

# The Circadian Rhythms of Blood Pressure and Heart Rate in the Hypertensive Subjects: Dippers and Non-Dippers

Wha Sook Seo and Hyun Soo Oh

*Department of Nursing, College of Medicine, Inha University, Incheon, Korea.*

The purpose of this study was to compare the circadian blood pressure and heart rate rhythm of dippers and non-dippers. Biochemical and clinical characteristics of dippers and non-dippers were also compared to determine whether non-dippers have an increased prevalence of hypertension-related conditions. The subjects were 123 out-patients with essential hypertension who had undergone ambulatory blood pressure monitoring at the University Hospital in Incheon, South Korea, from January 1, 1997 to December 31, 1998. Daytime values were determined between 6:00 AM and 8:00 PM and the nighttime values were determined between 8:00 PM and 6:00 AM.

Non-dippers were defined as those who showed a reduction in systolic blood pressure, diastolic blood pressure or heart rate less than 10% and they accounted for 25%, 32% and 31% of the subjects, respectively. The timings of the circadian systolic and diastolic blood pressure and heart rate in dippers were very consistent: showing the lowest values during the night, rising in the early morning and reaching a plateau in the late morning. Non-dippers' circadian rhythms of systolic and diastolic blood pressures fluctuated less than those of dippers, and the 24-hours heart rate rhythms of the dipper and non-dipper groups were completely reversed. None of the biochemical characteristics tested in the present study showed a significant difference between dippers and non-dippers whether dipper was classified by systolic or diastolic blood pressure or heart rate. Similarly, hypertension-related symptoms and complications were not associated with the dipper/non-dipper description, whether classified by sBP, dBP, or HR.

**Key Words:** Circadian rhythm, blood pressure, heart rate, dippers, non-dippers, hypertension

## INTRODUCTION

Time-related changes in cardiovascular parameters, such as blood pressure (BP), heart rate (HR), and coronary vascular tone that produce distinctive circadian rhythms have been recently reported.<sup>1</sup> It has also been suggested that sympathovagal tone appears to be a major biological determinant of circadian variations in cardiovascular function, and that sympathovagal tone can be modulated in a circadian fashion-related to sleep-wake activity.<sup>2,3</sup> Fox and Mulcahy<sup>1</sup> showed virtually identical circadian rhythms of BP and HR in normotensive subjects, i.e., both fell and remained relatively low throughout the night and then rose sharply in the early morning hours, to reaching a peak during the morning. One of the most specific characteristics of circadian BP in healthy subjects is its nighttime reduction of BP. O'Brien et al.<sup>4</sup> drew attention to the prognostic significance of the nighttime BP fall and first proposed 'dippers' and 'non-dippers' concept.<sup>4,5</sup> These terms are used to refer to subjects with small reductions in nighttime BP as "non-dippers" and to those with a fall in nighttime BP as "dippers".

Hypertension is often diagnosed and treated on the basis of casual BP measurements. However, the importance of ambulatory BP monitoring (ABMP) has been consistently emphasized.<sup>6</sup> ABMP can provide an average BP over a certain period under different conditions and is generally lower than casual BP measurements.<sup>7</sup> Several investigators have reported that the amount of target organ damage induced by hypertension is more closely related to the average value based upon a 24-hour profile of the BP than to a

Received November 24, 2001

Accepted February 27, 2002

Reprint address: requests to Dr. Wha Sook Seo, Department of Nursing, College of Medicine, Inha University, 253, Yonghyun-Dong, Nam-Gu, Incheon 402-751, Korea. Tel: 82-32-860-8206, Fax: 82-32-874-5880, E-mail: wschang@inha.ac.kr

casual single measurement.<sup>6</sup> In particular, it was proposed that hypertensive subjects without a nighttime BP fall (non-dippers) were more likely to suffer serious end organ damage than those whose BP falls during the night (dippers).<sup>7,8</sup> However, there is a wide variation in the circadian BP rhythm of hypertensive patients.<sup>9</sup>

The purpose of this study was to compare the circadian BP and HR of dippers and non-dippers. In addition, we compared the biochemical and clinical characteristics of dippers and non-dippers to determine whether non-dippers have an increased prevalence of hypertension-related conditions.

## MATERIALS AND METHODS

### Subjects

Data were collected from the medical records of 265 out-patients who underwent ambulatory BP monitoring at the University Hospital of Incheon, South Korea, from January 1, 1997 to December 31, 1998. All subjects were diagnosed as being essential hypertension by physicians. Among the 265 patients, 123 who completed 12 consecutive (every 2 hours over 24 hours) tests for systolic/diastolic BP and HR were included in the present study (mean age:  $55.38 \pm 10.82$  years; 50 men and 73 women).

### BP and HR measurements

Ambulatory BP and HR were monitored every 2 hours for 24 hours using a fully automatic ABP monitor (Spacelabs ABP monitor 90207-30, WA, Redmond, U.S.A.). The 24-hour period was divided into daytime and nighttime periods; daytime values were determined between 6:00 AM and 8:00 PM and the nighttime values were determined between 8:00 PM and 6:00 AM.<sup>9,10</sup> The mean values of 24-hour systolic BP (sBP), diastolic BP (dBP) and HR, daytime sBP, dBP and HR, and nighttime sBP, dBP and HR were computed. To inspect the circadian pattern visually, the 24-hour sBP, dBP, and HR profiles in dippers and non-dippers group were plotted.

### Biochemical and clinical characteristics

Biochemical parameters known to relate to complications of hypertension were compared for the dipper and the non-dipper groups. Serum cholesterol, triglycerides, high density lipoprotein (HDL), and low density lipoprotein (LDL) levels were also compared as risk factors of peripheral vascular disease.<sup>11</sup> In addition, serum BUN, creatinine and urine protein levels were compared as indicators of progression of nephropathy.<sup>2,12</sup>

The presence of hypertension-related symptoms, such as headache, dizziness, palpitation, chest pain or discomfort, dyspnea, epistaxis, neck stiffness, and blurred vision were compared in the two groups. In addition, the presence of hypertension-related complications, such as, angina, cerebrovascular accident, congestive heart failure, hyperlipidemia, and arrhythmia were also compared.<sup>7</sup> Data related to hypertension-related symptoms and complications were collected from the records of the physicians in charge.

### Classification of the dippers and non-dippers

'Non-dippers' are classically defined as those who show a reduction in BP of less than 10/5 mmHg or a difference of less than 10% between day and night.<sup>5,9,13</sup> In the present study, non-dippers were defined as those who showed a reduction in sBP, dBP or HR of less than 10% between day and night.

### Statistical analysis

Data are presented as means  $\pm$  S.D. Statistical differences in the mean values of BP- and HR-related parameters, and of the biochemical values of dippers and non-dippers were examined by MANOVA, ANOVA and the Mann-Whitney U test.

Logistic regression analysis was performed to determine whether differences between the dipper and non-dipper groups were significant in terms of the presence of hypertension-related symptoms and complications. A *p* value of  $\leq 0.05$  was considered statistically significant.

## RESULTS

### BP in non-dippers and dippers

The baseline characteristics of subjects ( $n=123$ ) are shown in Table 1. The 24-hour mean sBP of the subjects was  $136.98 (\pm 15.73)$  mmHg. Mean values of the nighttime sBP, daytime sBP, and the percentage of nighttime sBP reduction were  $132.56 (\pm 16.03)$  mmHg,  $140.49 (\pm 16.64)$  mmHg, and  $5.53 (\pm 6.22)\%$ , respectively. The 24-hour mean dBP was  $86.35 (\pm 11.39)$  mmHg. The mean nighttime dBP, daytime dBP, and the percentage of nighttime dBP reduction were  $83.14 (\pm 11.72)$  mmHg,  $88.88 (\pm 11.77)$  mmHg, and  $6.42 (\pm 6.43)\%$ , respectively.

sBP non-dippers (defined as those who show a nighttime dip in sBP of less than 10% compared to the daytime value) accounted for 25% ( $n=30$ ) of subjects. On the other hand, dBP non-dippers (who showed a nighttime dip in dBP of less than 10% of its daytime value) represented 32% ( $n=39$ ) of the subjects.

MANOVA showed that BP-related parameters were significantly different for dippers and non-dippers ( $p=0.00$ , Table 2). This difference appeared to be due to differences in the 24-hour

dBP, the nighttime sBP, the nighttime dBP, and the percentage nighttime sBP and dBP reductions of dippers and non-dippers.

In terms of circadian sBP rhythm, dippers' sBPs started to decrease in the early evening (around 18:00) and reached a minimum between 01:00 and 03:00 hours (Fig. 1A). The sBP increased rapidly from early morning until the late morning, and remained at this level for several hours. Non-dippers, on the other hand, had 24-hour sBP profile that fluctuated less, as shown in Fig. 1A. No significant difference in 24-hour mean sBP and daytime sBP was observed between non-dippers ( $138.63 \pm 14.82$  and  $140.01 \pm 15.03$  mmHg, respectively) and dippers ( $134.68 \pm 17.17$  and  $142.24 \pm 19.56$  mmHg, respectively).

The mean dBP of dippers behaved in the same manner as the mean sBP, i.e., it decreased rapidly in the early evening (around 18:00) reached a minimum between 01:00 and 03:00 hours, and then rose rapidly at 4:00 to plateau in the late morning (Fig. 1B). High dBPs were maintained during the daytime, and started to decrease in the early evening (Fig. 1B). The circadian dBP rhythm of non-dippers fluctuated less than that of the dippers' (Fig. 1B). The circadian dBP profile of non-dippers appeared to be similar to their sBP

**Table 1.** The Blood Pressure and Heart Rate in the Hypertensive Subjects ( $n=123$ )

Parameters	Mean $\pm$ S.D.
24-hour sBP (mmHg)	$136.98 \pm 15.73$
Nighttime sBP (mmHg)	$132.56 \pm 16.03$
Daytime sBP (mmHg)	$140.49 \pm 16.64$
The percentage of nighttime sBP reduction (%) <sup>1</sup>	$5.53 \pm 6.22$
24-hour dBP (mmHg)	$86.35 \pm 11.39$
Nighttime dBP (mmHg)	$83.14 \pm 11.72$
Daytime dBP (mmHg)	$88.88 \pm 11.77$
The percentage of nighttime dBP reduction (%) <sup>2</sup>	$6.42 \pm 6.43$
24-hour HR (/min)	$69.72 \pm 8.85$
Nighttime HR (/min)	$68.85 \pm 39.23$
Daytime HR (/min)	$71.43 \pm 14.19$
The percentage of nighttime HR reduction (%) <sup>3</sup>	$5.54 \pm 18.44$

sBP, systolic blood pressure; dBP, diastolic blood pressure; HR, heart rate.

<sup>1</sup>(Daytime sBP-Nighttime sBP)/Daytime sBP  $\times 100$ .

<sup>2</sup>(Daytime dBP-Nighttime dBP)/Daytime dBP  $\times 100$ .

<sup>3</sup>(Daytime HR-Nighttime HR)/Daytime HR  $\times 100$ .

Daytime: 6 AM-8 PM, Nighttime: 8 PM-6 AM.

**Table 2.** The Comparison of the BP-related Parameters between Dippers and Non-dippers

Multivariate Analysis Hottelling T	Variables	Mean (S.D.)		Univariate Analysis	
		Non-dippers (n=40)	Dippers (n=40)	F	p-value (2-tailed)
19.76 ( $p=0.00^*$ )	24-hour sBP (mmHg)	138.63 -14.82	134.68 -17.17	1.23	0.27
	Daytime sBP (mmHg)	140.01 -15.03	142.24 -19.56	0.33	0.57
	Nighttime sBP (mmHg)	137.2 -14.99	124.88 -14.69	13.96	0.00*
	The percentage of nighttime sBP Reduction (%)	1.93 -4.23	11.91 4.31	110.63	0.00*
	24-hour dBP (mmHg)	88.72 -11.7	83.98 -11.85	3.28	0.05*
	Daytime dBP (mmHg)	89.9 -12.18	89.2 -12.7	0.06	0.81
	Nighttime dBP (mmHg)	87.24 -11.51	77.35 -10.95	15.7	0.00*
	The percentage of nighttime dBP Reduction (%)	2.82 -4.61	13.21 -3.31	136.33	0.00*

sBP, systolic blood pressure; dBP, diastolic blood pressure.

Box M homogeneity test:  $p=0.79$ ,  $p=0.50$ .\* $p \leq 0.05$ .

profile. The mean nighttime dBP was 87.24 ( $\pm 11.51$ ) mmHg in non-dippers and 77.35 ( $\pm 10.95$ ) mmHg in dippers. The 24-hour mean dBP in non-dippers ( $88.72 \pm 11.70$  mmHg) was significantly higher than that in dippers ( $83.98 \pm 11.85$  mmHg) ( $p=0.05$ , Table 2). The mean daytime dBP was 89.90 ( $\pm 12.18$ ) mmHg in non-dippers and 89.20 ( $\pm 12.70$ ) mmHg in dippers, but this difference was not statistically significant (Table 2).

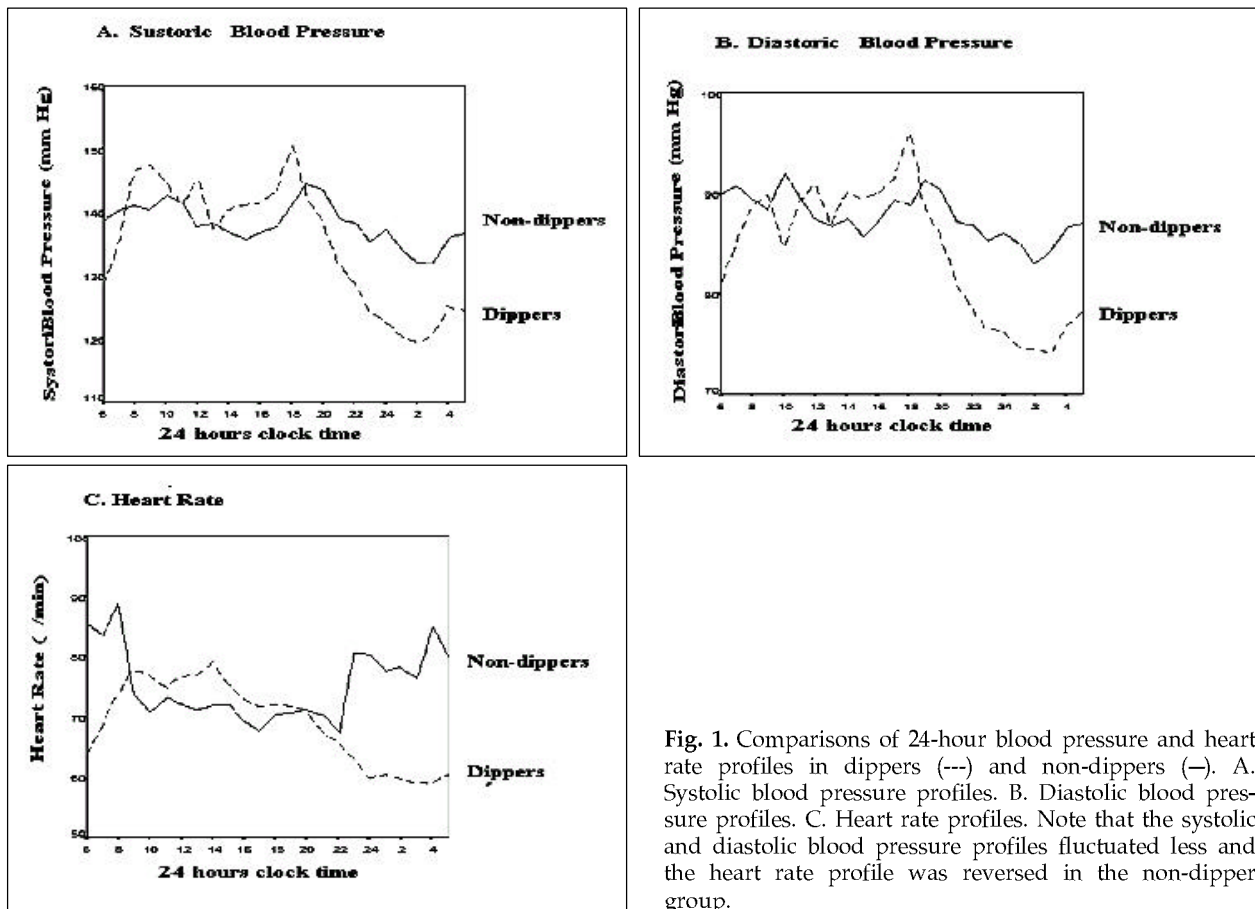
### HR in non-dippers and dippers

The baseline HR-related characteristics of the subjects ( $n=123$ ) are shown in Table 1. The mean 24-hour, nighttime, and daytime HRs of the subjects were 69.72 ( $\pm 8.85$ )/min, 68.85 ( $\pm 39.23$ )/min, and 71.43 ( $\pm 14.19$ )/min, respectively. The mean percentage nighttime HR reduction was 5.54 ( $\pm 18.44$ )%. HR non-dippers, defined as those who showed a nighttime dip in HR of less than

10% of the daytime value, accounted for 31% ( $n=38$ ) of the subjects.

MANOVA showed that HR-related parameters were significantly different in HR dippers and non-dippers ( $p=0.00$ , Table 3). Such differences appeared to be the result of differences in the daytime HR ( $p=.02$ ) and nighttime HR dipping ( $p=.00$ ).

The 24-hour HR profiles of non-dippers were the reverse of those of dippers: HR was higher at night and through the early morning than during the day (Fig. 1C). In the case of dippers, circadian HR was very similar to circadian sBP and dBP rhythm: i.e., the HR was higher during the day than at night (Fig. 1C). No statistical difference in the nighttime HR was found between the two groups (i.e., non-dippers:  $66.90 \pm 9.29$ /min, and dippers:  $64.31 \pm 8.53$ /min,  $p=0.38$ ). Unexpectedly, the daytime mean HR in non-dippers ( $69.25 \pm 9.23$ /min) was significantly lower than that of



**Table 3.** The Comparison of the HR-related Parameters between Dippers and Non-dippers

Multivariate analysis Hottelling T	Variables	Mean (S.D.)		Univariate Analysis	
		Non-dippers (n=20)	Dippers (n=20)	F	p-value (two-tailed)
0.46 (p=0.00*)	24-hour HR (/min)	68.84 (9.23)	71.43 (8.48)	0.81	0.37
	Daytime HR (/min)	69.25 (9.23)	76.71 (9.84)	5.77	0.02*
	Nighttime HR (/min)	66.90 (9.29)	64.31 (8.53)	0.80	0.38
	The percentage of nighttime HR reduction (%)	3.37 (4.05)	15.99 (6.03)	56.01	0.00*

HR, heart rate.

Box M homogeneity test: F=.89, p=.54.

\*p≤0.05.

dippers ( $76.71 \pm 9.84/\text{min}$ ) ( $p=0.02$ , Table 3). No significant difference in the 24-hour mean HRs of

non-dippers and dippers was found ( $68.84 \pm 9.23$  and  $71.43 \pm 8.48$ , respectively,  $p=0.37$ ).

### Biochemical and clinical characteristics of dippers and non-dippers

The biochemical characteristics of dippers and non-dippers are presented in Table 4. No biochemical characteristic examined was significantly different in the dipper and non-dipper groups, as classified by sBP, dBP or HR.

To determine whether hypertension-related symptoms or complications were different in the two groups, logistic regression was performed. Headache, dizziness, palpitation, chest pain or

discomfort, dyspnea, epistaxis, neck stiffness, and blurred vision were examined in the present study as hypertension-related symptoms. The analysis (Table 5) shows that the presence of such symptoms is not associated with the dipper/non-dipper description, whether classified by sBP, dBP, or HR ( $p=0.41$ ). Similarly, the presence of hypertension-related complications such as angina, cerebrovascular accident, congestive heart failure, hyperlipidemia, and arrhythmia were not associated with dippers or non-dippers, as classified by sBP, dBP or HR ( $p=0.11$ , Table 5).

**Table 4.** The Comparison of Biochemical Characteristics between Dippers and Non-dippers

	BP non-dipper	BP dipper	HR non-dipper	HR dipper
<b>Serum cholesterol</b>	n=24	n=22	n=20	n=20
Mean (S.D.)	194.46 (27.82)	191.59 (35.66)	196.74 (34.57)	198.47 (33.75)
F		0.09		0.03
p-value (2-tailed)		0.76		0.88
<b>Serum triglycerides</b>	n=24	n=22	n=20	n=20
Mean (S.D.)	192.88 (24.53)	172.00 (74.85)	197.30 (124.84)	184.59 (112.06)
F		0.50		0.11
p-value (2-tailed)		0.50		0.74
<b>Serum HDL</b>	n=24	n=22	n=20	n=20
Mean (S.D.)	44.42 (8.71)	48.95 (19.11)	48.09 (16.78)	44.59 (9.00)
F		1.10		0.61
p-value (2-tailed)		0.30		0.44
<b>Serum LDL</b>	n=18	n=9	n=16	n=15
Mean (S.D.)	118.47 (27.05)	118.22 (28.82)	123.19 (44.43)	115.60 (46.41)
Mann-WhitneyU		57.50		115.00
p-value (2-tailed)		0.23		0.84
<b>Serum BUN</b>	n=32	n=26	n=31	n=26
Mean (S.D.)	14.38 (4.10)	16.16 (5.63)	15.43 (7.39)	15.31 (4.10)
F		1.95		0.01
p-value (2-tailed)		0.17		0.94
<b>Serum creatinine</b>	n=32	n=26	n=31	n=26
Mean (S.D.)	1.06 (.37)	1.12 (.62)	1.07 (.57)	1.05 (.18)
F		0.23		0.03
p-value (2-tailed)		0.64		0.85
<b>Urine protein</b>	n=32	n=26	n=31	n=26
Mean (S.D.)	1.25 (.51)	1.04 (.53)	1.32 (.54)	1.19 (.49)
F		2.40		0.89
p-value (2-tailed)		0.13		0.35

**Table 5.** The Results of Logistic Regression Analyses for Hypertension-related Symptoms, and Hypertension-related Complications with the Predictors (Dippers and non-dippers as classified by either sBP, dBP or HR)

Model testing <sup>1</sup>			Significance test for each predictors				
$X^2$	$p$ -value	Overall percent <sup>2</sup>	n	variables	B	$p$ -value <sup>3</sup>	exp (B)
6.16	0.41	61.54%	80	sBP	1.14	0.2	3.12
				dBp	0.1	0.48	1.11
				HR	1.09	0.02*	2.96
Model testing <sup>4</sup>			Significance test for each predictors				
$X^2$	$p$ -value	Overall percent	n	variables	B	$p$ -value	exp (B)
10.36	0.11	64.10%	66	sBP	-0.73	0.29	0.48
				dBp	-5.94	0.42	0
				HR	0.97	0.05*	2.62

\* $p \leq 0.05$ .

sBP, systolic blood pressure; dBP, diastolic blood pressure; HR, heart rate.

<sup>1</sup>To test the significance of a model composed of predictors to explain the presence of hypertension-related symptoms (headache, dizziness, palpitation, chest pain or discomfort, dyspnea, epistaxis, neck stiffness, and blurred vision).<sup>2</sup>Overall percent for correct group classification.<sup>3</sup>one-tailed test.<sup>4</sup>To test the significance of a model composed of predictors to explain the presence of hypertension-related complications (angina, cerebrovascular accident, congestive heart failure, hyperlipidemia, and arrhythmia).

## DISCUSSION

Continuous monitoring of cardiovascular parameters such as BP and HR throughout the day have been recently recognized to provide information on the pattern and variability of these parameters and to allow their quantitation.<sup>1,14</sup> Studies have shown that the normal circadian rhythms of these parameters exhibit a relatively low level throughout the night, begins to rise in the early morning, and reaches a peak during the morning.<sup>1</sup> Such circadian rhythms were suggested to be mediated by plasma catecholamines<sup>1</sup> or direct sympathetic neural input to the heart and vasculature.<sup>15</sup> In the present study, the circadian rhythms of BP and HR in dippers displayed the same patterns as the normal circadian rhythm. Moreover, the timings of the circadian sBP, dBP and HR profiles in dippers were very consistent, showing lowest values during the night, rising in the early morning, and reaching a plateau in the late morning.

In non-dippers, the sBP and dBP profiles were relatively monotonous throughout the day, unex-

pectedly, the 24-hour HR profile in non-dippers was reversed, highest values were observed during the night and lowest values between the late morning and the early evening. Nighttime reductions in BP and HR have attracted a great deal of interest due to their physiological significance, because of the beneficial effect of reducing the wall tension of the heart and vasculature.<sup>8</sup> Studies have been showed that hypertensive subjects who exhibit smaller nighttime reductions (non-dippers) or a reversed pattern are at risk of more serious end organ damage than dippers. For example, hypertensive subjects with the smallest decrease in nighttime BP were reported to have more severe left ventricular hypertrophy, and higher levels of cardiovascular and cerebrovascular complications than subjects with normal nighttime BP decrease.<sup>2,7,10</sup> It has been suggested that the duration of exposure to increased levels of BP and wall stress over 24-hours in hypertensive subjects plays an important role in pathogenetic vasculature changes.<sup>8</sup> In other words, it is plausible that end organ damage in hypertensive subjects may be prevented by inducing a decrease

in nighttime BP in non-dippers.<sup>7</sup>

In the present study, the nighttime reduction rates of sBP, dBP and HR in the non-dippers were 1.93, 2.82 and 3.37%, respectively. Although there was wide variation among individuals, the ambulatory BP and HR in normotensive subjects decreased during the night by on average 20% of the daytime values.<sup>8,16</sup> Therefore, the nighttime reduction rate in the non-dippers in the present study seems to be very low. Verdecchia et al.<sup>8</sup> showed an inverse relationship between the percentage nighttime BP reduction and the degree of left ventricular hypertrophy. In addition to the nighttime reductions of these parameters, the durations of the reductions were also proposed to be important in terms of the cardiac and vascular structural changes in hypertensive patients.<sup>8</sup> Further research on this matter is necessary.

Although most studies on the circadian rhythms of cardiovascular parameters have focused on BP, ambulatory HR has also been proposed to be a potent risk marker in essential hypertension.<sup>9</sup> Kikuya et al.<sup>17</sup> showed that HR variability is an independent risk factor of cardiovascular mortality after adjusting for BP variability, and therefore, the combination of these two independent variables (BP and HR) has been suggested to be a powerful predictor of future cardiovascular mortality.<sup>18</sup> In our study, circadian HR rhythm in non-dippers was reversed, that is the nighttime HR values were higher than the daytime HR values, as shown in Fig. 1C. Surprisingly, the nighttime HR of non-dippers was not statistically different from that of the dippers. However, there was a significant difference in the daytime HR between the two groups: non-dippers' daytime HR (69.25/min) was lower than that in dippers (76.71/min). This difference in daytime HR appears to be responsible for the difference in the circadian HR pattern of dippers and non-dippers. Therefore, it seems that the flatness of the circadian HR patterns in non-dippers might be the result of diminished daytime HR values. On the other hand, the differences in the circadian sBP and dBP patterns of non-dippers and dippers were found to be mainly due to differences in the nighttime BP values. In other words, the flatness of the circadian BP patterns in non-dippers might be the result of diminished nighttime sBP and dBP

reductions.

In fact, the relationship between altered circadian rhythms and the occurrence of quite divergent hypertension-related complications has not yet been clarified.<sup>12</sup> However, it has been proposed that circadian rhythm reversal might be responsible for the occurrence of vascular events, since most sudden deaths, cerebrovascular hemorrhages, massive nasal bleeding, and vitreous hemorrhages are observed during the night and early morning.<sup>12</sup>

None of the biochemical characteristics tested in the present study was significantly different in dippers and non-dippers. Nakano reported that serum creatinine and microalbuminuria were significantly different in subjects with normal circadian and reversed circadian BP rhythm.<sup>12</sup> On the other hand, Kukla et al. showed that a decreased nighttime BP reduction (non-dipper) correlated with the occurrence of lacunar infarction, but not with serum cholesterol and triglyceride.<sup>10</sup> Based on these studies and the results of the present study, the relationship between such biochemical parameters and altered circadian rhythm cannot be concluded.

With respect to hypertension-related symptoms and complications, logistic regression showed that the presence of such symptoms and complications is not related to the dipper/non-dipper classification. This result suggests that the effects of a reduced nighttime BP and of a HR dip on hypertension-related symptoms and complications are not significant. However, the number of parameters related to hypertension-related symptoms and complications were limited in the present study. Therefore, we suggest that further studies are necessary to clarify the effect of altered circadian rhythms, especially reduced nighttime BP or HR fall, on the various hypertension-related symptoms and complications, which are indicators of disease progression and target organ damage in hypertension.

## REFERENCES

1. Fox KM, Mulcahy DA. Circadian rhythm in cardiovascular function. *Postgrad Med J* 1991;67:S33-6.
2. Nakano S, Uchida K, Kigoshi T, Azukizawa S, Iwasaki R, Kaneko M, et al. Circadian rhythm of blood pres-

- sure in normotensive subjects. *Diabetes Care* 1991;14:707-11.
3. Cooke-Ariel H. Circadian variations in cardiovascular function and their relation to the occurrence and timing of cardiac events. *Am J Health Syst Pharm* 1998;15 Suppl 3:S5-11.
  4. O'Brien E, Sceridan J, O'Malley K. Dippers and non-dippers. *Lancet* 1988;ii:397.
  5. Mallion J, Baguet J, Siche J, Tremel F, Gaudemaris RD. Clinical value of ambulatory blood pressure monitoring. *J Hypertens* 1999;7:585-95.
  6. Kumagai Y, Shiga T, Sunaga K, Cornelissen G, Fbihara A, Halberg F. Usefulness of circadian amplitude of blood pressure in predicting hypertensive cardiac involvement. *Chronobiologia* 1992;19:43-58.
  7. Imai Y, Tsuji I, Nagai K, Watanabe N, Ohkubo T, Sakuma M, et al. Circadian blood pressure variation related to morbidity and mortality from cerebrovascular and cardiovascular disease. *Ann NY Acad Sci* 1996;5:172-5.
  8. Verdecchia P, Schillaci G, Guerrieri M, Gatteschi C, Benemio G, Boldrini F, et al. Circadian blood pressure changes and left ventricular hypertrophy in essential hypertension. *Circulation* 1990;81:528-36.
  9. Verdecchia P, Schillaci G, Borgioni C, Ciucci A, Pede S, Porcellati C. Ambulatory pulse pressure - A potent predictor of total cardiovascular risk in hypertension. *Hypertension* 1998;32:983-8.
  10. Kukla C, Sander D, Schwarze J, Wittich I, Klingelhofer J. Changes of circadian blood pressure patterns are associated with the occurrence of lacunar infarction. *Arch Neurol* 1998;55:683-8.
  11. Alcalado JC, Pacy PJ, Beevers M, Dodson PM. Risk factors for peripheral vascular disease in hypertensive subjects with type 2 diabetes mellitus. *Diabet Med* 1992;9:904-7.
  12. Nakano S, Fukuda M, Hotta F, Ito T, Ishii T, Kitazawa M, et al. Reversed circadian blood pressure rhythm is associated with occurrences of both fatal and nonfatal vascular events in NIDDM subjects. *Diabetes* 1998;47:1501-6.
  13. Michell TH, Nolan B, Henry M, Cronin C, Baker H, Greely G. Microalbuminuria in patients with non-insulin-dependent diabetes mellitus relates to nocturnal systolic blood pressure. *Am J Med* 1997;102:531-5.
  14. Weber MA, Drayer JM, Nakamura DK, Wyle FA. The circadian blood pressure pattern in ambulatory normal subjects. *Am J Cardiol* 1984;54:115-9.
  15. Schofl C, Becker C, Prank K, Von Zur Muhlen A, Brabant G. Twenty-four-hour rhythms of plasma catecholamines and their relation to cardiovascular parameters in healthy young men. *European Journal of Endocrinology* 1997;137:675-83.
  16. Borne PV, Leeman M, Primo G, Degaute J-P. Reappearance of a normal circadian rhythm of blood pressure after cardiac transplantation. *Am J Cardiol* 1992;69:794-801.
  17. Kikuya M, Hozawa A, Ohokubo T, Tsuji I. Prognostic significance of blood pressure and heart rate variabilities: The Ohasama study. *Hypertension* 2000;36:901-8.
  18. Sesso HD, Stampfer MJ, Rosner B, Hennekens CH. Systolic and diastolic blood pressure, pulse pressure, and mean arterial pressure a predictors of cardiovascular disease risk in men. *Hypertension* 2000;36:801-8.