Relationship between circadian blood pressure variation and circadian protein excretion in CKD

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Agarwal R. Relationship between circadian blood pressure variation and circadian protein excretion in CKD. Am J Physiol Renal Physiol 293: F655–F659, 2007. First published June 20, 2007; doi:10.1152/ajprenal.00188.2007.—Circadian blood pressure changes are blunted in patients with chronic kidney disease (CKD). Proteinuria is the most important correlate of hypertension in CKD. However, little is known about the influence of circadian blood pressure changes and variation in protein excretion rate. Furthermore, the impact of blood pressure components, e.g., mean arterial pressure and pulse pressure, on proteinuria has not been evaluated. To analyze the relationship of circadian changes in blood pressure on urinary protein excretion patterns, glomerular filtration rate was measured with iothalamate clearance and 24-h ambulatory blood pressure with SpaceLabs 90207 monitor in 22 patients with CKD. It was found that hourly protein excretion rates were 31% higher during the night. Excretion results of sodium, potassium, chloride, urea, and creatinine were also between 30 and 40% higher at night. Systolic, mean arterial, and pulse pressures but not diastolic pressure were related to daytime protein excretion rate. At night, the relationship of systolic, diastolic, and mean arterial pressures was significantly lower and essentially flat with respect to protein excretion rate, but the relationship of pulse pressure and proteinuria was not different from that seen during the day. Circadian variation in blood pressure did not impact circadian sodium excretion rate. In conclusion, these data suggest that patients with CKD have patterns of proteinuria that share different relationships with blood pressure components depending on the awake-sleep state. Pulse pressure is related to proteinuria independent of the awake-sleep state. Reducing mean arterial pressure during the day and pulse pressure during the day or night may be effective antiproteinuric strategies.

chronic kidney disease; circadian variation; proteinuria; ambulatory blood pressure

BLOOD PRESSURE, RENAL HEMODYNAMICS, and urinary electrolyte excretion rates follow circadian patterns. In normal healthy volunteers, the glomerular filtration rate (GFR) peaks during the day and nadirs at night (8, 12). Tubular function similarly undergoes cyclic variation with an intensity that exceeds that seen with GFR. At night, urinary flow rate, urinary sodium excretion rate, and urinary potassium excretion rates fall (8). In patients with relatively mild kidney disease, the GFR rhythm is preserved (6). However, tubular function shows signs of impairment even in early kidney disease (5). The night-to-day ratio of sodium excretion rates in patients with lower GFR is higher than those with well-preserved GFR (5). Thus nocturnal natriuresis plays an increasing role in achieving sodium homeostasis in kidney disease. Some investigators have suggested that the blunted fall in blood pressure during sleep may be an adaptive mechanism for achieving nocturnal natriuresis (5).

Patients with chronic kidney disease (CKD) have a high prevalence of nondipping, that is, the lack of fall of blood pressure during sleep (9). In a large cross-sectional analyses of patients with CKD, nocturnal dipping was associated with higher estimated GFR, higher serum albumin, younger age, and lesser proteinuria (4). In longitudinal studies, increase in blood pressure is strongly associated with increase in proteinuria (7). However, it is not known how circadian changes in blood pressure relate to circadian changes in proteinuria. The purpose of this study was to describe the pattern of circadian variation in urinary protein excretion in hypertensive patients with CKD and examine its relationship with circadian variation in blood pressure. Whether circadian pattern in variation of blood pressure is related to circadian changes in urine sodium excretion rate was also analyzed.

METHODS

Subjects and Protocols

Nondialysis-dependent CKD patients between the ages of 18 and 80 years with proteinuria of ≥1 g/day and/or GFR <60 ml·min⁻¹·1.73 m² were the subjects of the study. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers were required to be kept at a constant dose for at least 3 mo before entry. All patients had baseline measurements of GFR. Then they were asked to collect a 24-h urine specimen in two urine jugs, one until bedtime on the first experimental day and the other overnight as an outpatient. Urine was analyzed for protein, creatinine, sodium, potassium, chloride, and urea. Ambulatory blood pressures were recorded simultaneously in all patients by the Spacelabs 90207 monitor as detailed below. The entire study was repeated after 1 mo in a subgroup of 15 patients without changing blood pressure therapy, diet, or drugs. In these 15 patients, plasma renin and aldosterone were also measured after 30 min of supine rest. The study was approved by the Institutional Review Board, and all patients gave written, informed consent.

Measurements

Ambulatory blood pressure monitoring. Ambulatory blood pressures were recorded every 20 min during the day (6:00 AM to 10:00 PM) and every 30 min during the night (10:00 PM to 6:00 AM) by the

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Table 1. Clinical characteristics of the study sample

<table>
<thead>
<tr>
<th>Clinical Characteristic of 22 Patients</th>
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</thead>
<tbody>
<tr>
<td>Age, yr</td>
</tr>
<tr>
<td>Men</td>
</tr>
<tr>
<td>Race</td>
</tr>
<tr>
<td>White</td>
</tr>
<tr>
<td>Black</td>
</tr>
<tr>
<td>Weight, kg</td>
</tr>
<tr>
<td>Height, cm</td>
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<tr>
<td>Body mass index, kg/m²</td>
</tr>
<tr>
<td>Etiology of chronic kidney disease</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
</tr>
<tr>
<td>Number receiving antihypertensive drugs</td>
</tr>
<tr>
<td>Number receiving ACE inhibitors</td>
</tr>
<tr>
<td>Number receiving loop diuretics</td>
</tr>
<tr>
<td>Urine protein/creatinine (median; interquartile range)</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate, ml·min⁻¹·1.73 m⁻²</td>
</tr>
<tr>
<td>Glomerular filtration rate, ml·min⁻¹·1.73 m⁻²</td>
</tr>
<tr>
<td>Plasma renin activity, ng·ml⁻¹·h⁻¹</td>
</tr>
<tr>
<td>Plasma aldosterone, ng/ml</td>
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</tbody>
</table>

Values are means (SD) or number of patients (percent). Plasma renin and aldosterone results were evaluated in 15 patients only. ACE, angiotensin-converting enzyme.

Spacelab 90207 ABP monitor (SpaceLabs Medical, Redmond, WA). The accuracy of ambulatory blood pressure was determined by auscultatory methods using a T-piece connected to a mercury sphygmomanometer. Data were analyzed by ABP Report Management System software, version 1.03.05 (SpaceLabs Medical). Ambulatory blood pressure and heart rates were averaged by the caliper function of the software over the exact interval during which the urine collections were made. These readings were designated as day and night recordings for the purposes of these analyses.

GFR. GFRs were measured by iothalamate clearance as previously described (2). A continuous subcutaneous infusion at a rate of 125 µg/h was started after a bolus intravenous injection 24 h before the actual measurements. The following day, six samples of plasma were collected at 0, 1, 1.5, 2, 2.5, and 3.0 h while the subjects were water loaded. Plasma iothalamate concentrations were analyzed with the use of a previously reported high-performance liquid chromatography technique (1). The ratio of infusion rate to steady-state plasma concentration yielded the iothalamate clearance. Average of these six collections was expressed as the GFR.

Statistical Analysis

Hourly protein excretion rates (mg/h) were calculated separately for day and night intervals. These values were log transformed to approximate a normal distribution. We tested the mean level of proteinuria across participants after accounting for correlated observation for subjects by fitting a mixed straight line model using the full-maximum-likelihood approach. A mixed model is necessary over ordinary least-squares regression to allow for correlated observations within individuals. Next, the effect of average systolic blood pressure during the day and during the night was modeled, and the intercept and slope of this model were calculated. Similar analyses were performed for diastolic, mean arterial pressure, and pulse pressure. Model comparisons were made by testing the −2 log-likelihood statistics by a chi-squared test (10). This was a pilot study, and no sample size was calculated a priori. All tests were two sided at an α-level of 0.05. Statistical analyses were carried out by standard procedures using SPSS software (version 14; SPSS, Chicago, IL).

RESULTS

The demographic characteristics of the study population are shown in Table 1; 82% of the study sample were men, and 59% were black; these individuals were generally obese and had 59% prevalence of diabetes mellitus as cause of CKD. ACE inhibitors were used in all but one patient; median proteinuria was 0.86 g/g creatinine, and estimated GFR by the four-component model of diet in renal disease equation was 40.3 ml·min⁻¹·1.73 m⁻². Four patients had CKD stage 1 or 2, 11 had CKD stage 3, and 7 had CKD stage 4 or 5.

The circadian changes in blood pressure electrolyte excretion patterns are shown in Table 2. No statistically or clinically meaningful changes in systolic, diastolic, or mean arterial pressure were seen from day to night. Pulse pressure was higher at night, due to slightly higher systolic and slightly lower diastolic blood pressures. Heart rate was 5% lower. Urine flow rate, sodium excretion, potassium excretion, chlo-

Table 2. Circadian variation in ambulatory BP and urine excretions

<table>
<thead>
<tr>
<th>Day</th>
<th>Night</th>
<th>Difference (95% CI)</th>
<th>P</th>
<th>%Change</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ambulatory BP parameters</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>148.2 (4.2)</td>
<td>148.7 (4.2)</td>
<td>0.6 (−3.6, 4.7)</td>
<td>0.78</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>83.0 (2.2)</td>
<td>80.8 (2.2)</td>
<td>−2.3 (0.4, −4.9)</td>
<td>0.093</td>
</tr>
<tr>
<td>Pulse pressure, mmHg</td>
<td>105.9 (2.8)</td>
<td>105.2 (2.8)</td>
<td>0.7 (−2.6, 4.0)</td>
<td>0.66</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>83.5 (2.7)</td>
<td>79.5 (2.7)</td>
<td>−4.0 (−6.3, −1.8)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Urinary parameters</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine flow rate, ml/h</td>
<td>101 (12)</td>
<td>127 (12)</td>
<td>27 (4, 49)</td>
<td>0.023</td>
</tr>
<tr>
<td>Urine sodium, mmol/l</td>
<td>6.7 (0.95)</td>
<td>9.3 (0.95)</td>
<td>2.6 (0.5, 4.7)</td>
<td>0.018</td>
</tr>
<tr>
<td>Urine potassium, mmol/l</td>
<td>2.1 (0.33)</td>
<td>2.9 (0.33)</td>
<td>0.8 (0.18, 1.4)</td>
<td>0.013</td>
</tr>
<tr>
<td>Urine chloride, mmol/l</td>
<td>6.4 (0.91)</td>
<td>8.6 (0.91)</td>
<td>2.2 (0.18, 4.2)</td>
<td>0.034</td>
</tr>
<tr>
<td>Urine creatinine, mg/l</td>
<td>55.8 (6.0)</td>
<td>74.2 (6.0)</td>
<td>18.4 (3.2, 31.7)</td>
<td>0.007</td>
</tr>
<tr>
<td>Log urine protein, mg/l</td>
<td>4.68 (0.25)</td>
<td>4.95 (0.25)</td>
<td>0.27 (0.033, 0.51)</td>
<td>0.026</td>
</tr>
<tr>
<td>Urine urea, g/l</td>
<td>0.329 (0.057)</td>
<td>0.421 (0.057)</td>
<td>0.092 (0.002, 0.183)</td>
<td>0.046</td>
</tr>
</tbody>
</table>

Numbers in parentheses show SE results. BP, blood pressure; CI, confidence interval; NS, not significant.
ride excretion, creatinine excretion, urea excretion, and protein excretion were all ~30–40% higher at night. The parallel changes in protein and creatinine excretion rates resulted in an unchanged protein-to-creatinine ratio from day to night.

Figure 1 shows the relationships of systolic, diastolic, mean arterial, and pulse pressures with protein excretion rates. Table 3 shows that systolic and mean arterial pressures were related to log of protein excretion rate during the day. At night, the relationships between protein excretion rate and systolic, diastolic, and mean arterial pressures were significantly reduced compared with those seen during the day. At night, for systolic pressure of 120 mmHg, log of protein excretion rate was 0.61 higher than that shown at day. Log protein excretion rate increased 0.18 mg·h⁻¹·10 mmHg⁻¹ in systolic pressure during the day and 0.06 mg/h during the night (Table 3). Pulse pressure vs. log protein excretion rate slopes were significant and similar both during the day and during the night. No differences from day to night were seen in log protein excretion rate after adjusting for pulse pressure in either the slope or the intercept. No relationships between systolic, diastolic, mean arterial, or pulse pressure and sodium excretion were seen.

Modifications of day-to-night blood pressure ratios and day-to-night urine electrolyte ratios were evaluated for ethnicity, diabetes mellitus, CKD stage, aldosterone, and aldosterone-to-renin ratio and the use of loop diuretics. No modification effect was noted (data not shown).

**DISCUSSION**

The major findings of this study are an increase in electrolyte, creatinine, urea, and protein excretion rates at night compared with day in patients with overt proteinuria. Furthermore, a significant and positive relationship between blood pressure and protein excretion rate exists during the day, which is blunted during the night. A strong relationship exists between pulse pressure and proteinuria that is not confounded by the time of day. This relationship between blood pressure and proteinuria is not shared between blood pressure and sodium excretion rate. The parallel changes in creatinine excretion rate and protein excretion rate during the night confirm the value of using the protein-to-creatinine ratio as a reproducible measurement of proteinuria (3).

**Circadian Renal Rhythms in Normal Subjects**

In normal subjects (8, 12), GFR is highest during the day and lowest during the night. However, the tubular secretion of creatinine has a rhythm that is opposite to that of GFR (12). In normal subjects, urinary electrolyte excretion during the night is decreased (8). Thus urine sodium excretion rate falls from

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**Table 3. Fitted functions to predict log protein-to-creatinine ratios**

<table>
<thead>
<tr>
<th></th>
<th>Day estimate</th>
<th>Night estimate</th>
<th>BP Estimate</th>
<th>Night × BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP, mmHg</td>
<td>4.16 (0.3)‡</td>
<td>0.61 (0.2)†</td>
<td>0.18 (0.07)*</td>
<td>−0.12 (0.06)*</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>4.64 (0.2)‡</td>
<td>0.32 (0.11)†</td>
<td>0.25 (0.14)</td>
<td>−0.3 (0.11)†</td>
</tr>
<tr>
<td>Pulse pressure, mmHg</td>
<td>4.02 (0.35)‡</td>
<td>0.44 (0.25)</td>
<td>0.26 (0.11)*</td>
<td>−0.08 (0.08)</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>4.38 (0.26)‡</td>
<td>0.55 (0.15)‡</td>
<td>0.24 (0.01)*</td>
<td>−0.23 (0.09)†</td>
</tr>
</tbody>
</table>

Values in parentheses are SE of estimates. Intercepts are calculated at systolic BP of 120 mmHg, diastolic BP of 80 mmHg, pulse pressure of 40 mmHg, and mean arterial pressure of 93.3 mmHg. BP estimate is made for 10 mmHg. *P < 0.05, †P < 0.01, ‡P < 0.001.
19 ± 5.2 to 6.0 ± 2.9 mmol/h and urine potassium excretion rate from 5.4 ± 1.8 to 0.79 ± 0.32 mmol/h at night. Urine flow rate falls from 211 to 60 ml/h at night following the GFR rhythm. The magnitude of changes in the urinary electrolytes is much larger than the GFR rhythms. Urine albumin and β-2 microglobulin excretion rates in normal individuals follow the GFR rhythm. The fractional reabsorption of sodium and water are maximal at night. It follows that circadian changes in hemodynamics and tubular function are responsible for the normal pattern of excretion in urinary electrolytes, water, creatinine, and protein. Thus tubular function is maximized during the night for reabsorption of electrolytes.

Circadian Renal Rhythms in Patients with CKD

Handling of electrolytes and protein by the diseased nephron may change with progression of CKD. For example, in 20 patients with early type 1 diabetic nephropathy with persistent albuminuria and daytime GFR of 82 ml/min, Hansen et al. (6) found no change in albuminuria from day to night, but diurnal variations in GFR were present. Electrolyte excretions were not reported. In 26 Japanese patients with various nondiabetic glomerulopathies and mean serum creatinine of 1.1 mg/dl, night-time excretion of sodium and protein was lower than that shown at daytime (5). However, the night-to-day ratio of urinary sodium excretion in those with lower creatinine clearance (16–62 ml/min) was more than twice that seen in the higher creatinine clearance group (106–151 ml/min). Night-to-day ratio of protein excretion was also higher in those with lower kidney function. Thus the patterns of electrolyte excretion and protein excretion may change with advancing kidney disease.

Few data exist for patients with more advanced kidney disease. Our data extend the above findings to a group of patients with more severe kidney disease, where reversal of diurnal rhythms was noted. Thus the nocturnal excretion of urine electrolytes, creatinine, urea, and protein exceeded that during the day. Importantly, protein excretion was related to pulse pressure in a log-linear way regardless of the time of the day. Daytime protein excretion was related to systolic and mean arterial pressures. Night-time protein excretion was not related to systolic and mean arterial pressure. Furthermore, the relationship between proteinuria and blood pressure was not shared by blood pressure and sodium excretion.

Some investigators have proposed that the rise in nocturnal blood pressure elevation with progressive loss of kidney function leads to natriuresis and proteinuria (5, 11). Our results do not support this notion. Systolic, diastolic, and mean arterial pressures were similar during the day and night. There was no relationship between the nocturnal systolic, diastolic, and mean blood pressures and proteinuria. Furthermore, we found no relationship between the night-to-day ratio of systolic or diastolic ambulatory blood pressures and the night-to-day ratio of any of the electrolyte, protein, creatinine, or urea excretion rates seen in this study. What could be the reason underlying the lack of relationship between blood pressure at night and proteinuria?

Nocturia, thought to be mediated by the loss of concentrating ability of the kidney, is an early feature of CKD. A generalized disturbance of tubular function may exist early in CKD. Renin-angiotensin-aldosterone system, the sympathetic nervous system, and vasopressin modulate sodium and water reabsorption in the kidney. These systems undergo a diurnal variation. Diurnal variability may be impaired in CKD. Our patients either had overt proteinuria or low GFR, indicating the presence of CKD. CKD may simultaneously be associated with the loss of normal circadian rhythms of electrolyte excretions as well as loss of nocturnal dipping. The steeper relationship of blood pressure and proteinuria during the day may be related to activity-induced changes in blood pressure and protein excretion rate. Orthostatic proteinuria may then form an important component of proteinuria in patients with CKD.

Limitations

There are some limitations to the study design. We had a small number of patients, and we had no normal controls. Thus we can only compare our data to those published in the literature for normal controls. Although we measured GFR in all patients, we could measure this only during the day for logistical reasons. Thus we cannot comment on the diurnal changes in GFR in the population of patients with more advanced kidney disease. The dietary sodium intake and water intake of our subjects was not controlled, and urine was collected as outpatients. These factors may influence the conclusions if the study is repeated in a controlled environment and fixed dietary intake. The antihypertensive drug therapy may have influenced circadian rhythms. However, in CKD patients with hypertension, it may be unethical to withdraw antihypertensive therapy for a significant length of time before making these measurements. Nonetheless, our data gathered in free-living CKD patients point out the inverted circadian rhythms of renal electrolyte and protein excretion rates.

Clinical Implications

This study demonstrates that, unlike normal healthy volunteers, patients with proteinuric kidney diseases taking a self-selected diet have an inverted rhythm of urinary electrolyte, creatinine, urea, and protein excretions. This inversion of rhythm is not related to the diurnal variation in blood pressure. There are several clinical research implications of these findings. Proteinuria can have a damaging effect on the renal tubules, and reduction in proteinuria may reduce tubular damage or alternatively signal tubular repair. The relationship of pulse pressure and proteinuria was not confounded by circadian rhythms. If pulse pressure and proteinuria are causally related, then measures directed to reduce pulse pressure such as through diuretics or ACE inhibitors may improve proteinuria regardless of the time of the day. On the other hand, reduction of mean arterial pressure during the day may be more useful in reducing proteinuria due to its steeper relationship with protein excretion rate during the day. It is also possible that these altered rhythms, like nondipping, may have prognostic significance. However, altering these rhythms with diet or drugs to demonstrate linkage with outcomes would require clinical trials.

REFERENCES


