

# The Effects of Unilateral Nephrectomy on Blood Pressure and Its Circadian Rhythm

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## Abstract

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**Objective** Hypertension and diurnal blood pressure (BP) variation are widely accepted as risk factors for renal damage. However, the effects of unilateral nephrectomy on BP and its circadian rhythm have not yet been clarified in patients with a compromised renal function, including dialysis patients.

**Methods** We investigated 22 unilateral nephrectomized patients (16 men and 6 women, age: 64.5±14.3 years). The function of the circulating renin-angiotensin system (RAS) (plasma renin activity and plasma angiotensin II) and 24-h ambulatory BP monitoring (ABPM) were evaluated before and after nephrectomy. Daytime and nighttime 24-h ABPM values were determined based on sleep and waking times.

**Results** In non-dialysis patients, the estimated glomerular filtration rate after nephrectomy was significantly lower than that before (before, 62.4±23.2 mL/min/1.73 m<sup>2</sup> vs. after, 43.7±16.8 mL/min/1.73 m<sup>2</sup>; p<0.01). No significant differences were noted in the levels of BPs and circulating RAS before and after nephrectomy. However, the night-to-day (N/D) ratio of systolic BP (SBP) was significantly higher after nephrectomy than before (before, 93.3±6.5% vs. after, 98.4±6.9%; p<0.01), and the patterns of circadian BP rhythm also significantly differed before and after nephrectomy (p=0.022). Namely, the rates of dipper patterns decreased and nondipper and riser patterns increased after nephrectomy. In contrast, in dialysis patients, no significant differences were observed in the N/D ratio of SBP or the patterns of circadian BP rhythm before and after nephrectomy.

**Conclusion** Unilateral nephrectomy affects the circadian rhythm of BP but not absolute values of BP.

**Key words:** blood pressure, circadian rhythm, night-to-day ratio, renal function, unilateral nephrectomy

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## Introduction

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Chronic kidney disease (CKD) is a global public health problem with adverse outcomes of kidney failure, cardiovascular disease, and premature death. The occurrence and progression of CKD are known to be strongly associated with hypertension. Bakris et al. noted a relationship between achieving blood pressure (BP) control and a decline in the glomerular filtration rate (GFR) (1). In addition, circadian BP rhythms have been classified into extreme dipper, dipper, nondipper, or riser patterns when the night-to-day (N/D) ratio of systolic BP is <0.80, 0.80 to <0.90, 0.90-1.00, and

>1.00, respectively (2). Circadian BP rhythms are gaining interest because increasing evidence has recently demonstrated that the disruption of the diurnal BP variation is an additional risk factor for cardiovascular disease (3), stroke (4), and end-stage renal disease (5).

The circulating renin-angiotensin system (RAS) plays an important role in BP and sodium homeostasis (6). In addition to the role of the circulating RAS, the tissue-specific RAS in the heart and kidneys has been shown to play an important role in the pathophysiology of tissue function (7-9). Fukuda et al. demonstrated that intrarenal RAS activation is associated with nocturnal hypertension. Namely, the immunostaining intensities of proximal tubular an-

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giotensinogen (AGT) were increased in IgA nephropathy patients compared with control individuals and they positively correlated with fractional tubular sodium reabsorption and the N/D ratio of BP (10). We also found in a previous study of non-CKD and CKD patients who were divided into risers and non-risers that the circadian rhythm of intrarenal RAS activation may lead to renal damage and hypertension, which are associated with diurnal BP variation (11).

Several previous reports have shown the influence of nephrectomy on the BP and its circadian rhythm. Bonnet et al. observed the changes in the BP and plasma renin activity (PRA) in a sheep model before and after bilateral nephrectomy and found that the BP was decreased after nephrectomy because the PRA was below the detection limit of the assay (12). However, none of these previous studies investigated the change in the BP circadian rhythm before and after nephrectomy. Uzu et al. did conduct 24-hour ambulatory BP monitoring (ABPM) before bilateral nephrectomy and 2 weeks later, before and after a hemodialysis (HD) session. These authors detected an increase in the postoperative daytime BP, and while the postoperative nighttime BP measured after the HD session was unchanged, the postoperative nighttime BP before the HD session was elevated compared with the values before the operation. Given these results, the authors concluded the importance of either or both the fluid status or kidneys in the genesis of the diurnal BP rhythm (13).

However, the potential influence of unilateral nephrectomy on the BP and its circadian rhythm is unknown. We therefore evaluated the change in the BP and its circadian rhythm following unilateral nephrectomy.

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## Materials and Methods

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### Recruitment of the patients

This study was approved by the ethics committee of Hamamatsu University School of Medicine (No. 25-92) and was conducted in accordance with the guidelines in the Declaration of Helsinki. All of the patients provided their written informed consent. We recruited 22 patients who were admitted to our hospital to undergo unilateral nephrectomy from September 2013 to October 2015. The patients' ages ranged from 20-80 years. The present study included patients with a range of renal function, taking many different types of antihypertensive medications. However, we excluded those patients in whom antihypertensive medications were newly prescribed or had been changed during their hospitalization.

### Study protocols

In HD patients, the vital signs such as height and body weight were measured on preoperative and postoperative days before the HD sessions. Blood samples were drawn just before the HD sessions. The same procedures were performed on preoperative and postoperative days for peritoneal

dialysis (PD) and non-dialysis patients. The number of days when the measurements were taken was  $0.88 \pm 0.99$  days before nephrectomy and  $8.24 \pm 1.79$  days after nephrectomy.

Blood samples were drawn at 9:00 AM after the patients had rested in the supine position for at least 15 min. The samples were then centrifuged at 3,000 rpm for 10 min at 4°C and stored at -80°C until the assay, as described previously (11).

### Measurements

The serum creatinine concentrations were measured in the clinical laboratory of the Hamamatsu University School of Medicine, University Hospital. The estimated GFR (eGFR) was calculated using the Japanese eGFR equation (14). The PRA and plasma angiotensin II (AngII) levels for the circulating RAS were determined by radioimmunoassay (SRL, Tokyo, Japan), and the human atrial natriuretic peptide (hANP) levels were determined by chemiluminescent enzyme immunoassay (SRL). During 24-h ABPM, the BP was measured noninvasively every 30 min using an automatic device (TM-2431; A and D, Tokyo, Japan). The daytime BPs were calculated as the average of the readings during waking hours, whereas the nighttime BPs were the average of the remaining values that were recorded in patients' behavior records, as described previously (11).

### Statistical analysis

The results are expressed as the mean  $\pm$  standard deviation. The dry weight was used as the body weight for HD patients. The significance of the differences between the preoperative and postoperative values was determined using Student's *t*-test for paired samples. Because PRA, plasma AngII, and hANP did not show normal distributions, logarithmic transformation was applied to them for Student's *t*-test. The significance of the differences in the circadian BP rhythms was examined using the chi-squared test. A  $p < 0.05$  was considered statistically significant. The statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software package, version 20 (SPSS Inc., Chicago, IL, USA).

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## Results

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### Total patient characteristics

We recruited 22 patients, and their characteristics are listed in Table 1. The reasons for nephrectomy were as follows: renal cell carcinoma in 18, renal pelvic carcinoma in 1, ureteral carcinoma in 2, and metastasis to the kidney in 1. The extent of cancer was limited in the removed kidney, and the remaining normal regions were well-functioning. Patients with a range of renal function were included in the present study. Dialysis was performed for all patients with eGFR  $< 15$  mL/min/1.73 m<sup>2</sup>, including 4 patients requiring HD and 1 requiring PD.

**Table 1. Characteristics of All Patients.**

Age, year	64.5 ± 14.3
Sex	Male 16 Female 6
Causes of nephrectomy	Renal cell carcinoma: 18 Renal pelvic carcinoma: 1 Ureteral carcinoma: 2 Metastasis in kidney: 1
Past history or Comorbidity	Heart disease: 5 Cerebrovascular disease: 1 Malignancy: 3 Hypertension: 9 Diabetes mellitus: 8 Others: 16
eGFR (mL/min/1.73m <sup>2</sup> )	eGFR ≥ 90: 2 60 ≤ eGFR < 90: 7 30 ≤ eGFR < 60: 6 15 ≤ eGFR < 30: 2 eGFR < 15 : 5
Use of antihypertensives	RAS blockers: 5 Diuretics: 3 Others: 7

eGFR: Estimated Glomerular Filtration Rate, RAS: Renin-angiotensin System

### **Changes in the clinical parameters before and after nephrectomy**

We compared the clinical parameters before and after operation in all of the patients (Table 2). Although the BPs during both the 24-h period and daytime were reduced by hospitalization and operation, no significant differences from the respective preoperation values were noted, except for differences in the preoperation and postoperation daytime diastolic BPs. In addition, no significant differences were noted in the circulating RAS activity and hANP before and after operation.

In contrast, the N/D ratio of systolic BP was significantly higher after nephrectomy than before (before, 94.7±6.4% vs. after, 100.8±9.7%;  $p<0.01$ ), and the patterns of circadian BP rhythm significantly differed before and after nephrectomy ( $p=0.025$ ). Namely, the prevalence of dipper patterns decreased while that of nondipper and riser patterns increased after nephrectomy.

### **Characteristics and changes in the clinical parameters before and after nephrectomy in non-dialysis patients**

We next divided the patients into non-dialysis and dialysis groups. The non-dialysis group comprised 12 men and 5 women, with a mean age of 65.4±14.8 years. Regarding the use of antihypertensives, 3 used RAS blockers, 2 used diuretics, and 4 used other agents.

We compared the clinical parameters before and after nephrectomy in non-dialysis patients. Although the body weight, BPs during daytime, and PRA tended to be reduced by hospitalization and operation, no significant differences from the respective preoperation values were noted. In addition, no significant differences were noted in the plasma AngII activity and hANP before and after operation.

In contrast, the N/D ratio of systolic BP was significantly

higher after nephrectomy than before (before, 93.3±6.5% vs. after, 98.4±6.9%;  $p<0.01$ ), and the patterns of circadian BP rhythm significantly differed before and after nephrectomy ( $p=0.022$ ). Namely, the prevalence of dipper patterns decreased while that of nondipper and riser patterns increased after nephrectomy. Furthermore, the serum creatinine levels after nephrectomy were significantly increased and the eGFR was significantly decreased after nephrectomy compared with before nephrectomy (Table 3).

### **Characteristics and changes in the clinical parameters before and after nephrectomy in dialysis patients**

The dialysis group comprised 4 men and 1 woman, with a mean age of 61.6±13.2 years. The causes of end-stage renal disease were diabetic nephropathy in 2 and chronic glomerulonephritis in 3. Regarding the dialysis method, 4 were receiving HD and 1 was receiving PD, with a mean dialysis period of 101.0±89.5 months. Regarding the use of antihypertensives, 1 used RAS blockers, 2 used diuretics, and 3 used other agents.

We compared the clinical parameters before and after nephrectomy in dialysis patients (Table 4). Although the plasma AngII tended to be reduced by hospitalization and operation, no significant differences from the preoperation values were noted. In contrast to the findings in non-dialysis patients, no significant differences were noted between N/D ratios of systolic BP measured before and after operation in the dialysis patients (before nephrectomy, 99.5±2.9% vs. after nephrectomy, 109.1±14.0%;  $p=0.24$ ).

## **Discussion**

In this study, we found that the N/D ratio of the systolic BP was significantly higher after nephrectomy than before, and the patterns of circadian BP rhythm significantly differed before and after nephrectomy in non-dialysis patients, who experienced a reduction in renal function. In contrast, no significant differences were noted in the N/D ratio of systolic BP or the patterns of circadian BP rhythm before and after nephrectomy in dialysis patients, whose renal function did not change.

The mechanism behind an abnormal circadian BP rhythm has been reported to reduce the glomerular filtration rate (15). In the present study, the decrease in mean eGFR and the percentage decrease in eGFR were 18.8±15.1 mL/min/1.73 m<sup>2</sup> and 28.2±23.0% in non-dialysis patients, respectively (data not shown). In contrast, in dialysis patients, whose mean dialysis period was 101.0±89.5 months, the renal function did not differ markedly before and after nephrectomy. This was likely because these patients had no residual renal function before nephrectomy, and the daily urinary volume of HD patients was almost nonexistent and no urinary sodium excretion was expected. These results support the hypotheses that insufficient natriuresis due to a decrease in the glomerular filtration elevates the nocturnal

**Table 2. Comparison of Clinical Parameters before and after Nephrectomy in All Patients.**

	Before nephrectomy	After nephrectomy	p value
Body weight (kg)	60.2±11.6	59.7±11.5	0.18
Body mass index (kg/m <sup>2</sup> )	22.9±3.6	21.4±6.0	0.26
SBP (24-h period) (mmHg)	134.3±19.5	129.3±21.4	0.23
DBP (24-h period) (mmHg)	79.8±10.4	76.2±9.1	0.065
MBP (24-h period) (mmHg)	97.6±12.5	93.6±12.1	0.13
SBP (daytime) (mmHg)	137.6±19.8	129.3±20.8	0.076
DBP (daytime) (mmHg)	82.1±11.8	76.9±9.7	0.029
MBP (daytime) (mmHg)	100.1±13.3	94.1±12.2	0.050
SBP (nighttime) (mmHg)	130.5±21.8	130.3±23.7	0.97
DBP (nighttime) (mmHg)	76.5±11.0	75.4±9.6	0.59
MBP (nighttime) (mmHg)	94.3±14.1	93.3±13.6	0.72
N/D ratio of SBP (%)	94.7±6.4	100.8±9.7	<0.01
Patterns of circadian BP rhythm	D:7/ND:8/R:7/ED:0	D:0/ND:9/R:12/ED:1	0.025
PRA (ng/mL/hr)	1.60±0.41	1.51±0.49	0.16
Plasma Ang II (pg/mL)	-0.030±0.46	-0.11±0.53	0.31
hANP (pg/mL)	1.02±0.38	1.02±0.28	0.98

SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, MBP: Mean Blood Pressure, N/D: Night-to-day, BP: Blood Pressure, D: Dipper, ND: Nondipper, R: Riser, ED: Extreme Dipper, PRA: Plasma Renin Activity, AngII: Angiotensin II, hANP: Human Atrial Natriuretic Peptide

**Table 3. Changes in Clinical Parameters before and after Nephrectomy in Non-dialysis Patients.**

	Before nephrectomy	After nephrectomy	p value
Body weight (kg)	59.0±11.8	58.2±11.8	0.065
Body mass index (kg/m <sup>2</sup> )	22.9±3.7	20.8±6.6	0.26
SBP (24-h period) (mmHg)	128.6±13.7	123.7±16.8	0.32
DBP (24-h period) (mmHg)	77.5±8.4	74.2±6.3	0.16
MBP (24-h period) (mmHg)	94.1±9.4	90.4±8.6	0.24
SBP (daytime) (mmHg)	132.7±15.7	124.7±15.9	0.16
DBP (daytime) (mmHg)	80.3±11.2	75.4±7.0	0.098
MBP (daytime) (mmHg)	97.3±11.5	91.6±8.6	0.13
SBP (nighttime) (mmHg)	123.7±15.7	122.8±18.7	0.86
DBP (nighttime) (mmHg)	73.6±8.8	72.4±6.6	0.57
MBP (nighttime) (mmHg)	90.2±11.0	88.8±9.8	0.67
N/D ratio of SBP (%)	93.3±6.5	98.4±6.9	<0.01
Patterns of circadian BP rhythm	D:7/ND:6/R:4/ED:0	D:0/ND:8/R:8/ED:1	0.022
sCr (mg/dL)	1.03±0.42	1.46±0.75	<0.01
eGFR (mL/min/1.73m <sup>2</sup> )	62.4±23.2	43.7±16.8	<0.01
eGFR ≥ 90	2	0	
60 ≤ eGFR < 90	7	2	
30 ≤ eGFR < 60	6	11	
15 ≤ eGFR < 30	2	3	
eGFR < 15	0	1	
PRA (ng/mL/hr)	1.42±0.29	1.29±0.34	0.098
Plasma Ang II (pg/mL)	0.013±0.48	0.0026±0.53	0.90
hANP (pg/mL)	1.01±0.42	1.04±0.31	0.83

SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, MBP: Mean Blood Pressure, N/D: Night-to-day, BP: Blood Pressure, D: Dipper, ND: Nondipper, R: Riser, ED: Extreme Dipper, sCr: Serum Creatinine, eGFR: Estimated Glomerular Filtration Rate, PRA: Plasma Renin Activity, AngII: Angiotensin II, hANP: Human Atrial Natriuretic Peptide

BP. Ideally, urinary sodium excretion levels should have been examined, but this was impossible, as the present study included HD patients who did not urinate, and so we did not collect urine from any of our patients.

Another mechanism of abnormal circadian BP rhythm is enhanced tubular sodium reabsorption (15) caused by intrarenal RAS activation (10, 11). The glomerular filtration pressure is well known to be increased after unilateral

nephrectomy, causing renal damage such as focal segmental sclerosis (16, 17). Chamberlain et al. reported that the GFR of the remaining kidney in a rat model was increased by approximately 50% within 8 days after uninephrectomy. However, conflicting results have also been reported; for example, previous reports have indicated that 3 to 6 months are needed after renal ablation to induce renal damage (17, 18). We also previously clarified that intrarenal RAS activation is

**Table 4. Changes in Clinical Parameters before and after Nephrectomy in Dialysis Patients.**

	Before nephrectomy	After nephrectomy	p value
Body weight (kg)	63.8±11.2	64.3±10.6	0.50
Body mass index (kg/m <sup>2</sup> )	22.9±3.5	23.1±3.4	0.60
SBP (24-h period) (mmHg)	153.6±25.3	148.4±26.1	0.55
DBP (24-h period) (mmHg)	87.6±13.4	83.0±14.1	0.25
MBP (24-h period) (mmHg)	109.6±15.6	104.4±16.8	0.34
SBP (daytime) (mmHg)	154.0±25.3	144.8±29.4	0.31
DBP (daytime) (mmHg)	88.4±13.2	82.0±15.9	0.11
MBP (daytime) (mmHg)	109.8±15.8	102.6±19.2	0.20
SBP (nighttime) (mmHg)	153.4±25.7	155.6±22.7	0.84
DBP (nighttime) (mmHg)	86.4±13.0	85.6±12.0	0.90
MBP (nighttime) (mmHg)	108.4±15.6	108.4±14.6	1.00
N/D ratio of SBP (%)	99.5±2.9	109.1±14.0	0.24
Patterns of circadian BP rhythm	D:0/ND:2/R:3/ED:0	D:0/ND:1/R:4/ED:0	0.49
PRA (ng/mL/hr)	-0.19±0.41	-0.55±0.17	0.14
Plasma Ang II (pg/mL)	1.06±0.17	0.97±0.14	0.056
hANP (pg/mL)	2.13±0.18	2.15±0.20	0.87

SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, MBP: Mean Blood Pressure, N/D: Night-to-day, BP: Blood Pressure, D: Dipper, ND: Nondipper, R: Riser, ED: Extreme Dipper, PRA: Plasma Renin Activity, AngII: Angiotensin II, hANP: Human Atrial Natriuretic Peptide

caused by renal damage (8, 9). These results suggest that any abnormalities in the circadian BP rhythm may not have been induced by intrarenal RAS activity due to renal damage in the present study, as the evaluation time after nephrectomy (8.24±1.79 days) would have been too short for changes to be apparent.

Urinary AGT excretion levels are known to be surrogate markers of intrarenal RAS activity (19, 20). While we would have liked to use the levels of urinary AGT to determine intrarenal RAS activity, this parameter could not be used to evaluate the differences in intrarenal RAS activity before and after operation in the present study, as we included HD patients who did not urinate. At present, we are conducting a study of renal transplantation donors to compare the differences in the 24-h BP values, fractional excretion of urinary sodium, and urinary levels of AGT before and after nephrectomy. In the near future, we hope to clarify the relationships among the circadian rhythm of BP, sodium excretion, and intrarenal RAS activity.

Goto et al. indicated that, although urinary sodium excretion levels were not evaluated, positive relationships existed between the change in creatinine clearance and an increase in the N/D ratio of the mean BP before and after nephrectomy in healthy subjects who underwent unilateral nephrectomy for kidney donation (21). These data support our present results. However, no significant relationships were found between the change in the eGFR and that in the N/D ratio of systolic BP before and after nephrectomy in non-dialysis patients in our study ( $r=-0.20$ ,  $p=0.46$ ; data not shown). Because the degree of preoperation renal function varied in our patients (eGFR 27 to 95 mL/min/1.73 m<sup>2</sup>), so did the degree of residual renal function after nephrectomy. Farmer et al. reported that the likelihood of an abnormal circadian BP rhythm increases with worsening renal function (22). Namely, the degree of renal damage before and

after nephrectomy significantly influences the levels of circadian rhythm of BP before and after nephrectomy, respectively. Our inclusion of patients with varied renal function may be the reason we noted no significant relationships between the change in the eGFR and in the N/D ratio of systolic BP before and after nephrectomy.

Uzu et al. demonstrated the importance of either or both the fluid status or kidneys in the genesis of the diurnal BP rhythm (13). We did not perform any image assessments such as evaluating the cardiographic rate or diameter of the inferior vena cava before and after nephrectomy in the present study. However, an evaluation of the intravascular volume using plasma hANP levels showed no significant differences between preoperation and postoperation volume. In addition, PRA is known to be a marker of fluid levels, and no significant differences were found between preoperation and postoperation PRA values. These results suggest that an abnormal circadian BP rhythm after nephrectomy is independent of any differences in the intravascular volume before and after operation.

Additional factors such as catecholamine or renal denervation may have influenced the BP trends in the present study. Katayama et al. reported that bilateral renal denervation in SHR/NDmcr-cp rats—a derivative of the spontaneously hypertensive rat (SHR) model with a leptin receptor mutation which exhibit obesity, hypertension, insulin resistance, glucose intolerance, and hyperlipidemia—not only significantly reduced BP but also normalized the BP circadian rhythm from the nondipper type to the dipper type. They further found that this improvement was associated with an increase in the urinary sodium excretion and the suppression of renal Na<sup>+</sup>-Cl<sup>-</sup> cotransporter upregulation (23). In our experiment, however, the circadian rhythm changed from the dipper type to the nondipper type, findings which completely conflict with those of Katayama et al. These re-

sults indicate that unilateral renal denervation due to unilateral nephrectomy has little potential to be associated with the BP circadian rhythm. Katayama et al. also reported that bilateral renal denervation did not influence urinary norepinephrine excretion levels, indicating that catecholamine does not markedly influence changes in the BP circadian rhythm.

The decrease in body weight after the operation may influence the circadian BP variation. Nordstrand et al. reported that both gastric surgery bypass graft and intensive lifestyle intervention reduced the number of subjects with nocturnal hypertension and the proportion of subjects classified as nondippers (24). Their findings therefore indicate that a decrease in the body weight following unilateral nephrectomy does not result in increases in the N/D ratio of BP or numbers of nondipper and riser patterns.

A deficiency in the circadian gene has been reported to induce cell cycle dysregulation and lead to carcinogenesis (25, 26). Therefore, an abnormal circadian rhythm may have contributed to the development of cancer in these patients. Whether or not resection of cancer influences abnormal circadian rhythm has thus far been unclear. However, because cancer is not the cause but the result of an abnormal circadian rhythm, resection does not likely improve an abnormal circadian rhythm of BP.

In summary, our study suggests that unilateral nephrectomy affects the circadian rhythm of BP but not the absolute values.

**The authors state that they have no Conflict of Interest (COI).**

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#### References

- Bakris GL, Williams M, Dworkin L, et al. Preserving renal function in adults with hypertension and diabetes: a consensus approach. National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. *Am J Kidney Dis* **36**: 646-661, 2000.
- Kario K, Shimada K. Risers and extreme-dippers of nocturnal blood pressure in hypertension: antihypertensive strategy for nocturnal blood pressure. *Clin Exp Hypertens* **26**: 177-189, 2004.
- Ohkubo T, Hozawa A, Yamaguchi J, et al. Prognostic significance of the nocturnal decline in blood pressure in individuals with and without high 24-h blood pressure: the Ohasama study. *J Hypertens* **20**: 2183-2189, 2002.
- Kario K, Pickering TG, Matsuo T, Hoshida S, Schwartz JE, Shimada K. Stroke prognosis and abnormal nocturnal blood pressure falls in older hypertensives. *Hypertension* **38**: 852-857, 2001.
- Agarwal R, Andersen MJ. Prognostic importance of ambulatory blood pressure recordings in patients with chronic kidney disease. *Kidney Int* **69**: 1175-1180, 2006.
- Kobori H, Nangaku M, Navar LG, Nishiyama A. The intrarenal renin-angiotensin system: from physiology to the pathobiology of hypertension and kidney disease. *Pharmacol Rev* **59**: 251-287, 2007.
- Yamamoto T, Nakagawa T, Suzuki H, et al. Urinary angiotensinogen as a marker of intrarenal angiotensin II activity associated with deterioration of renal function in patients with chronic kidney disease. *J Am Soc Nephrol* **18**: 1558-1565, 2007.
- Ohashi N, Yamamoto T, Huang Y, et al. Intrarenal RAS activity and urinary angiotensinogen excretion in anti-thymocyte serum nephritis rats. *Am J Physiol Renal Physiol* **295**: F1512-F1518, 2008.
- Huang Y, Yamamoto T, Misaki T, et al. Enhanced intrarenal receptor-mediated prorenin activation in chronic progressive anti-thymocyte serum nephritis rats on high salt intake. *Am J Physiol Renal Physiol* **303**: F130-F138, 2012.
- Fukuda M, Urushihara M, Wakamatsu T, Oikawa T, Kobori H. Proximal tubular angiotensinogen in renal biopsy suggests nondipper BP rhythm accompanied by enhanced tubular sodium reabsorption. *J Hypertens* **30**: 1453-1459, 2012.
- Isobe S, Ohashi N, Fujikura T, et al. Disturbed circadian rhythm of the intrarenal renin-angiotensin system: relevant to nocturnal hypertension and renal damage. *Clin Exp Nephrol* **19**: 231-239, 2015.
- Bonnet JM, Boivin R, Bernard N, Sassard J. Extrarenal renin-angiotensin systems are unable to maintain blood pressure in sheep. *Clin Exp Pharmacol Physiol* **27**: 684-689, 2000.
- Uzu T, Takeji M, Kanasaki M, et al. Change in circadian rhythm of blood pressure by bilateral radical nephrectomy and haemodialysis: a case report. *J Hum Hypertens* **20**: 549-550, 2006.
- Matsuo S, Imai E, Horio M, et al; Collaborators developing the Japanese equation for estimated GFR. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis* **53**: 982-992, 2009.
- Kimura G, Dohi Y, Fukuda M. Salt sensitivity and circadian rhythm of blood pressure: the keys to connect CKD with cardiovascular events. *Hypertens Res* **33**: 515-520, 2010.
- Chamberlain RM, Shirley DG. Time course of the renal functional response to partial nephrectomy: measurements in conscious rats. *Exp Physiol* **92**: 251-262, 2007.
- Park HW, Kim Y, Kim KH, Rozen S, Najafian B, Mauer M. Angiotensin II receptor blocker pretreatment of rats undergoing sudden renal ablation. *Nephrol Dial Transplant* **27**: 107-114, 2012.
- Ots M, Mackenzie HS, Troy JL, Rennke HG, Brenner BM. Effects of combination therapy with enalapril and losartan on the rate of progression of renal injury in rats with 5/6 renal mass ablation. *J Am Soc Nephrol* **9**: 224-230, 1998.
- Nishiyama A, Konishi Y, Ohashi N, et al. Urinary angiotensinogen reflects the activity of intrarenal renin-angiotensin system in patients with IgA nephropathy. *Nephrol Dial Transplant* **26**: 170-177, 2011.
- Kobori H, Alper AB Jr, Shenava R, et al. Urinary angiotensinogen as a novel biomarker of the intrarenal renin-angiotensin system status in hypertensive patients. *Hypertension* **53**: 344-350, 2009.
- Goto N, Uchida K, Morozumi K, et al. Circadian blood pressure rhythm is disturbed by nephrectomy. *Hypertens Res* **28**: 301-306, 2005.
- Farmer CK, Goldsmith DJ, Cox J, Dallyn P, Kingswood JC, Sharpstone P. An investigation of the effect of advancing uraemia, renal replacement therapy and renal transplantation on blood pressure diurnal variability. *Nephrol Dial Transplant* **12**: 2301-2307,

- 1997.
23. Katayama T, Sueta D, Kataoka K, et al. Long-term renal denervation normalizes disrupted blood pressure circadian rhythm and ameliorates cardiovascular injury in a rat model of metabolic syndrome. *J Am Heart Assoc.* **2**: e000197, 2013.
24. Nordstrand N, Hertel JK, Hofsø D, et al. A controlled clinical trial of the effect of gastric bypass surgery and intensive lifestyle intervention on nocturnal hypertension and the circadian blood pressure rhythm in patients with morbid obesity. *Surgery* **151**: 674-680, 2012.
25. Fu L, Pelicano H, Liu J, Huang P, Lee C. The circadian gene *Period2* plays an important role in tumor suppression and DNA damage response in vivo. *Cell* **111**: 41-50, 2002.
26. Filipski E, King VM, Li X, et al. Host circadian clock as a control point in tumor progression. *J Natl Cancer Inst* **94**: 690-697, 2002.

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