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 daytime:nighttime 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;51:891-898.)

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 hypertrophy and microalbuminuria, and the occurrence of nocturnal BP dipping has been associated with the development of target organ damage, such as left-ventricular hypertrophy and microalbuminuria. The occurrence of target organ damage, such as left-ventricular hypertrophy, 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.

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. 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-
concentration may reduce the capacity of the kidney to excrete NaCl. 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. For the analyses, we used the day and every 30 minutes at night. Additional methodological criteria have been described previously. 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 ± 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 (PNa, PK, UNa, and UK, 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_{cr}'), 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.

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>All</th>
<th>Tertile 1</th>
<th>Tertile 2</th>
<th>Tertile 3</th>
<th>P (Trend)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>325</td>
<td>109</td>
<td>108</td>
<td>108</td>
<td></td>
</tr>
<tr>
<td>D/N UNaV*</td>
<td>0.85 (0.59)</td>
<td>0.36 (0.12)</td>
<td>0.73 (0.13)</td>
<td>1.46 (0.63)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex, % women</td>
<td>55</td>
<td>55</td>
<td>56</td>
<td>56</td>
<td>0.94</td>
</tr>
<tr>
<td>Age, y</td>
<td>46.4 (11.5)</td>
<td>49.9 (11.9)</td>
<td>46.0 (10.7)</td>
<td>43.4 (11.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Height, cm</td>
<td>166 (9)</td>
<td>165 (9)</td>
<td>166 (8)</td>
<td>168 (8)</td>
<td>0.63</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>74.8 (15.7)</td>
<td>76.5 (15.6)</td>
<td>74.8 (14.6)</td>
<td>73.2 (16.8)</td>
<td>0.09</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.1 (5.1)</td>
<td>27.9 (5.0)</td>
<td>27.1 (5.1)</td>
<td>26.4 (5.0)</td>
<td>0.024</td>
</tr>
<tr>
<td>24-h SBP, mm Hg</td>
<td>127.3 (16.3)</td>
<td>131.2 (14.8)</td>
<td>126.6 (17.9)</td>
<td>123.9 (15.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>24-h DBP, mm Hg</td>
<td>81.9 (10.8)</td>
<td>83.7 (10.3)</td>
<td>81.4 (11.8)</td>
<td>80.6 (10.3)</td>
<td>0.026</td>
</tr>
<tr>
<td>P Na, mmol/L</td>
<td>140.3 (4.0)</td>
<td>139.9 (3.7)</td>
<td>140.4 (3.6)</td>
<td>140.7 (4.6)</td>
<td>0.15</td>
</tr>
<tr>
<td>P K, mmol/L</td>
<td>3.7 (0.3)</td>
<td>3.7 (0.3)</td>
<td>3.8 (0.3)</td>
<td>3.7 (0.3)</td>
<td>0.21</td>
</tr>
<tr>
<td>P creatinine, μmol/L</td>
<td>76 (16)</td>
<td>80 (18)</td>
<td>74 (17)</td>
<td>75 (14)</td>
<td>0.06</td>
</tr>
<tr>
<td>Fbg, mL/min</td>
<td>4.9 (2.2)</td>
<td>5.2 (2.6)</td>
<td>5.1 (2.3)</td>
<td>4.5 (1.5)</td>
<td>0.043</td>
</tr>
<tr>
<td>24 h V, mL/min</td>
<td>1.38 (0.75)</td>
<td>1.47 (0.87)</td>
<td>1.41 (0.76)</td>
<td>1.26 (0.61)</td>
<td>0.043</td>
</tr>
<tr>
<td>24 h C_{sbp}, mL/min†</td>
<td>110 (44)</td>
<td>106 (55)</td>
<td>112 (43)</td>
<td>114 (42)</td>
<td>0.008</td>
</tr>
<tr>
<td>C_{inulin}, mL/min†‡</td>
<td>111 (42)</td>
<td>112 (47)</td>
<td>112 (42)</td>
<td>110 (39)</td>
<td>0.67</td>
</tr>
<tr>
<td>MDRD, mL/min†</td>
<td>110 (36)</td>
<td>109 (37)</td>
<td>116 (29)</td>
<td>108 (40)</td>
<td>0.18</td>
</tr>
<tr>
<td>Na excretion, mmol/24 h</td>
<td>103 (53)</td>
<td>99 (51)</td>
<td>106 (55)</td>
<td>104 (52)</td>
<td>0.65</td>
</tr>
<tr>
<td>K excretion, mmol/24 h</td>
<td>43 (18)</td>
<td>41 (20)</td>
<td>45 (16)</td>
<td>43 (18)</td>
<td>0.50</td>
</tr>
</tbody>
</table>

Results are means (SD) unless otherwise specified. D/N UNaV 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.
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.23 Urine flow rate (V) and sodium and potassium excretion rates (U_{\text{Na}}*V and U_{\text{K}}*V, respectively) were calculated for the whole 24-hour period and for daytime and nighttime separately. Fractional excretion of sodium (F_{\text{Na}}) was calculated as U_{\text{Na}}*V/(P_{\text{Na}}*C_{\text{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_{\text{Na}} and U_{\text{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 F_{\text{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 only 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 fastering 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 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 ~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) μmol/min during daytime and nighttime, respectively, in T1 and 82 (SD: 40) and 62 (SD: 36) μmol/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_{\text{K}} (Table 3), and that of creatinine (not shown) showed fairly similar values in all of the tertiles during daytime. In subjects in T2
and T3, the UNa 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 UK were of similar magnitude but in opposite directions as those for UNa (Table S1). Sensitivity analyses that included an additional adjustment for GFR (measured using inulin clearance), 24-hour FENa, 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.

**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 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**

<table>
<thead>
<tr>
<th>Dependent Variable</th>
<th>Model</th>
<th>All</th>
<th>Tertile 1</th>
<th>Tertile 2</th>
<th>Tertile 3</th>
<th>P (Trend)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SBP</strong></td>
<td>M1</td>
<td>118.2 (16.9)</td>
<td>123.3 (15.9)</td>
<td>117.6 (18.0)</td>
<td>113.5 (15.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>M2</td>
<td>119.3 (15.2)</td>
<td>122.2 (14.7)</td>
<td>119.1 (16.1)</td>
<td>116.7 (14.3)</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>M3</td>
<td>119.4 (15.2)</td>
<td>122.4 (14.7)</td>
<td>118.9 (16.1)</td>
<td>116.7 (14.2)</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>M4</td>
<td>119.3 (14.9)</td>
<td>122.1 (14.4)</td>
<td>118.9 (16.1)</td>
<td>116.8 (13.9)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>DBP</strong></td>
<td>M1</td>
<td>75.9 (11.8)</td>
<td>78.3 (11.4)</td>
<td>75.5 (12.4)</td>
<td>73.7 (11.0)</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>M2</td>
<td>76.8 (11.0)</td>
<td>78.1 (11.1)</td>
<td>76.3 (11.7)</td>
<td>75.9 (10.0)</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td>M3</td>
<td>76.8 (11.0)</td>
<td>78.2 (11.1)</td>
<td>76.3 (11.6)</td>
<td>75.9 (10.1)</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>M4</td>
<td>76.7 (10.9)</td>
<td>78.0 (10.9)</td>
<td>76.3 (11.6)</td>
<td>75.9 (9.9)</td>
<td>0.12</td>
</tr>
<tr>
<td><strong>PP</strong></td>
<td>M1</td>
<td>42.3 (10.5)</td>
<td>45.0 (10.1)</td>
<td>42.1 (11.3)</td>
<td>39.8 (9.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>M2</td>
<td>43.1 (9.6)</td>
<td>44.9 (9.5)</td>
<td>43.2 (9.8)</td>
<td>41.4 (9.2)</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td>M3</td>
<td>43.1 (9.5)</td>
<td>44.7 (9.5)</td>
<td>43.2 (9.9)</td>
<td>41.4 (9.1)</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td>M4</td>
<td>43.1 (9.5)</td>
<td>44.5 (9.5)</td>
<td>43.1 (9.8)</td>
<td>41.5 (9.0)</td>
<td>0.010</td>
</tr>
</tbody>
</table>

Nocturnal BP dipping, day-night difference in percentage of day value

<table>
<thead>
<tr>
<th>Dependent Variable</th>
<th>Model</th>
<th>All</th>
<th>Tertile 1</th>
<th>Tertile 2</th>
<th>Tertile 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SBP</strong></td>
<td>M1</td>
<td>9.9 (7.3)</td>
<td>8.5 (6.9)</td>
<td>10.2 (7.4)</td>
<td>11.1 (7.3)</td>
</tr>
<tr>
<td></td>
<td>M2</td>
<td>9.8 (7.1)</td>
<td>8.8 (6.7)</td>
<td>10.0 (7.2)</td>
<td>10.6 (7.4)</td>
</tr>
<tr>
<td></td>
<td>M3</td>
<td>9.7 (7.1)</td>
<td>8.8 (6.7)</td>
<td>9.8 (7.1)</td>
<td>10.6 (7.4)</td>
</tr>
<tr>
<td></td>
<td>M4</td>
<td>9.8 (6.8)</td>
<td>8.7 (6.3)</td>
<td>10.0 (6.8)</td>
<td>10.8 (7.0)</td>
</tr>
<tr>
<td><strong>DBP</strong></td>
<td>M1</td>
<td>10.4 (7.8)</td>
<td>9.5 (7.7)</td>
<td>10.1 (8.4)</td>
<td>11.5 (7.3)</td>
</tr>
<tr>
<td></td>
<td>M2</td>
<td>10.2 (7.5)</td>
<td>10.1 (7.4)</td>
<td>9.9 (8.1)</td>
<td>10.7 (7.1)</td>
</tr>
<tr>
<td></td>
<td>M3</td>
<td>10.2 (7.5)</td>
<td>10.1 (7.4)</td>
<td>9.9 (8)</td>
<td>10.8 (7.1)</td>
</tr>
<tr>
<td></td>
<td>M4</td>
<td>10.3 (7.4)</td>
<td>10.1 (7.3)</td>
<td>10.0 (7.8)</td>
<td>10.8 (7.0)</td>
</tr>
<tr>
<td><strong>PP</strong></td>
<td>M1</td>
<td>8.4 (15.2)</td>
<td>6.1 (14.5)</td>
<td>9.5 (16.4)</td>
<td>9.7 (14.6)</td>
</tr>
<tr>
<td></td>
<td>M2</td>
<td>8.6 (15.2)</td>
<td>6.5 (14.4)</td>
<td>9.6 (16.4)</td>
<td>9.8 (14.7)</td>
</tr>
<tr>
<td></td>
<td>M3</td>
<td>6.4 (15.3)</td>
<td>4.8 (14.5)</td>
<td>7.3 (16.4)</td>
<td>7.2 (15.1)</td>
</tr>
<tr>
<td></td>
<td>M4</td>
<td>8.7 (14.4)</td>
<td>6.4 (13.5)</td>
<td>9.4 (15.4)</td>
<td>10.3 (14.0)</td>
</tr>
</tbody>
</table>

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.
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 urinary 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 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. When ABPM was repeated, a 40% change in the dipping or nondipping pattern was observed in a large Italian clinical study. 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, 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

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### 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

<table>
<thead>
<tr>
<th>Variable</th>
<th>All</th>
<th>Tertile 1</th>
<th>Tertile 2</th>
<th>Tertile 3</th>
<th>(P) (Trend)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daytime urine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(V), mL/min</td>
<td>1.15 (0.79)</td>
<td>1.06 (0.84)</td>
<td>1.22 (0.83)</td>
<td>1.17 (0.68)</td>
<td>0.05</td>
</tr>
<tr>
<td>(U_{\text{crea}}/P_{\text{crea}})</td>
<td>141 (106)</td>
<td>140 (112)</td>
<td>143 (114)</td>
<td>140 (91)</td>
<td>0.40</td>
</tr>
<tr>
<td>(U_{\text{Na}}, \text{mmol/L})</td>
<td>72 (51)</td>
<td>56 (42)</td>
<td>70 (45)</td>
<td>90 (58)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(U_{\text{K}}, \text{mmol/L})</td>
<td>42 (30)</td>
<td>42 (29)</td>
<td>42 (30)</td>
<td>42 (30)</td>
<td>0.88</td>
</tr>
<tr>
<td>Nighttime urine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(V), mL/min</td>
<td>1.77 (0.97)</td>
<td>2.17 (1.09)</td>
<td>1.74 (0.94)</td>
<td>1.41 (0.68)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(U_{\text{crea}}/P_{\text{crea}})</td>
<td>94 (68)</td>
<td>74 (52)</td>
<td>103 (80)</td>
<td>107 (65)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(U_{\text{Na}}, \text{mmol/L})</td>
<td>59 (37)</td>
<td>63 (36)</td>
<td>64 (43)</td>
<td>51 (32)</td>
<td>0.008</td>
</tr>
<tr>
<td>(U_{\text{K}}, \text{mmol/L})</td>
<td>19 (14)</td>
<td>16 (12)</td>
<td>20 (14)</td>
<td>20 (16)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

\[D/N\] indicates urine to plasma creatinine concentrations; \(U_{\text{crea}}\), urine creatinine concentration; \(D/N\), daytime/nighttime.

Table adapted from Bankir et al. Blood Pressure and Daytime Sodium Excretion.
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, cyclosporin, 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 subjects19 and subjects with higher BMI 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.35 Differences in the fractional excretion of creatinine around the clock have been described 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 UNa 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 UNa, 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 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 nondippers16,20 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

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

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