. Urine osmolality was not measured, but the ratio of urine:plasma creatinine concentrations was used as an index of urine concentration, as validated previously.²⁵ Urine flow rate (V) and sodium and potassium excretion rates ($U_{Na} \cdot V$ and $U_K \cdot V$, respectively) were calculated for the whole 24-hour period and for daytime and nighttime separately. Fractional excretion of sodium (FE_{Na}) was calculated as $U_{Na} \cdot V / (P_{Na} \cdot C_{creat})$.

Reported smoking and alcohol consumption were obtained by trained health professionals using a standardized questionnaire. Measurements of body mass index (BMI) and fasting blood glucose have been described previously.²⁶

Statistical Analyses

The data were divided into sex-specific tertiles (T1, T2, and T3) according to the day:night ratio of urinary sodium excretion. A nonparametric test was used to evaluate trends across tertiles. The Wilcoxon matched-pairs signed-rank test was used to compare day and night values within each tertile. The ASSOC program (5.2v) in the Statistical Analysis for Genetic Epidemiology package was used to conduct multiple linear regression models while accounting for familial correlations and also to estimate heritability to assess familial aggregation of nocturnal dipping. The following dependent variables were used: night values and differences between daytime and nighttime values (ie, nocturnal dipping) for systolic (SBP), diastolic (DBP) and pulse pressure (PP; ie, 6 models). All of the models were adjusted for age, sex, BMI, ascertainment, 24-hour sodium and potassium excretion, urine flow rate (milliliters per minute), and urinary creatinine concentration in day and night urine. Models with DBP or PP as the dependent variable were also adjusted for age² to account for the nonlinear relation of DBP with age. We used the daytime and nighttime urinary U_{Na} and U_K (millimoles per liter) as the covariates of interest. Sensitivity analyses were conducted that included an additional adjustment for the following: (1) GFR measured using inulin clearance; (2) 24-hour FE_{Na} ; (3) reported tobacco consumption; (4) reported alcohol consumption; and (5) fasting blood glucose.

Results

We stratified the sample using the day:night ratio of urinary sodium excretion rate to evaluate whether a disturbed circadian pattern of sodium excretion was associated with a difference in the level of BP and/or its nocturnal dipping. The characteristics of the 325 subjects, divided into sex-specific tertiles of day:night ratio of urinary sodium excretion rate, are presented in Table 1. Subjects in T3 can be qualified as "high daytime sodium excretors," because they excrete sodium at a rate that is 46% higher during daytime than during nighttime, whereas subjects in T1 are "low daytime sodium excretors," excreting 3 times less sodium during daytime than during nighttime. Despite this different circadian pattern of sodium excretion, the total 24-hour sodium excretion was similar across tertiles (Table 1). Subjects in T1 were significantly older than those in T2 and T3 by ≈ 6 and 4 years, respectively. In addition, subjects in T1 tended to have a higher BMI and fasting blood glucose than subjects in T3 and a lower creatinine clearance. GFR measured using inulin clearance was similar across tertiles (Table 1). Heritability estimates of SBP, DBP and PP nocturnal dipping were not significantly different from 0 ($P > 0.10$).

Marked differences in BP were observed across tertiles of the day:night ratio of urinary sodium excretion rate (Figure). During both daytime and nighttime, SBP and DBP were highest in T1, lower in T2, and even lower in T3. The magnitude of the difference was larger for SBP than for DBP, resulting also in a progressive decline in PP values from T1

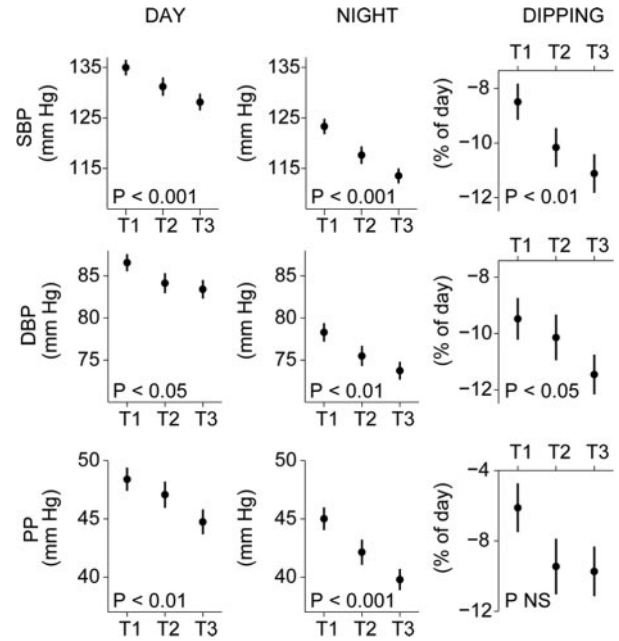


Figure. BP, PP, and nocturnal dipping, by tertiles of day:night ratio of urinary sodium excretion rate. Dots and bars represent tertile-specific means and SEs, respectively. Dipping represents the nocturnal BP decrease (nighttime BP minus daytime BP), expressed in percentage of the daytime BP. The x axis shows sex-specific tertiles (T1, T2, and T3) of the day:night ratio of the urinary sodium excretion rate. P values are from a nonparametric test for trend across tertiles.

to T3. The nocturnal BP dipping was significantly lower in T1 than in other tertiles, especially for SBP. Adjustment for age (model M2 in Table 2) but not 24-hour creatinine clearance (model M3) substantially modified the results for nighttime BP and the percentage dipping in nighttime BP (Table 2). Age explained $\approx 40\%$ of the trend observed across tertiles. Fully adjusted models (M4), including BMI and 24-hour urinary sodium and potassium excretion showed similar trends than age-adjusted models. The reproducibility of the dipping pattern, estimated using correlation coefficients between BP dipping on 2 ABPMs 6 weeks apart in 55 subjects, was 0.53 for SBP and 0.37 for DBP ($P < 0.001$).

Although 24-hour urinary sodium and potassium excretion rates were similar across tertiles of the day:night ratio of urinary sodium excretion rate (Table 1), strikingly different excretion rates were observed during day and night. Mean sodium excretion rate was 41 (SD: 24) and 120 (SD: 63) $\mu\text{mol}/\text{min}$ during daytime and nighttime, respectively, in T1 and 82 (SD: 40) and 62 (SD: 36) $\mu\text{mol}/\text{min}$, respectively, in T3. The excretion rate of any given solute is the product of its concentration in the urine by the urine flow rate. The lower sodium excretion rate observed in T1 during daytime was largely because of a low sodium concentration in the urine, whereas the urine flow rate was only marginally lower in T1 than in the 2 other tertiles (Table 3). This defect seemed to be selective for sodium, because other urinary variables, such as the index of overall urinary concentration, the U_K (Table 3), and that of creatinine (not shown) showed fairly similar values in all of the tertiles during daytime. In subjects in T2

Table 2. Nighttime BP and Nocturnal Dipping by Tertiles of Day:Night Ratio of Urinary Sodium Excretion Rate, Either Unadjusted or Adjusted for Age and 24-Hour Creatinine Clearance

Dependent Variable	Model	All	Tertile 1	Tertile 2	Tertile 3	P (Trend)
Nighttime BP, mm Hg						
SBP	M1	118.2 (16.9)	123.3 (15.9)	117.6 (18.0)	113.5 (15.3)	<0.001
	M2	119.3 (15.2)	122.2 (14.7)	119.1 (16.1)	116.7 (14.3)	0.002
	M3	119.4 (15.2)	122.4 (14.7)	118.9 (16.1)	116.7 (14.2)	0.002
	M4	119.3 (14.9)	122.1 (14.4)	118.9 (16.1)	116.8 (13.9)	0.002
DBP	M1	75.9 (11.8)	78.3 (11.4)	75.5 (12.4)	73.7 (11.0)	0.004
	M2	76.8 (11.0)	78.1 (11.1)	76.3 (11.7)	75.9 (10.0)	0.13
	M3	76.8 (11.0)	78.2 (11.1)	76.3 (11.6)	75.9 (10.1)	0.10
	M4	76.7 (10.9)	78.0 (10.9)	76.3 (11.6)	75.9 (9.9)	0.12
PP	M1	42.3 (10.5)	45.0 (10.1)	42.1 (11.3)	39.8 (9.3)	<0.001
	M2	43.1 (9.6)	44.6 (9.5)	43.2 (9.8)	41.4 (9.2)	0.006
	M3	43.1 (9.5)	44.7 (9.5)	43.2 (9.9)	41.4 (9.1)	0.006
	M4	43.1 (9.5)	44.5 (9.5)	43.1 (9.8)	41.5 (9.0)	0.010
Nocturnal BP dipping, day-night difference in percentage of day value						
SBP	M1	9.9 (7.3)	8.5 (6.9)	10.2 (7.4)	11.1 (7.3)	0.005
	M2	9.8 (7.1)	8.8 (6.7)	10.0 (7.2)	10.6 (7.4)	0.050
	M3	9.7 (7.1)	8.8 (6.7)	9.8 (7.1)	10.6 (7.4)	0.044
	M4*	9.8 (6.8)	8.7 (6.3)	10.0 (6.8)	10.8 (7.0)	0.019
DBP	M1	10.4 (7.8)	9.5 (7.7)	10.1 (8.4)	11.5 (7.3)	0.048
	M2	10.2 (7.5)	10.1 (7.4)	9.9 (8.1)	10.7 (7.1)	0.44
	M3	10.2 (7.5)	10.1 (7.4)	9.9 (8)	10.8 (7.1)	0.41
	M4*	10.3 (7.4)	10.1 (7.3)	10.0 (7.8)	10.8 (7.0)	0.42
PP	M1	8.4 (15.2)	6.1 (14.5)	9.5 (16.4)	9.7 (14.6)	0.15
	M2	8.6 (15.2)	6.5 (14.4)	9.6 (16.4)	9.8 (14.7)	0.20
	M3	6.4 (15.3)	4.8 (14.5)	7.3 (16.4)	7.2 (15.1)	0.41
	M4*	8.7 (14.4)	6.4 (13.5)	9.4 (15.4)	10.3 (14.0)	0.07

Results are means (SDs). Night BP dipping is the difference between night and day BPs, expressed in percentage of day BP. M1 indicates unadjusted model; M2, model adjusted for age; M3, model adjusted for age and 24-hour creatinine clearance; M4, model adjusted for age, BMI, 24-hour sodium, and potassium excretions (millimoles per 24 hours), and 24-hour creatinine clearance.

*M4 is the model adjusted for baseline BP in addition to covariates listed for M4.

and T3, the U_{Na} was significantly lower at night than during day, but not in subjects in T1. The fractional excretion of sodium in T1 was much lower during daytime and much higher during nighttime than in the 2 other tertiles: T1 to T3 were 0.33 (SD: 0.19), 0.42 (SD: 0.21), and 0.49 (SD: 0.24) during daytime and 0.74 (SD: 0.45), 0.52 (SD: 0.29), and 0.38 (SD: 0.21) during nighttime, respectively (P for trend <0.0001 for both).

The online supplemental table (Table S1), available at <http://hyper.ahajournals.org>, presents the regression coefficients (and SEs) found in multiple linear regression models (all accounting for familial correlations), 1 for each dependent variable using either concentrations or excretion rates. Daytime sodium concentration was negatively and strongly associated with nighttime SBP, DBP, and PP and positively associated with the nighttime dip of SBP and PP. This suggests that, at constant urine flow rate, subjects who are less able to concentrate sodium in the urine during daytime fail to decrease their BP at night. Coefficients for daytime and nighttime U_K were of similar magnitude but in opposite directions as those for U_{Na} (Table S1). Sensitivity analyses

that included an additional adjustment for GFR (measured using inulin clearance), 24-hour FE_{Na} , tobacco consumption, alcohol intake, or fasting blood glucose did not substantially change the results and led to the same conclusions (results not shown). Urinary sodium excretion (millimoles per 24 hours), a proxy of dietary sodium intake, was positively and independently associated with nighttime SBP, DBP, and PP but was not a significant determinant of nocturnal SBP, DBP, or PP dipping. By contrast, neither GFR, measured using inulin clearance, nor 24-hour FE_{Na} was a significant determinant of nocturnal SBP, DBP, or PP dipping.

Discussion

The main finding of our study is that, in a large group of subjects from African descent, individuals who are poor daytime sodium excretors have an increased nighttime BP and a blunted nocturnal BP dipping. The magnitude of this effect is highly clinically relevant, because it represents a 10-mm Hg difference for nighttime SBP between the first and third tertiles of the day:night ratio of urinary sodium excretion rate. More importantly, this study provides the first

Table 3. Daytime and Nighttime Urinary Excretion Rates and/or Concentrations and Corresponding Day:Night Ratios by Tertiles of Day:Night Ratio of Urinary Sodium Excretion Rate

Variable	All	Tertile 1	Tertile 2	Tertile 3	P (Trend)
Daytime urine					
V, mL/min	1.15 (0.79)	1.06 (0.84)	1.22 (0.83)	1.17 (0.68)	0.05
U _{creat} /P _{creat}	141 (106)	140 (112)	143 (114)	140 (91)	0.40
U _{Na} , mmol/L	72 (51)	56 (42)	70 (45)	90 (58)	<0.001
U _K , mmol/L	42 (30)	42 (29)	42 (30)	42 (30)	0.88
Nighttime urine					
V, mL/min	1.77 (0.97)	2.17 (1.09)	1.74 (0.94)	1.41 (0.68)	<0.001
U _{creat} /P _{creat}	94 (68)	74 (52)	103 (80)	107 (65)	<0.001
U _{Na} , mmol/L	59 (37)	63 (36)	64 (43)	51 (32)	0.008
U _K , mmol/L	19 (14)	16 (12)	20 (14)	20 (16)	0.08
Daytime:nighttime ratios					
D/N V	0.72 (0.45)	0.51 (0.32)	0.75 (0.40)	0.91 (0.50)	<0.001
D/N U _{creat} /P _{creat}	1.66 (1.02)	2.03 (1.26)	1.53 (0.93)	1.43 (0.68)	0.0001
D/N U _{Na} V	0.85 (0.59)	0.36 (0.12)	0.73 (0.13)	1.46 (0.63)	<0.001
D/N U _K V	1.52 (0.85)	1.16 (0.69)	1.49 (0.69)	1.89 (0.99)	<0.001
D/N U _{creat} V	1.43 (0.52)	1.24 (0.47)	1.41 (0.49)	1.64 (0.63)	<0.001

U_{creat}/P_{creat} indicates urine to plasma creatinine concentrations; U_{creat}, urine creatinine concentration; D/N, daytime/nighttime.

evidence that the low sodium excretion during daytime is due essentially to an inability to concentrate sodium in the urine, because no significant difference in urinary volume was found across tertiles of the day:night ratio of urinary sodium excretion rate, and nighttime BP was negatively and highly significantly associated with daytime urine sodium concentration. This relationship was still significant after adjustment for total 24-hour sodium and potassium excretion and for the other possible considered confounding factors. Familial clustering had no major influence on our results, because heritability estimates for nocturnal BP dipping were not significantly different from 0. This is, to our knowledge, the largest study to date that has explored the relationships between the circadian variations in urinary electrolyte excretion and those in BP and the first such study in a population of African descent.

Several previous studies have suggested that a reduced nocturnal fall in BP is associated with a reduced excretion of sodium during daytime. This has led to the hypothesis that the relative increase in blood pressure observed during the night is a pressure-natriuresis mechanism favoring a compensatory rise in sodium excretion and the maintenance of sodium balance.^{13,18} In accordance with this hypothesis, small groups of subjects with salt-sensitive hypertension exhibiting a nondipping profile have been found to recover a normal dipping pattern after 1 week of sodium restriction¹⁶ or administration of thiazide diuretics.²⁰ In contrast, salt-insensitive subjects show a normal nocturnal dipping that is not modified by the low-salt diet or the diuretic.¹⁶ A blunted circadian pattern of fluid and sodium excretion has recently been described in young normotensive African Americans,²⁷ a population with high prevalence of sodium-sensitive hypertension and known to exhibit a lower dipping of night-time BP than whites.^{28–30} However, none of these latter studies could analyze the association between the circadian changes

in sodium excretion and those of BP, either because ABPM was not performed or because urinary electrolyte excretion was not measured separately during daytime and nighttime.

Some authors have shown limited reproducibility of the nocturnal BP dipping in individual subjects.^{31,32} When ABPM was repeated, a 40% change in the dipping or nondipping pattern was observed in a large Italian clinical study.³¹ In the present study, the correlation coefficients between repeated ABPM were 0.53 for SBP dipping and 0.37 for DBP dipping, which show significant but moderate reproducibility. One potential limiting factor for an adequate determination of the dipping pattern is the difference in the number of BP measurements between daytime and nighttime. To avoid any imbalance in the number of measurements, 10 daytime and 10 nighttime BP values were randomly selected for each subject to calculate mean daytime and nighttime BPs. In each tertile, there was no significant difference in mean daytime or nighttime BP between 10 and all of the measures. Our finding of a significant association between the circadian variations in BP and urinary sodium excretion rate may provide an additional explanation for the relatively low reproducibility of the dipping pattern in some studies. Indeed, if the dipping profile of BP depends on sodium excretion, as suggested by the work of Uzu and colleagues,^{16,20} and by our data, the nocturnal fall in BP may vary considerably from day to day depending on sodium intake. Because this parameter is rarely measured in clinical studies investigating the dipping pattern of BP, investigators may miss an important confounding factor.

Our data reveal, for the first time in a large group of subjects, the wide range of interindividual variation in the circadian pattern of sodium excretion. The mean day:night ratio of sodium excretion rate varied over more than a 3-fold range between the 2 extreme tertiles. T1 subjects excreted 64.6% of their total daily sodium during nighttime versus

48.2% in T2 and 33.2% in T3 subjects. This shows that overnight urine collection is inappropriate for estimating 24-hour sodium excretion, for comparing sodium intakes in different subjects, and for evaluating sodium sensitivity of BP, as underlined previously.³³ Despite similar and relatively low 24-hour sodium excretion (≈ 100 mmol/24 hours) across tertiles, some subjects were poor daytime sodium excretors and showed a reduced nocturnal BP dipping, whereas others had a better daily excretion and a larger dipping. Our results suggest that, even at relatively low dietary sodium intakes, some subjects may still be nondippers. Accordingly, the optimal level of sodium intake may not be the same for all of the subjects.

In the hypothesis by Fukuda et al,¹⁸ the impaired capacity to excrete sodium may be due either to a reduced glomerular filtration rate or to a primary increase in tubular sodium reabsorption. In accordance with this concept, an abnormal BP dipping has been reported in several clinical conditions associated with an impaired renal function (eg, aging or renal transplantation) or an increased sodium reabsorption (eg, primary hyperaldosteronism, ciclosporin, or administration of nonsteroidal antiinflammatory drugs) as reviewed recently.³⁴ The present study does not allow us to determine the mechanism(s) whereby a low daytime sodium excretion rate is associated with an increased nocturnal BP. Nevertheless, our data suggest that the principal mechanism is an increased tubular sodium reabsorption rather than a limitation in GFR. Whether it is because of a generalized tubular dysfunction or an early stage of renal injury (eg, reduced nephron number) cannot be ascertained from our data. Subjects in T1 were slightly older and heavier than those in T2 and T3. Previous findings in whites showed that older subjects³⁵ and subjects with higher BMI³⁶ tend to excrete more sodium during the night than during the day. Subjects of T1 showed, on average, no evidence of renal dysfunction, as illustrated by the similar GFR across tertiles and by the similar index of urinary concentration during daytime, suggesting no impairment in the capacity to concentrate urine. Daytime creatinine clearance was lower in T1 subjects than in T2 and T3 subjects but rose at night instead of going down, as generally observed in normal subjects.³⁷ Differences in the fractional excretion of creatinine around the clock have been described³⁸ and probably result from variations in creatinine secretion and/or reabsorption.

The lower daytime fractional excretion of sodium observed in T1 than in the 2 other tertiles points to a greater tubular sodium reabsorption resulting in a low concentration of sodium in the urine during daytime. For the same 24-hour sodium excretion, daytime urine flow rate in T1 was close to that of T3 (1.06 versus 1.17 mL/min), but U_{Na} was markedly lower (56 versus 90 mmol/L). Because all of the solutes are excreted in the same volume of fluid, the ability to adjust the excretion of a given solute independent of that of others depends on the capacity of the kidney to adapt the concentration of each solute selectively in the urine. The ability of the kidney to adapt urine sodium concentration is relatively limited, because sodium reabsorption is used to energize the reabsorption and/or secretion of several other solutes (by cotransport and countertransport, respectively), and, unlike

potassium, sodium is not known to undergo active secretion. Note that U_{Na} , even in the "good" daily excretors of T3, is only 90 mmol/L during daytime, a value distinctly lower than that of plasma and extracellular fluids. In T1 subjects, a too-intense neurohormonal activity and/or some genetic factors could enhance tubular reabsorption in the proximal tubule^{39,40} and/or in the distal nephron.

An increase in potassium intake has also been shown to reduce BP.⁴¹ Here, we find a positive association between the nocturnal BP dipping and urinary potassium excretion rate during daytime, a relationship that is independent of and inverse to that with sodium. Potassium usually exhibits variations in its excretion rate during daytime and nighttime that are of a much greater amplitude than the rates for other electrolytes and creatinine, and a large fraction of the total 24-hour potassium is excreted during daytime.³⁷ Recent studies in rats suggest that the beneficial effect of potassium on BP may be because of the fact that its secretion induces an increase in urine flow rate selectively during the active period (nighttime for rats but daytime for humans), thus enhancing the day:night ratio of the sodium excretion rate.⁴²

This study has some advantages and some limitations. Daytime and nighttime durations were not arbitrarily fixed for all of the participants but corresponded with each subject's own rhythm, and daytime in our sample ranged from 9 to 19 hours (interquartile range: 13 to 15 hours). The cross-sectional nature of this study cannot disentangle causes from consequences: it cannot differentiate whether an inability to excrete sodium during daytime increases BP at nighttime or whether an increased nighttime BP induces a greater proportion of sodium to be excreted during the night and a lesser proportion during the following day. However, the experimental evidence that diuretics or a low-salt diet are able to restore a normal BP dipping in nondippers^{16,20} is consistent with the first sequence of events. Although this does not compensate for a truly random design, the large number of subjects in our study allowed controlling analytically for several potential confounders. Also, we do not know the timing of meals and, hence, the participants' sodium loads. We cannot exclude that T1 subjects ate more salt in the evening than during daytime and, in this respect, differ from T3 subjects. This is, however, unlikely, because large and systematic differences in eating habits across tertiles would be needed to explain our findings. Part of the increased nighttime BP could be due to having to get up at night because of higher urine volume. This may additionally contribute to poor sleep quantity and quality, possibly induced by cuff inflation for ABPM. Such sleep disturbances may reduce the prognostic significance of nighttime BP.⁴³

Perspectives

Because nighttime BP is associated with target organ damages and cardiovascular events, it is crucial to identify its clinical and physiological determinants. In this study performed on a large group of normotensive and hypertensive subjects, we demonstrate that sodium excretion during daytime is a significant determinant of nighttime BP. This observation has 2 important implications. First, it highlights the importance of considering sodium intake as a major

confounding factor whenever investigating or trying to explain circadian variations of BP. Second, because a low-sodium diet and diuretics have been found to restore a normal diurnal pattern of BP in nondippers, our findings further support the recommendation of a low-sodium intake in hypertension not only to lower BP but also to restore a normal diurnal rhythm of BP and, hence, to further reduce the patients' cardiovascular risk.

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Disclosures

None

References

- Verdecchia P, Schillaci G, Guerrieri M, Gatteschi C, Benemio G, Boldrini F, Porcellati C. Circadian blood pressure changes and left ventricular hypertrophy in essential hypertension. *Circulation*. 1990; 81:528–536.
- Bianchi S, Bigazzi R, Baldari G, Sgheri G, Campese VM. Diurnal variations of blood pressure and microalbuminuria in essential hypertension. *Am J Hypertens*. 1994;7:23–29.
- Kario K, Pickering TG, Matsuo T, Hoshida S, Schwartz JE, Shimada K. Stroke prognosis and abnormal nocturnal blood pressure falls in older hypertensives. *Hypertension*. 2001;38:852–857.
- Ohkubo T, Hozawa A, Nagai K, Kikuya M, Tsuji I, Ito S, Satoh H, Hisamichi S, Imai Y. Prediction of stroke by ambulatory blood pressure monitoring versus screening blood pressure measurements in a general population: the Ohasama study. *J Hypertens*. 2000;18:847–854.
- O'Brien E, Sheridan J, O'Malley K. Dippers and non-dippers. *Lancet*. 1988;2:397–397.
- Verdecchia P, Porcellati C, Schillaci G, Borgioni C, Ciucci A, Battistelli M, Guerrieri M, Gatteschi C, Zampi I, Santucci A, Santucci C, Reboldi G. Ambulatory blood pressure. An independent predictor of prognosis in essential hypertension. *Hypertension*. 1994;24:793–801.
- Ingelsson E, Bjorklund-Bodegard K, Lind L, Arnlöv J, Sundström J. Diurnal blood pressure pattern and risk of congestive heart failure. *JAMA*. 2006;295:2859–2866.
- Staessen JA, Thijs L, Fagard R, O'Brien ET, Clement D, de Leeuw PW, Mancia G, Nachev C, Palatini P, Parati G, Tuomilehto J, Webster J. Predicting cardiovascular risk using conventional vs ambulatory blood pressure in older patients with systolic hypertension. Systolic Hypertension in Europe Trial Investigators. *JAMA*. 1999;282:539–546.
- Sega R, Facchetti R, Bombelli M, Cesana G, Corrao G, Grassi G, Mancia G. Prognostic value of ambulatory and home blood pressures compared with office blood pressure in the general population: follow-up results from the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study. *Circulation*. 2005;111:1777–1783.
- Clement DL, De Buyzere PJ, De Bacquer DA, de Leeuw PW, Duprez DA, Fagard RH, Gheeraert PJ, Missault LH, Braun JJ, Six RO, Van Der Niepen P, O'Brien E. Prognostic value of ambulatory blood-pressure recordings in patients with treated hypertension. *N Engl J Med*. 2003; 348:2407–2415.
- Smolensky MH, Haus E. Circadian rhythms and clinical medicine with applications to hypertension. *Am J Hypertens*. 2001;14:280S–290S.
- Baumgart P. Circadian rhythm of blood pressure: internal and external time triggers. *Chronobiol Int*. 1991;8:444–450.
- Sachdeva A, Weder AB. Nocturnal sodium excretion, blood pressure dipping, and sodium sensitivity. *Hypertension*. 2006;48:527–533.
- Uzu T, Kimura G, Yamauchi A, Kanasaki M, Isshiki K, Araki S, Sugimoto T, Nishio Y, Maegawa H, Koya D, Haneda M, Kashiwagi A. Enhanced sodium sensitivity and disturbed circadian rhythm of blood pressure in essential hypertension. *J Hypertens*. 2006;24:1627–1632.
- Routledge F, McFetridge-Durdle J. Nondipping blood pressure patterns among individuals with essential hypertension: a review of the literature. *Eur J Cardiovasc Nurs*. 2006;6:9–26.
- Uzu T, Ishikawa K, Fujii T, Nakamura S, Inenaga T, Kimura G. Sodium restriction shifts circadian rhythm of blood pressure from nondipper to dipper in essential hypertension. *Circulation*. 1997;96:1859–1862.
- Staessen JA, Birkenhager W, Bulpitt CJ, Fagard R, Fletcher AE, Lijnen P, Thijs L, Amery A. The relationship between blood pressure and sodium and potassium excretion during the day and at night. *J Hypertens*. 1993;11:443–447.
- Fukuda M, Goto N, Kimura G. Hypothesis on renal mechanism of non-dipper pattern of circadian blood pressure rhythm. *Med Hypotheses*. 2006;67:802–806.
- Uzu T, Nishimura M, Fujii T, Takeji M, Kuroda S, Nakamura S, Inenaga T, Kimura G. Changes in the circadian rhythm of blood pressure in primary aldosteronism in response to dietary sodium restriction and adrenalectomy. *J Hypertens*. 1998;16:1745–1748.
- Uzu T, Kimura G. Diuretics shift circadian rhythm of blood pressure from nondipper to dipper in essential hypertension. *Circulation*. 1999;100: 1635–1638.
- Choukroun G, Schmitt F, Martinez F, Drüeke TB, Bankir L. Low urine flow reduces the capacity to excrete a sodium load in humans. *Am J Physiol*. 1997;273:R1726–R1733.
- Bankir L, Fernandes S, Bardoux P, Bouby N, Bichet DG. Vasopressin-V2 receptor stimulation reduces sodium excretion in healthy humans. *J Am Soc Nephrol*. 2005;16:1920–1928.
- Bochud M, Elston RC, Maillard M, Bovet P, Schild L, Shamlaye C, Burnier M. Heritability of renal function in hypertensive families of African descent in the Seychelles (Indian Ocean). *Kidney Int*. 2005;67:61–69.
- Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, Hogg RJ, Perrone RD, Lau J, Eknoyan G. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med*. 2003;139:137–147.
- Perucca J, Bouby N, Valeix P, Bankir L. Sex differences in urine concentration across differing ages, sodium intake and level of kidney disease. *Am J Physiol Regul Integr Comp Physiol*. 2006;292:R700–R705.
- Bochud M, Nussberger J, Bovet P, Maillard MR, Elston RC, Paccaud F, Shamlaye C, Burnier M. Plasma aldosterone is independently associated with the metabolic syndrome. *Hypertension*. 2006;48:1–7.
- Bankir L, Perucca J, Weinberger MH. Ethnic differences in urine concentration: possible relationship to blood pressure. *Clin J Am Soc Nephrol*. 2007;2:304–312.
- Gretler DD, Fumo MT, Nelson KS, Murphy MB. Ethnic differences in circadian hemodynamic profile. *Am J Hypertens*. 1994;7:7–14.
- Agyemang C, Bhopal R, Bruijnzeels M, Redekop WK. Does nocturnal blood pressure fall in people of African and South Asian descent differ from that in European white populations? A systematic review and meta-analysis. *J Hypertens*. 2005;23:913–920.
- Hyman DJ, Ogbonnaya K, Taylor AA, Ho K, Pavlik VN. Ethnic differences in nocturnal blood pressure decline in treated hypertensives. *Am J Hypertens*. 2000;13:884–891.
- Omboni S, Parati G, Palatini P, Vanasia A, Muiesan ML, Cuspidi C, Mancia G. Reproducibility and clinical value of nocturnal hypotension: prospective evidence from the SAMPLE study. Study on Ambulatory Monitoring of Pressure and Lisinopril Evaluation. *J Hypertens*. 1998;16: 733–738.
- Manning G, Rushton L, Donnelly R, Millar-Craig MW. Variability of diurnal changes in ambulatory blood pressure and nocturnal dipping status in untreated hypertensive and normotensive subjects. *Am J Hypertens*. 2000;13:1035–1038.
- Staessen J, Broughton PM, Fletcher AE, Markowe HL, Marmot MG, Rose G, Semmence A, Shipley MJ, Bulpitt CJ. The assessment of the relationship between blood pressure and sodium intake using whole-day, daytime and overnight urine collections. *J Hypertens*. 1991;9:1035–1040.

34. Burnier M, Coltamai L, Maillard M, Bochud M. Renal sodium handling and nighttime blood pressure. *Sem Nephrol.* 2007;27:565–571.
35. Kirkland JL, Lye M, Levy DW, Banerjee AK. Patterns of urine flow and electrolyte excretion in healthy elderly people. *BMJ (Clin Res Ed).* 1983; 287:1665–1667.
36. Bankir L, Sellin F, Maillard M, Chioloro A, Burnier M. Influence of moderate body weight excess on the nycthemeral pattern of blood pressure, renal function and sodium and water excretion in patients with essential hypertension [in French]. *Arch Mal Coeur Vaiss.* 2004;97: 777–781.
37. Koopman MG, Koomen GC, Krediet RT, de Moor EA, Hoek FJ, Arisz L. Circadian rhythm of glomerular filtration rate in normal individuals. *Clin Sci (Lond).* 1989;77:105–111.
38. van Acker BA, Koomen GC, Koopman MG, Krediet RT, Arisz L. Discrepancy between circadian rhythms of inulin and creatinine clearance. *J Lab Clin Med.* 1992;120:400–410.
39. Wurzner G, Chioloro A, Maillard M, Nussberger J, Hayoz D, Brunner HR, Burnier M. Renal and neurohormonal responses to increasing levels of lower body negative pressure in men. *Kidney Int.* 2001;60: 1469–1476.
40. Doris PA. Renal proximal tubule sodium transport and genetic mechanisms of essential hypertension. *J Hypertens.* 2000;18:509–519.
41. Whelton PK, He J, Cutler JA, Brancati FL, Appel LJ, Follmann D, Klag MJ. Effects of oral potassium on blood pressure. Meta-analysis of randomized controlled clinical trials. *JAMA.* 1997;277:1624–1632.
42. Perucca J, Bankir L. Dietary potassium supplementation increases urine volume and alters the circadian pattern of sodium excretion. Possible mechanism for its lowering effect on blood pressure [abstract]. *FASEB J.* 2007;21:A510.
43. Verdecchia P, Angeli F, Borgioni C, Gattobigio R, Reboldi G. Ambulatory blood pressure and cardiovascular outcome in relation to perceived sleep deprivation. *Hypertension.* 2007;49:777–783.



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