Kidney Dysfunction and Nocturnal Blood Pressure

Patients With Renal Dysfunction Require a Longer Duration Until Blood Pressure Dips During the Night

Michio Fukuda, Masashi Mizuno, Tamaki Yamanaka, Masahiro Motokawa, Yuichi Shirasawa, Takae Nishio, Sota Miyagi, Atsuhiro Yoshida, Genjiro Kimura

Abstract—We have postulated that the diminished renal capacity to excrete sodium causes nocturnal blood pressure (BP) elevation, which enhances pressure natriuresis in compensation for impaired daytime natriuresis. If such a mechanism holds, high BP during sleep at night may continue until excess sodium is sufficiently excreted into urine. This study examined whether the duration, defined as “dipping time,” until nocturnal mean arterial pressure began to fall to <90% of daytime average became longer as renal function deteriorated. Ambulatory BP measurements and urinary sodium excretion rates were evaluated for daytime and nighttime to estimate their circadian rhythms in 65 subjects with chronic kidney disease. Dipping time showed an inverse relationship with creatinine clearance (Ccr; \( r = -0.61, P < 0.0001 \)) and positive relationships with night/day ratios of mean arterial pressure (\( r = 0.84, P < 0.0001 \)) and natriuresis (\( r = 0.61, P < 0.0001 \)). Both of which were also inversely correlated with Ccr (mean arterial pressure: \( r = -0.58, P < 0.0001 \); natriuresis: \( r = -0.69, P < 0.0001 \)). When divided into tertiles by Ccr (mL/min), hazard ratios of nocturnal BP dip adjusted for age, gender, and body mass index were 0.37 (95% CI: 0.17 to 0.79; \( P = 0.01 \)) for the second tertile (Ccr: 50 to 90) and 0.20 (95% CI: 0.08 to 0.55; \( P = 0.002 \)) for the third tertile (Ccr: 5 to 41) compared with the first tertile (Ccr: 91 to 164). These findings demonstrate that patients with renal dysfunction require a longer duration until BP falls during the night. The prolonged duration until BP dip during sleep seems an essential component of the nondipper pattern of the circadian BP rhythm. (Hypertension. 2008;52:1155-1160.)

Key Words: chronic kidney disease ■ natriuresis ■ blood pressure ■ circadian rhythm ■ nondipper ■ cardiovascular events

In healthy subjects, blood pressure (BP) normally dips during the night by 10% to 20% from daytime. In some patients with hypertension or chronic kidney disease (CKD), however, BP fails to dip during the night, and these patients have been called “nondippers,” whereas those with a normal nocturnal BP dip are called “dippers.” We reported previously in patients with essential hypertension that, as BP became sodium sensitive, nocturnal dip in BP was diminished.1-3 Because glomerular filtration capability is one of the major factors determining sodium sensitivity,4,5 as a function of loss of glomerular filtration rate, the nocturnal dip in BP may be less pronounced. We recently illustrated this quantitative relationship in CKD and healthy donors after unilateral nephrectomy,7 where in fact there was an inverse relationship between glomerular filtration rate and the night: day ratio of BP. Therefore, we have postulated that reduced renal capacity to excrete sodium into urine causes nocturnal elevation of BP, ie, nondippers, to compensate for diminished daytime natriuresis by enhancing pressure natriuresis during sleep.1,3,6,8,9 If pressure natriuresis during sleep compensates for reduced daytime renal sodium excretion, high BP during sleep at night may continue until excess sodium is sufficiently excreted into urine. In this study, to ascertain the renal mechanisms of nondippers, we examined whether a longer duration is in fact required until a nocturnal BP begins to fall as renal function deteriorates.

Patients and Methods

Study Population

The subjects were 65 patients (33 men and 32 women; aged 16 to 80 years old; mean age: 47 ± 18 years; body mass index [BMI]: 22.2 ± 4.1 kg/m²; body weight: 58.2 ± 14.2 kg) who were hospitalized with CKD at Nagoya City University Hospital. CKD was defined as the presence of kidney damage or a decreased glomerular filtration rate of <60 mL/min per 1.73 m² for ≥3 months, according to Kidney Disease Outcomes Quality Initiative CKD criteria.10 Patients with diabetic nephropathy or nephrotic syndrome and those receiving antihypertensive agents or diuretics were excluded from the study. All of the participants were enrolled consecutively after informed consent was obtained. To examine the nighttime BP profile according to the level of renal function, the subjects were classified into tertiles based on their measured creatinine clearance (Ccr; mL/min): first tertile (Ccr: 91 to 164 with mean of 122 ± 21; n = 22), second tertile (Ccr: 50 to 90 with mean of 69 ± 11; n = 21), and third tertile (Ccr: 5 to 41 with mean of 18 ± 12; n = 22).

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Arterial pressure (MAP) was calculated as diastolic BP plus one third of the nighttime MAP reached and remained average continuously for 30 minutes noninvasively with a validated automatic device (model ES-H531, Terumo). The BP values were not considered valid for 65 subjects with CKD are summarized in Table 1. The average values of serum creatinine and Ccr were 161 ± 183 μmol/L (1.8 ± 2.1 mg/dL) and 70 ± 45 mL/min, respectively. According to office BP (average: 126 ± 21/75 ± 13 mm Hg), 17 subjects showed their BP as ≥140/90 mm Hg; 4 of 22 in the first tertile, 3 of 21 in the second tertile; and 10 of 22 in the third tertile (P = 0.04), with different levels of renal function. Thirty-four subjects had their BP as >130/80 mm Hg, which was the goal of the antihypertensive therapy for CKD patients: 10 of 22, 9 of 21, and 15 of 22, respectively (P = 0.2). According to ambulatory BP monitoring, the numbers of daytime hypertensive subjects (>135/85 mm Hg) were 6 of 22, 2 of 21, and 11 of 22 (P = 0.01), respectively. On the other hand, the numbers of nighttime hypertensive subjects (>120/75 mm Hg) were 6 of 22, 7 of 21, and 15 of 22 (P = 0.01), respectively. Daytime, nighttime, and 24-hour MAP were 91 ± 13, 88 ± 15, and 90 ± 13 mm Hg. The 24-hour averages of MAP were inversely correlated with Ccr (r = −0.25; P = 0.04). As renal function deteriorated, the nighttime MAP was significantly increased (first tertile: 81 ± 11; second tertile: 85 ± 12; third tertile: 97 ± 16 mm Hg; P = 0.0005), whereas the daytime MAP remained unchanged (first tertile: 91 ± 14; second tertile: 88 ± 7; third tertile: 94 ± 17 mm Hg; P = 0.3). Day-night changes in MAP were significantly influenced by the level of renal function, because there was a significant interaction (P < 0.0001) by 2-way ANOVA, indicating that nocturnal decline in MAP was less pronounced as renal function deteriorated. The night/day ratio of MAP was significantly higher in the third tertile than in the first tertile (P < 0.0001) and was inversely correlated with Ccr (r = −0.58; P < 0.0001). The 24-hour U_{NaV} did not differ across tertiles (P = 0.07). As renal function deteriorated, however, the daytime U_{NaV} was reduced (first tertile: 5.4 ± 1.7; second tertile: 5.1 ± 1.9; third tertile: 3.1 ± 1.7 mmol/h; P < 0.0001), whereas the nighttime U_{NaV} tended to be enhanced (first tertile: 3.3 ± 1.7; second tertile: 3.9 ± 1.6; third tertile: 4.5 ± 2.1 mmol/h; P = 0.08). Day-night changes in U_{NaV} were also significantly influenced by the level of renal function, because there was a significant interaction (P < 0.0001) by 2-way ANOVA, indicating that nocturnal decline in U_{NaV} was less pronounced as renal function deteriorated. The night/day ratio of U_{NaV} was

Statistical Analyses

Statistical analyses were performed using SPSS 15.0J (SPSS, Inc). Results are expressed as means ± SDs throughout the article except in Figure 1, where SEM was used to avoid the overlap of the lines. The significance of differences across tertiles with different levels of renal function was tested by 1-way ANOVA, followed by a Fisher protected least significant difference test for comparison between the first and third tertiles. The presence of the interaction in MAP and U_{NaV} between day and night change and renal function was studied using 2-way ANOVA. The significance of differences in the sex distribution across tertiles was examined by χ² test. Correlations among variables were evaluated by the least-squares method (r) and Spearman rank correlation (ρ) on an appropriate basis.

Because some of the subjects showed no nocturnal BP dip during sleep, regression analysis alone would be insufficient to evaluate the relationship of DT with other variables. Therefore, we adopted time-dependent end point analyses to study the nocturnal BP profile. The first occurrence of nocturnal BP dip was settled as the end point, and the cumulative incidence rate of the first occurrence of the nocturnal dip during 9 hours between 9 PM and 6 AM was compared by Kaplan-Meier analysis across tertiles with different levels of renal function, followed by a log-rank test to estimate the statistical significance. To determine whether renal function was predictive of nocturnal BP dip, hazard ratios and their 95% CIs for nocturnal BP dip were calculated using the Cox proportional hazard regression model. This model incorporated baseline demographic variables, including age, sex, and BMI as well as Ccr. P values of ≤0.05 were considered statistically significant in all of the analyses.
Table 1.  Participant Characteristics According to Renal Function Levels

<table>
<thead>
<tr>
<th>Variable</th>
<th>All</th>
<th>First Tertile</th>
<th>Second Tertile</th>
<th>Third Tertile</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ccr, mL/min</td>
<td>70±45 (n=65)</td>
<td>122±21 (n=22)*</td>
<td>69±11 (n=21)*</td>
<td>18±12 (n=22)*</td>
<td></td>
</tr>
<tr>
<td>Male/female</td>
<td>33/32</td>
<td>12/10</td>
<td>8/13</td>
<td>13/9</td>
<td>0.4‡</td>
</tr>
<tr>
<td>Age, y</td>
<td>46.8±17.6</td>
<td>41.4±16.2</td>
<td>38.1±14.0</td>
<td>60.7±13.6§</td>
<td>&lt;0.0001†</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>58.2±14.2</td>
<td>62.6±13.9</td>
<td>55.8±9.9</td>
<td>55.9±17.3</td>
<td>0.2†</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>22.2±4.1</td>
<td>23.1±3.6</td>
<td>21.3±3.0</td>
<td>22.2±5.4</td>
<td>0.4†</td>
</tr>
<tr>
<td>Pcr, μmol/L</td>
<td>161±183</td>
<td>64±10</td>
<td>72±21</td>
<td>344±222§</td>
<td>&lt;0.0001†</td>
</tr>
<tr>
<td>Night/day ratios</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-hour BP, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>122±20</td>
<td>115±17</td>
<td>118±14</td>
<td>131±24§</td>
<td>0.01†</td>
</tr>
<tr>
<td>Diastolic</td>
<td>73±12</td>
<td>73±12</td>
<td>71±7</td>
<td>77±14</td>
<td>0.3†</td>
</tr>
<tr>
<td>UNaV, mmol/d</td>
<td>104±43</td>
<td>111±37</td>
<td>112±35</td>
<td>87±44</td>
<td>0.07†</td>
</tr>
<tr>
<td>UNaV, mmol/h</td>
<td>4.5±2.0</td>
<td>5.4±1.7</td>
<td>5.1±1.9</td>
<td>3.1±1.7§</td>
<td>&lt;0.0001†</td>
</tr>
<tr>
<td>Daytime</td>
<td>3.9±1.9</td>
<td>3.3±1.7</td>
<td>3.9±1.6</td>
<td>4.5±2.1</td>
<td>0.08†</td>
</tr>
<tr>
<td>Nighttime</td>
<td>78±49</td>
<td>105±59</td>
<td>75±40</td>
<td>54±30§</td>
<td>0.001†</td>
</tr>
<tr>
<td>Night/day ratios</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP</td>
<td>0.97±0.11</td>
<td>0.90±0.06</td>
<td>0.97±0.11</td>
<td>1.04±0.11§</td>
<td>&lt;0.0001†</td>
</tr>
<tr>
<td>UNaV</td>
<td>1.05±0.67</td>
<td>0.59±0.23</td>
<td>0.86±0.38</td>
<td>1.69±0.70§</td>
<td>&lt;0.0001†</td>
</tr>
<tr>
<td>DT, h</td>
<td>5.1±3.4</td>
<td>2.7±2.0</td>
<td>5.2±3.8</td>
<td>7.3±2.6§</td>
<td>&lt;0.0001†</td>
</tr>
</tbody>
</table>

Subjects were divided into tertiles based on Ccr (mL/min): first tertile (Ccr: 91 to 164; n=22), second tertile (Ccr: 50 to 90; n=21), and third tertile (Ccr: 5 to 41; n=22). Pcr indicates serum creatinine; UNa, urinary sodium concentration; Values are means±SDs.

*Differences across tertiles were significant (P<0.0001).

†Differences between first and third tertiles were significant by posthoc analysis (Fisher protected least significant difference).

§Differences between first and third tertiles were significant by ANOVA or Fisher exact test.

significantly higher in the third tertile than in the first tertile (P<0.0001) and was inversely correlated with Ccr (r=−0.69; P<0.0001). Urinary sodium concentration was significantly lowered during both daytime (P=0.001) and nighttime (P=0.01), as renal function deteriorated from the first to third tertiles.

BP profiles during the night were compared across tertiles with different levels of renal function (Figure 1). In the first tertile, BP reached soon after the initiation of sleep to <90% of daytime averages and hardly exceeded the level again. In the third tertile, on the other hand, BP almost continued elevated throughout the night above the daytime averages and hardly fell to <90% of the daytime averages. BPs in the second tertile behaved as their intermediates between the first and third tertiles. DT until nocturnal dip of MAP <90% of the daytime average differed across tertiles (P<0.0001) and was significantly longer in the third tertile than in the first tertile (P<0.0001), as shown in Table 1. DT was inversely correlated with Ccr in nonparametric regression (r=−0.61; P<0.0001) and showed positive relationships with the night: day ratios of MAP (r=0.84; P<0.0001) and UNaV (r=0.61; P<0.0001; Figure 2). Even if 24 patients who did not reach nocturnal BP dip were excluded, the similar relationships were obtained in the remaining 41 subjects (DT and Ccr: r=−0.35, P=0.03; DT and night/day ratio of MAP: r=0.50, P=0.002; DT and night/day ratio of UNaV: r=0.38, P=0.02; n=41). In addition, the night/day ratio of MAP was positively correlated with the night/day ratio of UNaV (r=0.57; P<0.0001; n=65). During the 9 hours between 9 PM and 6 AM, 41 of the 65 subjects attained a nocturnal BP dip. In 23 of these 41 patients, nocturnal MAP never exceeded 90% of the daytime average once it had fallen. On the other hand, in the remaining 18 patients, MAP exceeded the 90% of the daytime average again very slightly.

In 24 individuals who showed no nocturnal dip, most of the 18 BP readings during the night exceeded daytime averages. In 19 of 24 subjects, nighttime BP never reached <90% of daytime averages, whereas in 5 of 24 subjects, nighttime BP fell to <90% of daytime averages for only <1 hour. Because DT was defined as 9 hours in all 24 of the subjects who showed no nocturnal dip, regression analysis alone would be insufficient to evaluate the relationships between DT and other variables. Therefore, we compared the cumulative incidence rate of the nocturnal BP dip across tertiles with different levels of renal function using Kaplan-Meier analyses (Figure 3), being significantly different (P<0.0001 by log-rank test) and higher in the first tertile than in the third tertile. These findings indicate that, as renal function deteriorated from the first to the third tertiles, the probability of nocturnal BP dip was reduced. Cox proportional regression model, including baseline variables such as age, sex, and BMI as well as Ccr, identified independent factors for nocturnal BP dip (Table 2). This model indicated that only Ccr was a significant determinant of nocturnal BP dip (hazard ratio: 1.017; 95% CI: 1.008 to 1.026; P=0.0002), with a higher Ccr being associated with a higher incidence of nocturnal BP dip.
Age, sex, and BMI did not influence the nocturnal BP dip. Hazard ratios of nocturnal BP dip adjusted for age, sex, and BMI were 0.37 (95% CI: 0.17 to 0.79; P=0.01) in the second tertile and 0.20 (95% CI: 0.08 to 0.55; P=0.002) in the third tertile compared with the first tertile. Results on DT were essentially same for both systolic and diastolic BPs as for MAP in our study subjects.

**Discussion**

Our study showed that, as renal function deteriorated in patients with CKD, nocturnal BP remained elevated for a longer duration during sleep until BP began to fall. This duration, DT, was positively correlated with the night/day ratios of BP and urinary sodium excretion and was negatively correlated with Ccr, supporting our hypothesis that BP must remain elevated during the night until excess sodium is sufficiently excreted by pressure natriuresis in patients with sodium-sensitive hypertension, including CKD. These findings pointed out for the first time that the prolonged duration until nocturnal BP dip is one of the essential components of the nondipper pattern of the circadian BP rhythm. Nocturnal dip in BP during sleep was observed in 41 of 65 patients, and in 23 of these 41 patients MAP continued to exceed 90% of the daytime average once the dip was achieved. In the remaining 18 of 41 patients, MAP rose again and exceeded slightly the 90% of the daytime average after the first dip. However, this BP re-elevation lasted only for no more than 1 hour, and then the nighttime MAP remained lowered thereafter. Thus, at least in CKD patients, BP generally does not rise again once BP falls during sleep, indicating that DT can be estimated fairly precisely. The highly significant relationship between DT and the night/day ratio of MAP suggests that nondipping phenomenon, defined as a night/day ratio of MAP ≤0.9, is almost exclusively explained by the prolongation of the duration until MAP falls to <90% of the daytime average. These findings all indicate that DT seems meaningful and becomes longer as renal function deteriorates.

We found that 24 of the 65 subjects showed no nocturnal BP dip entirely between 9PM and 6 AM and their DTs were not obtained, although we defined 9 hours in their regression analyses. These results made it difficult to analyze the relationships between DT and other parameters. Therefore, nocturnal dip of MAP to <90% of its daytime average was...
settled as the end point, and the cumulative incidence rate of the first occurrence of the nocturnal dip was compared by Kaplan-Meier analysis across tertiles with different levels of renal function. As renal function deteriorated, the cumulative incidence rate was significantly reduced. In addition, Cox proportional regression analysis identified renal function as the sole determinant of a nocturnal BP dip. Age differed across tertiles but was not a significant determinant, and even after adjustments for age, sex, or BMI, renal function was found to be an independent risk factor for nocturnal BP dip. We believe that these results show that nocturnal BP dip is manipulated mainly by renal dysfunction. These time-dependent end point analyses clearly showed, irrespective of the data distribution, that a longer duration was required until nocturnal BP dip as renal function deteriorated.

It would be useful to examine whether a higher rate of urinary sodium excretion continues for a longer time during sleep until a simultaneous dip in BP during sleep, as we discussed above. It is very difficult to test this relationship in humans, however, because the insertion of a bladder catheter would be necessary to measure the urinary sodium excretion rate precisely every hour during sleep. Recently, the circadian acrophase of BP rhythm was reported to be delayed with a blunted amplitude as renal function deteriorated in 214 children with mild-to-moderate renal dysfunction.\textsuperscript{11} In addition, association between the nondipper pattern of circadian rhythm of BP and impaired renal capacity to excrete sodium into urine was confirmed based on a large number of subjects (n=325).\textsuperscript{12} These 2 reports are consistent with our hypothesis mentioned. Bankir et al\textsuperscript{12} showed that the low rate of sodium excretion during daytime was because of a lower daytime sodium concentration in the urine and that daytime sodium concentration was negatively and strongly associated with nighttime MAP (\(r=-0.14; P=0.09\)). Both daytime and nighttime urinary sodium concentrations were lowered in parallel as renal function deteriorated from the first to the third tertiles, being independent of regulation of circadian rhythms. This is contrast to \(U_{\text{Na}}V\), because daytime \(U_{\text{Na}}V\) was significantly reduced from the first to the third tertiles, whereas nighttime \(U_{\text{Na}}V\) tended to be increased. In addition, daytime \(U_{\text{Na}}V\) was not correlated with daytime MAP (\(r=-0.14; P=0.3\)), whereas nighttime \(U_{\text{Na}}V\) tended to be positively associated with nighttime MAP (\(r=0.22; P=0.08\)). These findings suggest that \(U_{\text{Na}}V\) is a key to determine circadian BP rhythm in both our study and that of Bankir.\textsuperscript{12} A tight pressure-natriuresis relationship during the night, but not during the day, has been reported,\textsuperscript{13} also supporting our hypothesis and the importance of \(U_{\text{Na}}V\). Relative contributions of \(U_{\text{Na}}V\) and urinary sodium concentration in this relationship may be different among study populations with different levels of renal function.

A nondipper pattern of circadian BP rhythm\textsuperscript{14–19} and sodium sensitivity of BP\textsuperscript{20–22} are considered to be risk factors for cardiovascular disease (CVD), and both tend to be enhanced as renal function deteriorates. It is also well known that BP during sleep has a greater impact on CVD than the daytime BP or the 24-hour BP.\textsuperscript{23–25} Recently, it has been recognized that even mild renal dysfunction is a strong predictor for future CVD,\textsuperscript{26–28} and the risks of CVD are enhanced as renal function deteriorates.\textsuperscript{27,28} However, the precise mechanisms through which renal dysfunction causes CVD remain unknown. We, therefore, propose that nondipping of BP may be an important mechanism causing CVD in patients with CKD as a function of renal impairments. DT may not only be a more quantitative index for the circadian BP rhythm but may also be a novel marker for an accurate prediction of future CVD.

There are several limitations in this study. First, the lack of a control group of people without CKD does not allow for comparison of the results presented here. Second, the present study is cross-sectional but not longitudinal. Because we measured data only at the single point, potential day-to-day variability could not be considered. Because patients were studied under hospitalization, in addition, different data on circadian BP rhythm might be obtained in free-living people. Finally, our subjects were limited to particular patients whose BP remained almost normal on a regular salt diet without antihypertensive agents or diuretics, which could have potentially influenced the circadian rhythms of BP and natriuresis.\textsuperscript{29,30} It should, therefore, be noted that our study could not establish a clear cause-effect relationship.

In conclusion, our results demonstrate that patients with greater renal dysfunction in CKD require a longer duration until BP falls during the night. The prolonged duration until BP dip during sleep seems an essential component of the nondipper pattern of the circadian BP rhythm and may be a more quantitative index of the nondipper pattern of circadian BP rhythm.

**Perspectives**

As renal function deteriorates, nocturnal dip in BP is diminished, and longer duration is required until BP dips during the night. DT, introduced for the first time in this study, may express the nondipper phenomenon quantitatively in a different viewpoint from the night/day ratio of BP. Although both of them are highly correlated to each other, we think that DT reflects more physiological meaning and a comprehensive state, including renal function and sodium retention, than just their night/day ratio. Because it is well known that BP during sleep has a greater impact on CVD than BP during daytime, circadian BP rhythm itself must be considered as one of the important risk factors for CVD. DT may be used as a novel marker to quantitatively analyze circadian BP rhythm. Furthermore, shortening DT may become a new target of antihypertensive therapy in future.

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