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ORIGINAL ARTICLE

Night-time blood pressure load is associated with higher left ventricular mass index in renal transplant recipients

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The absence of nocturnal fall in blood pressure (BP) is named as nondipper status, which has been shown to be an additional risk factor for the development of left ventricular hypertrophy and cardiovascular events in several high-risk groups. The aim of this study was to determine the influences of the nondipper status and nocturnal blood pressure loads on left ventricular mass index (LVMI) in renal transplant recipients. A total of 35 nondiabetic renal transplant recipients were included into the study. A 24-h ambulatory blood pressure monitoring (ABPM) was performed for all recipients. The nondipper status was defined as either an increase in night-time mean arterial pressure (MAP) or a decrease of no more than 10% of daytime MAP. LVMI was measured by using two-dimensional guided M-mode echocardiography. The night-time systolic blood pressure (SBP) load was defined as the percentage of the time, during which SBP exceeded 125 mmHg during night time. The nondipping was common among renal transplant recipients, of whom 60% were nondipper in our study. LVMI was significantly higher in the nondipper group *vs* the dipper group (133 ± 35 g/m^2 *vs* 109 ± 26 g/m^2, $P = 0.04$). A fall in MAP at night time was 14.5 ± 4.3% in the dipper group, while it was 1.4 ± 6.1% in the nondipper group ($P < 0.001$). On stepwise multiple regression analysis, night-time SBP load and haemoglobin were independent predictors of LVMI ($R^2 = 0.53$). In conclusion, nondipping is common after renal transplantation. Night-time SBP load and low haemoglobin are closely related to the increase in LVMI in renal transplant recipients. ABPM may be a more useful tool in optimizing treatment strategies to reduce cardiovascular events in renal transplant recipients.
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Introduction

Cardiovascular disease is the most common cause of death in renal transplant recipients.[1] The same epidemiological risk factors for the coronary artery disease in the general population are likely to contribute to cardiovascular events in renal transplant recipients, but these risk factors may not have the same predictive power as they do in the general population. Echocardiographic assessment of the left ventricular mass (LVM) provides additional prognostic information beyond that given by traditional risk factors.[2] Based upon longitudinal data from the Framingham Heart Study,[3,4] increases in the LVM predict a higher incidence of clinical cardiovascular outcomes, including death attributable to cardiovascular disease.

Left ventricular hypertrophy (LVH) was linked to adverse outcome following renal transplantation.[5] High systolic blood pressure (SBP) had a major influence for the development of LVH in patients with end-stage renal disease (ESRD).[6] However, there are important discrepancies in clinical studies between the severity of hypertension and the left ventricular mass.[7,8] Additional factors, such as uraemia, volume overload, high cardiac output state caused by anaemia or arteriovenous fistula, could be more operative in the development of LVH in ESRD patients or renal transplant recipients. On the other hand, office or clinic measurements of BP may not adequately reflect the severity of hypertension. Ambulatory blood pressure monitoring (ABPM) may be more informative about the severity of BP elevation than clinic measurements in renal failure and following renal transplantation.[9,10] Additionally, the possibility of noninvasive measurement of

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BP at night and during sleep by ambulatory monitoring devices has stimulated interest in the pathophysiological significance of night-time BP. Blood pressure at night was reported to be independently associated with end-organ damage above the risk associated with daytime values.[11,12] A second type of risk has been given more attention, and it has become usual to subdivide the hypertensive patients into 'dippers' and 'nondippers' on the basis of a 10% reduction in the nocturnal mean arterial pressure (MAP). Individuals who exhibit $<10\%$ fall in nocturnal MAP have been termed as 'nondippers'. According to this subdivision, nondipper hypertensives would have a greater risk of LVH[13] and cardiovascular events[14] than the dipper. Although nondipper status has also been reported in renal transplant recipients,[9,15] the exact role of abnormalities of circadian variation in BP on left ventricular mass remained controversial in this high-risk population. Lipkin *et al*[9] studied 28 normotensive renal transplant recipients, of whom seven (25%) were nondipper, and nondippers had significantly higher left ventricular mass index (LVMI) compared with the dipper recipients. On the other hand, McGregor *et al*[15] reported a 68% of nondipping in a group of 19 renal transplant recipients and found no relation between nondipper status and LVMI.

The aim of this study was to determine the influences of the nondipper status and nocturnal BP loads on LVMI, as assessed by ABPM and echocardiography, in renal transplant recipients.

Methods

A total of 35 nondiabetic renal transplant recipients were enrolled. Patients were excluded if they had cerebrovascular or peripheral vascular disease, valvular or coronary artery disease, and a history of poor compliance with their antihypertensive drug therapy. Renal transplant recipients, in whom antihypertensive treatment had been changed during the preceding 12 months, and with the duration of renal transplantation less than 12 months, were also excluded. Functional arteriovenous fistula, serum creatinine above 2.5 mg/dl, and $\geqslant 20\%$ increase in serum creatinine at any time during the preceding 12 months were other exclusion criteria. None of the patients had undergone previous nephrectomy. In the remaining 35 renal transplant recipients, the duration of renal transplantation were between 12 and 24 months in thirteen between 25 and 36 months in seven, between 37 and 48 months in three, between 49 and 60 months in two, and more than 61 months in ten. The aetiologies for pretransplant renal failure were chronic glomerulonephritis in 33%, hypertensive nephrosclerosis in 28%, chronic pyelonephritis in 21%, and unknown in 18% of the recipients. All of the recipients received 240 mg of slow-release formulation of diltiazem daily in two equal doses in order to increase plasma level of cyclosporine-A.

A 24-h ABPM was performed using Spacelab® 90207 oscillometric device (Spacelabs Medical, Redmond, WA, USA) with readings for every 20 min from 07.00 to 23.00 h and every 30 min from 23.00 to 07.00 h for all of the recipients. Monitors were calibrated against a mercury sphygmomanometer at the beginning of each session, and monitoring practice was in accordance with the guideline.[16] All recipients completed a sleep and activity diary during ABPM and night times were defined as self-reported actual patient sleep times. Subjects were then classified as 'dippers' and 'nondippers'. If mean night-time MAP was at least 10% less than mean daytime MAP, the condition was defined as 'dipper status'.[17] SBP load was defined as the percentage of the time, during which SBP exceeded 135 mmHg during daytime or 125 mmHg during night time. Diastolic BP (DBP) load was defined as the percentage of the time, during which DBP exceeded 85 mmHg during daytime or 75 mmHg during night time.[18]

A two-dimensional guided M-mode echocardiography was performed by standard methods using an ultrasound system (Ultramark 9, Advanced Technology Laboratories, Bothell, WA, USA) with a 2.25-MHz transducer by the same physician for all participants. Left ventricular internal dimension (LVID), interventricular septal (IVST), and posterior wall thickness (PWT) were measured at end diastole according to the American Society of Echocardiography (ASE) recommendations.[19] LVM was calculated by using the formula:[20] ASE-cube LVM $= 1.04$ $[(\text{LVID}+\text{IVST}+\text{PWT})^3-\text{LVID}^3]$. Since ASE-cube LVM calculation results in overestimation of LVM by about 25%, the regression formula developed by Devereux and Reichek[21] was used to correct LVM measurements: 0.80 (ASE-cube LVM)+0.6. LVMI was then calculated as the ratio of LVM to the body surface area (BSA). The cutoff level for LVH was defined as LVMI $\geqslant 134\ \text{g/m}^2$ in men and $\geqslant 110\ \text{g/m}^2$ in women.[22]

Serum and urine creatinine was measured by a computerized autoanalyzer (Hitachi 717, Boehringer Mannheim, Germany) and creatinine clearance was calculated. Haemoglobin was determined as the mean value of measurements during the last 12 months. Total blood cyclosporine-A levels were measured by FPIA using a monoclonal antibody (Abbot, IL, USA).

Statistical analysis

All data were expressed as mean $\pm$ s.d. The comparisons between baseline characteristics of dipper and nondipper groups were made by using Mann–Whitney U test and Fisher's exact test, where appropriate. Stepwise multiple regression analysis was performed using LVMI as the dependent

variable, and age, gender, haemoglobin, serum creatinine, 24-h SBP load, 24-h DBP load, daytime SBP load, daytime DBP load, night-time SBP load, night-time DBP load, duration of dialysis before transplantation, and duration of follow-up after transplantation as the independent variables. A *P*-value less than 0.05 was considered significant. Statistical analyses were conducted by using SPSS computer program.

Results

In all, 14 (40%) were dipper and 21 (60%) were nondipper among 35 renal transplant recipients. The clinical characteristics of the dipper and nondipper recipients are presented in Table 1. There were no significant differences between the groups regarding age, gender, duration of dialysis before transplantation, duration of follow-up after transplantation, number of antihypertensive medications, creatinine clearance, and BSA. Cyclosporine-A (147 ± 41 ng/ml in dippers *vs* 169 ± 39 ng/ml in nondippers; $P = 0.17$) and haemoglobin levels (13.4 ± 1.7 g/dl *vs* 12.4 ± 1.6 g/dl, respectively, $P = 0.18$) also did not differ significantly. LVMI was significantly higher in the nondipper group compared with the dipper group (133 ± 35 g/m^2 *vs* 109 ± 26 g/m^2; $P = 0.04$) (Table 1). LVID indexes were similar in both groups ($P = 0.85$). Five of the recipients in the dipper group and five in the nondipper group received angiotensin-converting enzyme inhibitor once daily. Seven patients in the nondipper group received $\geqslant 3$ antihypertensive drugs, of which none was a loop diuretic (data not presented in Table 1).

According to ABPM data, which are presented in Table 2, daytime SBP load ($52 \pm 39\%$ *vs* $21 \pm 23\%$; $P = 0.02$), night-time SBP load ($67 \pm 41\%$ *vs* $20 \pm 20\%$; $P = 0.006$), and night-time DBP load ($74 \pm 27\%$ *vs* $46 \pm 24\%$; $P = 0.006$) were significantly higher in the nondipper group compared with the dipper group. A fall in MAP at night time was $14.5 \pm 4.3\%$ in the dipper group, while it was only $1.4 \pm 6.1\%$ in the nondipper group ($P < 0.001$). SBP and DBP declines in the dippers at night time were $11.8 \pm 4.0\%$ and $17.6 \pm 3.9\%$, which were significantly different from the corresponding declines in the nondippers ($0.3 \pm 6.7\%$ and $2.0 \pm 6.8\%$, respectively; $P < 0.001$ for both).

On stepwise multiple regression analysis, night-time SBP load and haemoglobin were independent determinants of LVMI ($R^2 = 0.53$) among age, gender, haemoglobin, serum creatinine, cyclosporine-A level, 24-h SBP load, 24-h DBP load, daytime SBP load, daytime DBP load, night-time SBP load, night-time DBP load, duration of dialysis before transplantation, and duration of follow-up after transplantation [LVMI = 174.3−7.76 haemoglobin + 2.77 night-time SBP load] (Figure 1).

Discussion

Out of 35 renal transplant recipients, 21 (60%) were nondipper, while 14 (40%) were dipper in this study. Several observational studies have reported that, loss of diurnal variability of BP and exposure to a higher haemodynamic load at night time further increased the risk for experiencing cardiovascular outcomes. Verdecchia *et al*[14] noted a ten-fold increase in cardiovascular outcomes in nondippers *vs* normotensives and white-coat hypertensives in a longitudinal study, with female nondippers having a worse prognosis. Ohkubo *et al*[23] have also reported a significant increase in cardiovascular mortality (adjusted relative hazard of 2.56, $P < 0.02$) over a mean of 5.1 years in 1542 Japanese subjects, whose nocturnal BP did not fall $\geqslant 10\%$ during sleep.

The majority of the patients with uncomplicated essential hypertension exhibit a fall in nocturnal MAP of $\geqslant 10\%$ below the daytime MAP. Certain subgroups tend to be nondippers, including diabetic

Table 1 Comparison of clinical characteristics of renal transplant recipients, which are grouped according to their dipper and nondipper status

	Dipper (n = 14)	*Nondipper* (n = 21)	P-*value*
Age (years)	34 ± 9	35 ± 9	NS
Gender (male/female)	9/5	16/5	NS
Duration of dialysis before Tx. (months)	21.5 ± 15	17.2 ± 13	NS
Duration of follow-up after Tx. (months)	54.6 ± 33.6	38.2 ± 38.1	NS
Creatinine clearance (ml/min)	56 ± 21	55 ± 17	NS
Serum creatinine (mg/dl)	1.3 ± 0.4	1.5 ± 0.6	NS
Antihypertensive drugs (*n*)	1.4 ± 0.5	1.9 ± 0.9	NS
Presence of LVH (%)	6/14 (43)	12/21 (57)	NS
LVID index (mm/m^2)	27.5 ± 3.4	27.8 ± 3.4	NS
LVMI (g/m^2)	109 ± 26	133 ± 35	0.04
BSA (m^2)	1.76 ± 0.23	1.82 ± 0.2	NS
Cyclosporine-A level (ng/ml)	147 ± 41	169 ± 39	NS
Haemoglobin (g/dl)	13.4 ± 1.7	12.4 ± 1.6	NS

Values are expressed as mean $\pm$ s.d. Tx.: transplantation; LVH: left ventricular hypertrophy; LVMI: left ventricular mass index; BSA: body surface area; NS: not significant.

Table 2 ABPM data of the dipper and nondipper renal transplant recipients

	Dipper (n = 14)	*Nondipper* (n = 21)	P-*value*
24-h SBP (mmHg)	122 ± 8	135 ± 17	0.01
24-h DBP (mmHg)	80 ± 5	85 ± 9	NS
24-h MAP (mmHg)	95 ± 5	102 ± 12	NS
Daytime SBP (mmHg)	127 ± 8	135 ± 16	NS
Daytime DBP (mmHg)	85 ± 5	85 ± 9	NS
Daytime MAP (mmHg)	99 ± 5	102 ± 11	NS
Night-time SBP (mmHg)	113 ± 9	135 ± 20	0.004
Night-time DBP (mmHg)	72 ± 6	84 ± 11	0.006
Night-time MAP (mmHg)	86 ± 6	101 ± 14	0.002
Daytime SBP load (%)	21 ± 23	52 ± 39	0.02
Daytime DBP load (%)	50 ± 21	49 ± 32	NS
Night-time SBP load (%)	20 ± 20	67 ± 41	0.006
Night-time DBP load (%)	46 ± 24	74 ± 27	0.006
SBP change (%)	−11.8 ± 4.0	−0.3 ± 6.7	<0.001
DBP change (%)	−17.6 ± 3.9	−2.0 ± 6.8	<0.001
MAP change (%)	−14.5 ± 4.3	−1.4 ± 6.1	<0.001

Values are expressed as mean ± s.d. ABPM: ambulatory blood pressure monitoring; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; NS: not significant.

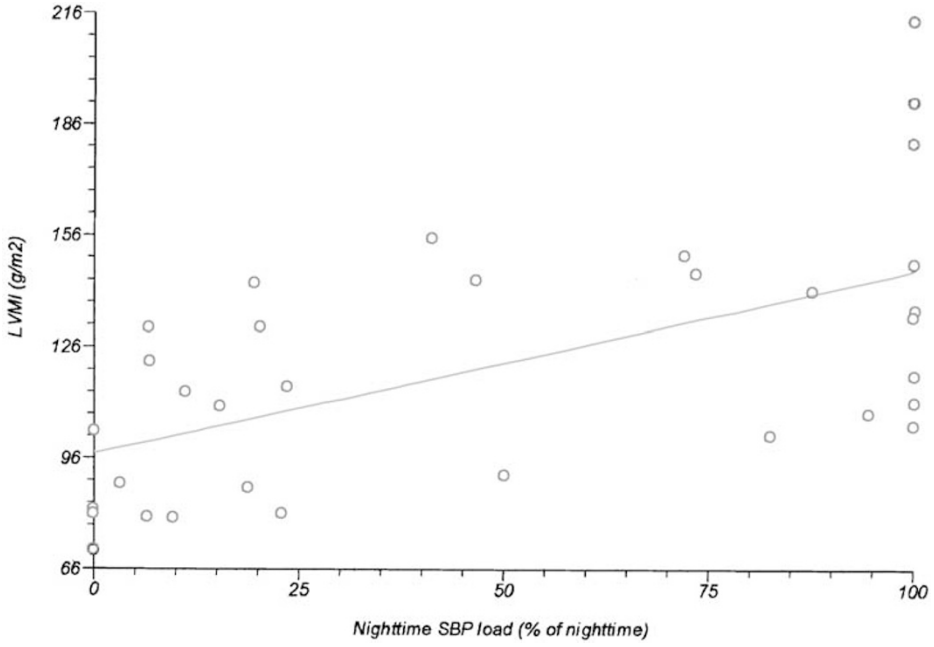

Figure 1 Correlation between LVMI and night-time SBP load ($r = 0.58$, $P = 0.003$). LVMI: left ventricular mass index; SBP: systolic blood pressure.

patients, black patients, older patients, and patients with various forms of secondary hypertension.[2] The absence of night-time drop in BP has been previously linked to target-organ damage, such as LVH[12] and stroke[11] in hypertension. The nondipper status has also been reported in renal transplant recipients, but the exact role of abnormalities of circadian variation in BP for the development of LVH remained controversial. LVMI of the nondipper group was significantly higher compared with the LVMI of the dipper group in our study. Lipkin *et al*[9] studied 28 normotensive renal transplant recipients, of whom 16 were on cyclosporine-based and 12 were on azathioprine-based immunosuppressive regimen. Seven nondipper recipients (25%), five from cyclosporine- and two from azathioprine-based groups, had higher LVMI (124 ± 15 g/m^2 *vs* 89 ± 7 g/m^2) compared with 21 dipper recipients. Their lower proportion of nondipper status and lower LVMI compared with the findings in our study could partially be explained by their inclusion of only normotensive renal transplant recipients. On the other hand, McGregor *et al*[15] reported 68% of nondipping status in a heterogenous group of 19

renal transplant recipients and found no correlation between nondipping status and LVMI, which is in contrast with the findings of our study. Therefore, our study adds to clarify the issue of controversy regarding the role of abnormality of circadian variation in BP in the development of target-organ damage in renal transplant recipients.

ABPM shows a significant correlation with LVMI in most clinical studies, with the coefficient of correlation being greater for systolic than for diastolic BP. [24] Based upon data from meta-analysis of 19 studies, performed by Fagard *et al*,[24] the strength of the relation between LVMI and ABPM is greater than for office or clinic BP. Concordant with previous reports, this study also demonstrated a significant correlation between LVMI and night-time SBP load. On stepwise multiple regression analysis, low haemoglobin, in addition to the night-time SBP load, were independent determinants of LVMI ($R^2 = 0.53$). It is evident from previous reports that decreased haemoglobin is one of the determinants of LVH in ESRD patients.[25] Foley *et al*[26] reported the influence of the duration of dialysis before transplantation on LVMI, but our study could not have detected such a correlation. Although data on LVMI at the time of transplantation are not available and regression of LVMI is time dependent, LVMI did not correlate with the duration of follow-up after transplantation in this cross-sectional analysis.

The differences between daytime and night-time BPs could be scarcely reproducible in the same subjects, as night-time BP is influenced by the quality of sleep, and this is not commonly monitored in ABPM studies. Significant variability (40%) in the classification of subjects as dippers and nondippers by repeating the recording twice, after several months, has been reported previously.[27] This limited reproducibility may improve with using more precise definitions of daytime and night-time periods based on patients' diary, as carried out in this study. However, the problem of obtaining a reliable and reproducible characterization of dipping status in the individual patient could not be satisfactorily solved yet, because of interference by several other confounders, such as age, diabetes mellitus, smoking habits, degree of working activity during the daytime hours, and body position at night.[28]

This study carries the limitations inherent to all cross-sectional studies and 35 renal transplant recipients composed a small study group. Another important limitation was that pretransplant data about the diurnal BP variability of the recipients were not presented.

In conclusion, nondipping is common after renal transplantation. Night-time SBP load and low haemoglobin are closely related to the increase in LVMI in renal transplant recipients. ABPM may be more useful in the management of post-transplant hypertension and in optimizing treatment strategies to reduce cardiovascular events in renal transplant recipients.

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