Original Article

Circadian Blood Pressure Rhythm Is Disturbed by Nephrectomy

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We recently illustrated a close relationship between glomerular filtration rate and circadian rhythm of blood pressure (BP) in patients with chronic kidney disease. However, it remains undetermined from such cross-sectional findings which occurs first, the loss of kidney function or the lack of nocturnal BP fall. In the present study, we examined whether circadian rhythm of BP is affected by unilateral nephrectomy for kidney donation to clarify this important issue. Fifteen healthy subjects (4 men, 11 women; aged 33 to 65 years; mean age 55±2 years) who underwent unilateral nephrectomy for kidney donation were studied. Ambulatory BP was monitored for 24 h, while serum and urinary samples were collected to estimate creatinine clearance before and on the 8th day after nephrectomy. Then, changes in the night/day ratios of mean arterial BP were analyzed in relation to the decrease in 24-h creatinine clearance as a marker of glomerular filtration rate by nephrectomy. Creatinine clearance was reduced by 29% in average from 84±6 to 60±4 ml/min by nephrectomy, while 24-h mean arterial BP values were 91±3 and 94±4 mmHg (p=0.08) before and after nephrectomy. Although mean BP (daytime, nighttime or night/day ratio) was not altered significantly by nephrectomy, the decrease in creatinine clearance was positively correlated with the increase in the night/day ratio of mean BP (r=0.61, p=0.017). The decrease in creatinine clearance was not correlated with changes in either 24-h, daytime or nighttime mean BP. Our results suggest that unilateral nephrectomy disturbs the circadian rhythm of BP as a function of renal dysfunction without affecting absolute levels of BP. Non-dipping of BP seems the consequence of the loss of renal function, rather than the cause. (*Hypertens Res* 2005; 28: 301–306)

***Key Words*: blood pressure, circadian rhythm, dipper, nephrectomy, renal function**

Introduction

We previously reported in patients with essential hypertension that as blood pressure (BP) became more sodium sensitive, nocturnal decline in BP was diminished (*1–3*). Since glomerular filtration capability is one of the major factors determining sodium sensitivity (*4*, *5*), as a function of loss of

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Table 1. Renal Function and Blood Pressure before and after Kidney Donation

Parameters		Before Rx	*p*	After Rx
Serum creatinine (mg/dl)		0.72±0.04	<0.0001	1.14±0.08
Creatinine clearance (ml/min)		84±6	<0.0001	60±4
Urinary albumin (mg/day)		17±2	0.080	21±2
Pulse rate (bpm)	Day	75±2	0.21	78±2
	Night	66±3	0.19	71±2
	24 h	73±2	0.15	77±2
Systolic BP (mmHg)	Day	125±5	0.25	128±6
	Night	112±5	0.12	116±7
	24 h	122±5	0.22	125±6
Diastolic BP (mmHg)	Day	77±3	0.052	80±4
	Night	70±3	0.09	73±4
	24 h	76±3	0.049	78±4
Night/day ratio of MAP		0.89±0.01	0.61	0.91±0.02

Values are mean±SEM (n=15). Rx, unilateral nephrectomy for donation; BP, blood pressure; MAP, mean arterial pressure. To convert serum creatinine in mg/dl to μmol/l, multiply by 88.4.

glomerular filtration rate (GFR) the nocturnal decline in BP may be less pronounced. We recently illustrated this quantitative relationship in chronic kidney disease (*6*), where in fact there was an inverse relationship between GFR and the night/day ratio of mean arterial BP (MAP). In consideration of this finding, together with the well known facts that in patients with renal dysfunction the nocturnal BP fall is lost (*6–10*) and is restored from non-dipper to dipper patterns after kidney transplantation (*11*) and by sodium restriction and diuretics (*2*, *3*, *12*), circadian rhythm of BP is likely to be determined at least in part by the kidneys. On the other hand, the non-dipper type of circadian BP rhythm is often considered to be a risk factor for the progression of nephropathy (*10*, *13*, *14*). In particular, an increase in systolic BP (SBP) during sleep has been reported to precede the development of microalbuminuria in persons with type 1 diabetes (*13*). Therefore, it was not clear in the cross-sectional studies which comes first, the lack of nocturnal BP fall or the loss of kidney function. In the present study, we examined whether circadian rhythm of BP is affected by unilateral nephrectomy for kidney donation to clarify this important issue.

Methods

Patients and Study Protocol

Between July 2003 and January 2004, 24 kidney donors underwent unilateral nephrectomy for living related renal transplantation in Nagoya Daini Red Cross Hospital. Among them, 15 consecutive patients (4 men, 11 women) who gave informed consent were enrolled in this study. Their mean age was 54.5±2.3 years, and their mean body mass index was 23.8±0.5 kg/m^2. They had no medication except for that related to surgery, and ate a relatively low-sodium diet containing approximately 6–9 g/day of NaCl with the same levels of calorie and protein intake throughout the hospitalization. They were allowed their usual daily life activities on the study days, but were asked to get up at 07:00 and to go to sleep at 22:00. Ambulatory BP was monitored for 24 h, at 15 min intervals in the daytime (07:00 to 22:00) and 30 min intervals in the nighttime (22:00 to 07:00), noninvasively with a validated automatic device (model TM-2430; A & D, Tokyo, Japan). Daytime BP was calculated as the average of the 60 readings between 07:00 and 22:00, and nighttime BP was the average of the remaining 18 readings. MAP was calculated as diastolic BP (DBP) plus one third of the pulse BP. Serum creatinine concentration as well as 24-h urinary excretion rates for creatinine and albumin were measured. Twenty-four hour creatinine clearance (C_{cr}) was calculated as a marker of GFR. These examinations were performed before nephrectomy on the 4th day of admission, and then were repeated on the 8th day after nephrectomy. Although the patients were hospitalized during both the study before and that after nephrectomy, there was a time between the two studies (ranging from 2 weeks to 3 months) when they were not in the hospital.

Statistical Analysis

Results are expressed as the mean±SEM. The significance of differences in serum creatinine concentration, creatinine clearance, urinary albumin excretion rate and night/day ratios of MAP between before and after nephrectomy were determined by Student's *t*-test for paired samples. The significance of differences in pulse rate and BP between before and after nephrectomy as well as between daytime and nighttime was tested by 2-way analysis of variance. The correlations between the percentage decrease in C_{cr} by nephrectomy and changes in night/day ratios of MAP were obtained by the least-squares method.

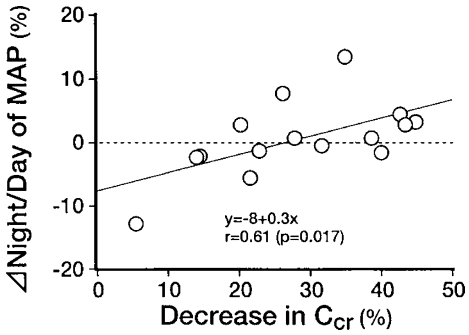

Fig. 1. *Relationship between the percentage decrease in* C_{cr} *by nephrectomy and the change in the night/day ratio of MAP by nephrectomy. The percentage decrease in* C_{cr} *was calculated as (*C_{cr} *before nephrectomy –* C_{cr} *after nephrectomy) /* C_{cr} *before nephrectomy × 100. The change in the night/day ratio of MAP was obtained as the difference between the night/day ratio of MAP after nephrectomy and the night/day ratio of MAP before nephrectomy. There was a positive relationship (*r = *0.61,* p = *0.017). MAP, mean arterial pressure;* C_{cr}*, creatinine clearance as a marker of glomerular filtration rate.*

Results

We studied 15 healthy individuals before and after unilateral nephrectomy for living kidney donation; their characteristics are listed in Table 1. On the 8th day after nephrectomy, the mean serum creatinine concentration was elevated from 0.72±0.04 to 1.14±0.08 mg/dl (69.8±3.5 to 100.8±7.1 μmol/l), and creatinine clearance as a marker of GFR was reduced by 29% in average from 84±6 to 60±4 ml/min. The urinary albumin excretion rate was not altered by nephrectomy, but remained within normal limits—defined as less than 30 mg/day—even after nephrectomy. We checked urinary collection using the creatinine excretion rate, and found all met criteria satisfied with 16–25 mg/kg/day (0.14–0.22 μmol/kg/day) for men and 12–22 mg/kg/day (0.11–0.19 μmol/kg/day) for women (*15*). In addition, creatinine clearance was significantly correlated with the glomerular filtration rate ($r=0.69$, $p<0.0001$, $n=30$) as estimated by the Cockroft-Gault formula (*16*) using age, weight, sex and serum creatinine, indicating the overall validity of the urine collection.

Pulse rate and BP were all reduced from day to night ($p<0.0001$), while none of them was altered by nephrectomy except the 24-h average of DBP. Twenty-four hour MAP was 91±3 and 94±4 mmHg ($p=0.08$) before and after nephrectomy. The night/day ratio of MAP was not altered significantly by nephrectomy (Table 1). However, the percentage decrease in C_{cr} by nephrectomy was significantly correlated with the change in night/day ratio of MAP, as shown in Fig. 1. The percentage decrease in C_{cr} was not correlated with changes in either 24-h MAP ($r=-0.25$, $p=0.37$), daytime MAP ($r=-0.31$, $p=0.27$), nighttime MAP ($r=0.41$, $p=0.13$) or albumin excretion rate ($r=0.25$, $p=0.38$). The percentage decrease in C_{cr} was not correlated with age ($r=0.17$, $p=0.55$).

Discussion

The present study suggested for the first time that as renal function deteriorates in healthy donors undergoing unilateral nephrectomy, the nocturnal dip in BP is diminished without significantly affecting the absolute levels of BP. Our data revealed a quantitative relationship between renal function and non-dipping phenomena of BP after kidney donation. It is well known that GFR is reduced to approximately 70% of its initial function (30% loss) after unilateral nephrectomy (*17*, *18*), and this is consistent with the present data. However, in the present study the degree of loss in renal function varied from 5% to 45% (mean, 29%) among subjects, and was positively correlated with the degree of loss in nocturnal BP dip.

We previously reported in patients with essential hypertension that as BP became more sodium sensitive, nocturnal decline in BP was diminished (*1–3*). Since glomerular filtration capability is one of the major factors determining sodium sensitivity (*4*, *5*), as a function of GFR loss the nocturnal decline in BP may be less pronounced. We recently illustrated this quantitative relationship in a study on patients with chronic kidney disease, in whom we found an inverse relationship between C_{cr} and the night/day ratio of MAP (*6*), as seen also in the present study. These findings are compatible with a high sodium sensitivity of BP in glomerulopathy, which has been reported even when GFR is maintained at a relatively normal level (*19*, *20*) and becomes much higher as renal function deteriorates (*21*, *22*). However, it was not clear in this cross-sectional study which comes first, the lack of nocturnal BP fall or the loss of kidney function. In the present study, we showed quantitatively that GFR loss by nephrectomy causes a lack of nocturnal dip in BP. Our findings were also compatible with the proposal that as the number of nephrons is reduced BP becomes more sodium sensitive (*4*, *23–25*). On the other hand, the non-dipper type of circadian BP rhythm is often considered to be a risk factor for the progression of nephropathy (*10*, *13*, *14*). However, since the degree of non-dipping was closely correlated with the degree of loss of renal function, as discussed above, non-dipping might be correlated with the progression of nephropathy. Our clear results that it might be a phenotype of impaired renal functional reserve and renal dysfunction, together with the well known facts that in patients with renal dysfunction the nocturnal BP fall is lost and they manifest as non-dipper (*6–10*), suggest that circadian rhythm of BP is determined mostly by the kidneys. The importance of the kidneys in the genesis of circadian BP rhythm is consistent with reports that the circadian rhythm of BP is normalized from non-dippers to dippers after kidney transplantation (*11*) and by sodium restriction and diuretics (*2*, *3*, *12*, *26–28*). Therefore, careful study will be required to conclude that non-dipping of BP causes the

progression of nephropathy (*10*, *13*, *14*), although an increase in SBP during sleep is reported to precede the development of microalbuminuria in persons with type 1 diabetes (*13*). If latent renal dysfunction exists to make the circadian BP rhythm that of a non-dipper, as seen in healthy donors in this study, the progression of nephropathy can be accelerated by mechanisms other than non-dipping of BP. For example, glomerular capillary hypertension, which occurs to compensate for GFR, accelerates the progression.

From experimental and theoretical analyses, in general, a reduction in renal mass to only 30% of normal (70% loss) is believed necessary to cause even slight elevation in BP (*29*). In addition, there are specific abnormalities within the kidney that can cause hypertension, such as increased afferent arteriolar resistance, decreased glomerular filtration coefficient and enhanced tubular reabsorption of sodium (*4*, *29–31*). Compared to these specific abnormalities, removal of renal mass is less likely to disturb the maintenance of constant sodium balance and BP (*29*), simply because a glomerulotubular balance of sodium is maintained when the renal mass is removed. These seem to be the reasons why no significant elevation in BP was found after unilateral nephrectomy in the present study and previous reports (*32*). Isograft transplantation to 5/6 nephrectomized rats (*33*) as well as to uremic patients with essential hypertension (*34*) normalized BP, which was consistent with the idea that there is a threshold amount of remaining renal mass beyond which hypertension occurs. Clearly renal function must be reduced to less than half of normal, and even to approximately 30% of normal (*29*), before BP is elevated. To the best of our knowledge, there exist no data on the degree of GFR loss required to disturb circadian BP rhythms. Our data suggest that less degree of renal dysfunction may disturb circadian BP rhythm than that required to elevate absolute levels of BP.

Recently, it has been recognized that renal dysfunction, even in mild degree, is a strong predictor for future cardiovascular events (*35–37*). However, the precise mechanisms by which renal dysfunction causes cardiovascular events remain unknown. Many investigators have reported that non-dippers were clearly exposed to greater risks for cardiovascular complication, such as left ventricular hypertrophy, cerebrovascular disease and insulin resistance, than dippers (*38–44*). Sodium sensitive subjects, whose circadian BP rhythm is expected to be non-dipper (*1–3*), are also known to have high risks for cardiovascular events, independently of BP (*45–47*). It is also known that BP during sleep has a greater impact on cardiovascular events than BP during the daytime or 24-h BP (*48*). We therefore hypothesize that non-dipping of BP as a function of GFR loss may be one of the mechanisms causing cardiovascular events in patients with renal dysfunction. Although numerous studies have reported the safety of kidney donation for living kidney transplantation (*32*, *49*, *50*), recent data from a study following kidney donors for more 30 years demonstrated that some of the donors did in fact develop renal dysfunction (*51*), suggesting the need for prospective trials for long-term follow-up of kidney donors to determine whether they develop cardiovascular events or renal dysfunction after nephrectomy.

A major limitation of the present study was that circadian BP rhythm can not be detected precisely during hospitalization, especially after nephrectomy. This may be the reason why the night/day ratio of MAP was not altered in average after nephrectomy. Thus, our results must be confirmed by larger studies with BP measurement outside of the hospital setting.

In conclusion, the present study suggested that in kidney donors with unilateral nephrectomy, circadian rhythm of BP was disturbed as a function of GFR loss without affecting absolute levels of BP. Non-dipping of BP seemed to be the consequence of the loss of renal function. The threshold to disturb the circadian rhythm of BP may be less severe in renal dysfunction than that to cause hypertension. Therefore, in patients with renal dysfunction, the amount of GFR loss necessary to disturb the circadian rhythm of BP may be less than the amount necessary to cause hypertension.

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