Tohoku J. Exp. Med., 1997, **183**, 1-20

Determinants of Circadian Blood Pressure Variation: A Community-Based Study in Ohasama

AKIMITSU NISHIYAMA, YUTAKA IMAI, TAKAYOSHI OHKUBO,[1] ICHIRO TSUJI,[1] KENICHI NAGAI,[3] NORIKO KIKUCHI, JUNKO KATO, MAKOTO SEKINO, AKIKO AIHARA, MASAHIRO KIKUYA, HIROSHI SATOH[2] and SHIGERU HISAMICHI[1]

The Second Department of Medicine, [1]Department of Public Health, and [2]Department of Environmental Health Science, Tohoku University School of Medicine, Sendai 980-77, and [3]Ohasama Hospital, Iwate 028-32

NISHIYAMA, A., IMAI, Y., OHKUBO, T., TSUJI, I., NAGAI, K., KIKUCHI, N., KATO, J., SEKINO, M., AIHARA, A., KIKUYA, M., SATOH, H. and HISAMICHI, S. *Determinants of Circadian Blood Pressure Variation: A Community-Based Study in Ohasama.* Tohoku J. Exp. Med., 1997, **183** (1), 1-20 —— We investigated factors affecting the nocturnal decline in blood pressure (BP). A cross sectional study was done in 706 community-based untreated subjects ≧20 years of age. Screening and ambulatory BPs were measured and the effects of age and the ambulatory BP on the nocturnal decline were examined. Bivariate analysis demonstrated that the magnitude of the decline and the percent decline in the nocturnal BP increased with increase in daytime ambulatory BP and decreased with increase in nighttime ambulatory BP. Although the magnitude of the nocturnal decline in BP increased with increasing daytime BP, the nocturnal BP in hypertensives was still higher than those in normotensives. The magnitude decreased with increasing age in men but not in women, while the percent decline decreased with increasing age in both men and women. Since bivariate analysis demonstrated that the daytime BP, nighttime BP, and standard deviation of the 24-hour BP strongly correlated with the magnitude of the nocturnal decline, these parameters were excluded as independent variables from the multivariate analysis. In the multivariate analysis the nighttime pulse pressure was negatively and daytime pulse pressure was positively associated with the magnitude of the decline and the percent decline in the nocturnal BP. A non-dipping circadian variation was frequently observed in elderly normotensive men but the rate of nondipper was rather low in hypertensive individuals in the general population. A marked dipping pattern was frequently observed in hypertensive women ≧70 years of age. The nocturnal BP levels in subjects with daytime hypertension are higher than those in subjects with daytime normotension. Therefore, BP must ideally be lowered over 24-hour period in hypertensive subjects. The diminished magnitude

Received June 4, 1997; revision accepted for publication July 9, 1997.

Address for reprints: Dr. Yutaka Imai, The Second Department of Medicine, Tohoku University School of Medicine, 1-1 Seiryomachi, Aoba-ku, Sendai 981-77, Japan.

of the decline and the decrease in the percent decline in the nocturnal BP in the elderly may be mediated by the disturbed baroreflex function due to the decrease in compliance of large elastic artery. However, in some elderly hypertensive women, excess nocturnal decline in BP is observed. In such subjects, we should take care of the nocturnal BP levels during treatment.——— ambulatory monitoring; blood pressure; nocturnal decline; dipper; non-dipper

Ambulatory 24-hour blood pressure (BP) recordings typically show higher daytime BPs and lower nighttime BPs in both hypertensive patients and normotensive subjects (Bevan et al. 1969; Littler et al. 1975; Millar-Craig et al. 1978; Mancia et al. 1983). The BP pattern in hypertensive patients is usually similar to that in normotensive subjects except for the presence of an upward shift (Millar-Craig et al. 1978; Messerli et al. 1982; Pickering et al. 1982; Imai et al. 1990c). However, disturbed circadian variation in BP, manifested by a decrease in or loss of the nocturnal decline in BP or an increase in nocturnal BP has been observed in the presence of various pathophysiological conditions (Imai et al. 1990a). The absence or decrease in the nocturnal decline in BP in some patients with essential hypertension may constitute an additional risk factor for cardiovascular and cerebrovascular complications (Kobrin et al. 1984; Gosse et al. 1988; O'Brien et al. 1988; Verdecchia et al. 1990; Klein et al. 1991; Kuwajima et al. 1992; Palatini et al. 1992; Shimada et al. 1992;Verdecchia et al. 1993). Several studies on ambulatory BP monitoring have examined the magnitude of the nocturnal decline in BP in relation to age and ambulatory BP levels (Drayer et al. 1982; Messerli et al. 1982; Pickering et al. 1982; Imai et al. 1990c; Munakata et al. 1991; O'Brien et al. 1991; Hayashi et al. 1992; Staessen et al. 1992; Imai et al. 1993a, b; Middeke and Schrader 1994; Mancia et al. 1995; Wiinberg et al. 1995). We previously reported the age and gender specific characteristics of the circadian BP variation in 474 untreated subjects from the general Japanese population (Imai et al. 1993a, b). A few systematic analyses of circadian BP variation in a general population have also been reported (Staessen et al. 1992; Mancia et al. 1995). We analyzed ambulatory BP recordings obtained in 823 untreated subjects in the general population of a rural community in northern Japan to determine the factors that influence nocturnal BP levels and the degree of the nocturnal decline in BP.

Subjects and Methods

Study population

The present study is a part of longitudinal observational study of the subjects who participated in our project of ambulatory BP monitoring at Ohasama Town, Iwate Prefecture, Japan, since 1986. Ohasama Town, characterized as a rural community, has the total population of 8040 in 1991. An ambulatory BP monitoring study was conducted in the Uchikawame and Kamegamori regions of

Ohasama between 1986 and 1991. The socioeconomic and demographic characteristics in Uchikawame have been reported elsewhere (Imai et al. 1993b). Geographic and socioeconomic background in Kamegamori were similar to those in Uchikawame. The most common cause of death among the residents of this town was cerebrovascular disease, followed by cancer and heart disease. As compared with the mortality in Japan, standardized mortality ratio (SMR) of the residents at Ohasama Town during 1988-1992 was 0.98 for all-cause, 1.31 for cerebrovascular disease, 0.99 for cancer, and 0.59 for heart disease. The study was approved by the Institutional Review Board of Tohoku University School of Medicine.

To be eligible as candidates for this project, the subjects had to be at least 20 years old and to be working near or staying at their own houses during the daytime. The latter condition was necessary because public health nurses visited the subjects to attach ambulatory BP monitoring devices during the daytime on working days (from Monday through Friday). Of the total, 2728 were at least 20 years of age, but 1040 were excluded because they worked away from home. Of the remaining 1688 subjects, 23 who were bedridden and 90 who were staying at hospitals were also excluded. Thus, 1575 persons were eligible for the study. This group consisted mainly of farmers, housewives, and retired people. Of the eligible 1575 subjects, 383 declined to participate in the study for various reasons, and 1192 subjects (395 men aged 61.7±13.4 years and 797 women aged 57.8±13.5 years), 75.7% of all eligible persons, participated in the monitoring of ambulatory BP (Table 1). There were no significant differences in the SMR for the period 1988-1994 (0.80 for all cause mortality for nonparticipants), or in the level of education or economic condition between the study subjects and the residents who were excluded or who declined to participate.

Of 1192 subjects, 823 (274 men aged 57.6±13.2 years and 549 women aged 53.5±12.6 years) were not receiving antihypertensive drugs. Information regarding antihypertensive medications was obtained from questionnaires sent to each household and from medical records at Ohasama Prefectural Hospital. The average ambulatory BP in 274 men was 124.4±13.2/73.6±8.0, and those in 549 women was 118.4±12.5/69.3±7.3 mmHg. The subjects who have a history of stroke, coronary heart disease, diabetes mellitus and other major complications were eligible unless they were taking antihypertensive medications and unless they adopted exclusion criteria mentioned above. We investigated the determinants of the nocturnal decline in BP in 706 subjects (217 men aged 60.2±12.2 years and 489 women aged 54.7±11.6 years) in whom ambulatory BP and screening BP data and the body mass index (BMI) were available.

Blood pressure measurements

During November and December of 1987 and 1989, physicians and public health nurses conducted health education classes on ambulatory BP monitorings in Uchikawame and Kamegamori. Of the 796 households in these regions, members of 637 households (80%) attended these classes. Public health nurses visited the remaining households to provide information on ambulatory BP monitoring. The subjects over 20 years of age were invited to attend the program. The program was instituted from 1988 to 1989 in Uchikawame and 1990 to 1991 in Kamegamori. Ambulatory BP was monitored using an ABPM 630 (Nippon Colin, Komaki), a fully automatic device that preset to measure BP every 30 minutes. Normal daily activities were allowed, and patients were told to keep their non-dominant arm still and relaxed to the side during measurements. BP was measured by both the cuff-oscillometric method and the microphone method, but we used only data obtained by the cuff-oscillometric method for analysis.

At medical examinations, blood pressure (screening BP) was measured twice consecutively by nurses or technicians with the subjects seated after at least 2 minutes of rest between 09 : 00 and 12 : 00 or between 13 : 00 and 16 : 00 using an automatic BP measuring device (USM 700F; Ueda Electric Work Co., Ltd., Tokyo) based on the microphone method. We used a standard arm cuff to obtain the ambulatory and screening BPs because the arm circumference was less than 34 cm in most subjects. All the BP measurement devices had been validated (Imai et al. 1990b, 1991).

Analysis of data

For inclusion in analysis, ambulatory BP monitoring period of more than 8 hours during the waking hour (daytime) and more than 4 hours during the time the subjects were in bed (nighttime) was required as estimated from the subjects' diaries. If the 24-hour ambulatory BP monitoring data were not complete, the 24-hour average ambulatory BP was calculated as follows: 24-hour average ambulatory BP = (daytime average × waking hours + nighttime average × sleeping hours)/24, where "sleeping hours" were those spent in bed. The mean monitoring time was 23.4 ± 1.6 hours; the mean number of measurements was 46.5 ± 3.8 times ($n = 823$). Since the study was based on a general population survey, the quality of sleep in each individual was disregarded. Artificial readings during ambulatory BP monitoring were defined according to previously described criteria (Imai et al. 1987) and were automatically omitted from the analysis.

The magnitude of the nocturnal decline in BP was calculated as follows: daytime average ambulatory BP − nighttime average ambulatory BP. The percent decline in the nocturnal BP was also calculated as follows: [(daytime average ambulatory BP − nighttime average ambulatory BP)/daytime average ambulatory BP] × 100. Bivariate linear regression analysis was performed to determine factors that influence the magnitude of the decline and the percent decline in the nocturnal BP using screening BP, ambulatory BP (24-hour, daytime and nighttime), the standard deviation (S.D.) of ambulatory BP, heart rate (HR), the S.D. of HR, age, sex, BMI, pulse pressure and the white coat effect (screening BP − ambulatory BP). Multivariate stepwise linear regression analysis was performed to obtain the best-fit model showing the most important independent variables influencing the magnitude of the nocturnal decline in BP or the percent decline in nocturnal BP using the SAS PHREG (SAS Insitute Inc. 1988). Age, sex, screening BP, ambulatory BP (24-hour, daytime and nighttime), HR, the S.D. of HR, pulse pressure, and the white coat effect were used as independent variables.

Values are expressed as the mean±S.D. Data were analyzed using the Student's *t*-test. The slopes of the regression equation were compared by analysis of covariance (ANCOVA) using the SAS GLM procedure (SAS Institute Inc. 1988). A p level <0.05 was accepted as indicating statistical significance.

RESULTS

Age-dependent changes in blood pressure

The 706 untreated subjects who had measurements of both screening and ambulatory BPs were classified by age and sex. Screening and ambulatory BPs increased gradually with age in both men and women. After age 60, the ambulatory diastolic BP (DBP) tended to fall in men but remained stable in women, resulting in a wider pulse pressure in the older age groups (Fig. 1). The rise in ambulatory systolic BP (SBP) with age was significantly smaller in men ($Y=0.17X+113.5$, $r=0.16$, $p<0.05$, where Y is SBP and X is age) than in women ($Y=$

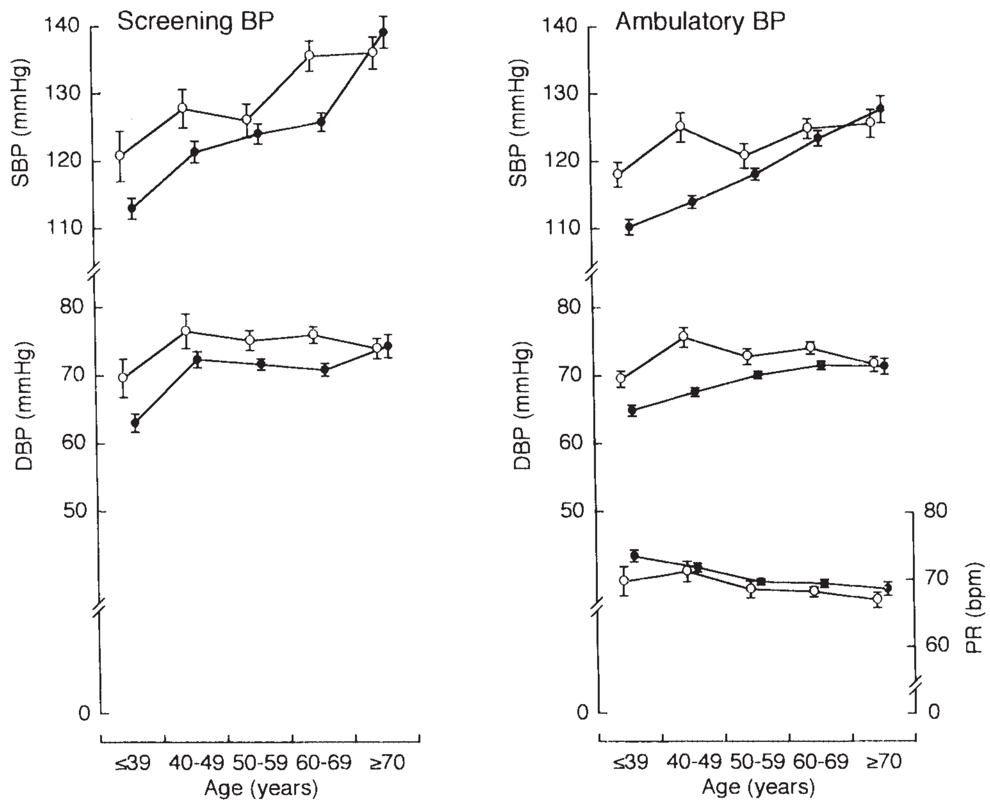

Fig. 1. Age-dependent change in screening and ambulatory blood pressure(BP) in 706 untreated subjects of the cohort. SBP, systolic BP; DBP, diastolic BP; PR, pulse rate; ○, men; ●, women

0.43X+95.0, $r=0.431$, $p<0.001$, ANCOVA; $p<0.001$). The ambulatory SBP was significantly higher in young men than in young women (age≦39 years, $p<0.001$ and 40-49 years, $p<0.001$). The ambulatory SBP was similar in elderly men and women (Fig. 1).

The HR decreased gradually with age in men ($r=-0.174$, $p<0.001$) and women ($r=-0.238$, $p<0.001$). The S.D. of the 24-hour ambulatory SBP increased gradually with age in women ($r=0.475$, $p<0.001$) but not in men ($r=0.094$, $p>0.05$). The S.D. of the HR decreased gradually with age in men ($r=-0.282$, $p<0.001$) and women ($r=-0.128$, $p<0.01$).

Effects of age and blood pressure on the magnitude of the nocturnal decline in blood pressure.

The magnitude of the nocturnal decline in BP in men decreased with increasing age (SBP, $r=-0.25$, $p<0.001$ and DBP, $r=-0.22$, $p<0.001$) but was not affected by age in women (SBP, $r=-0.05$, $p>0.05$ and DBP, $r=0.04$, $p>0.05$). The magnitude of the nocturnal decline in BP increased with increasing daytime SBP and DBP both in men (SBP, $r=0.42$, $p<0.001$ and DBP, $r=0.48$, $p<0.001$) and women (SBP, $r=0.43$, $p<0.001$ and DBP, $r=0.49$, $p<0.001$). Although the

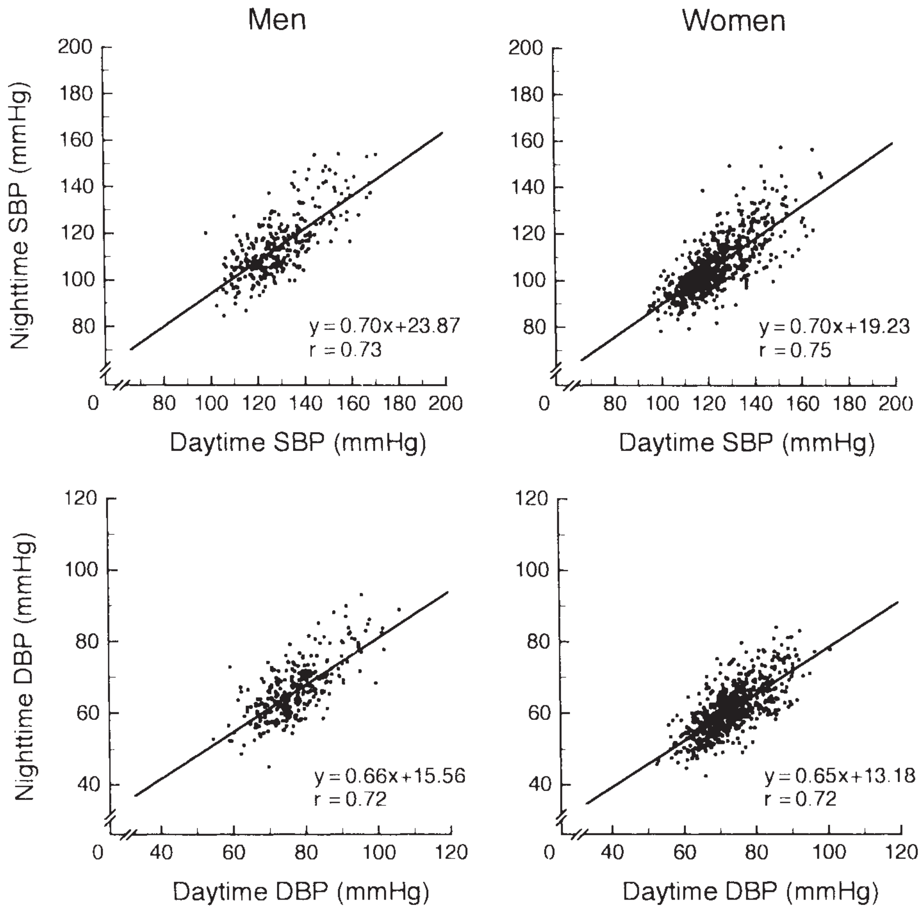

Fig. 2. The relationship between daytime blood pressure (BP) and nighttime BP. SBP, systolic BP; DBP, diastolic BP

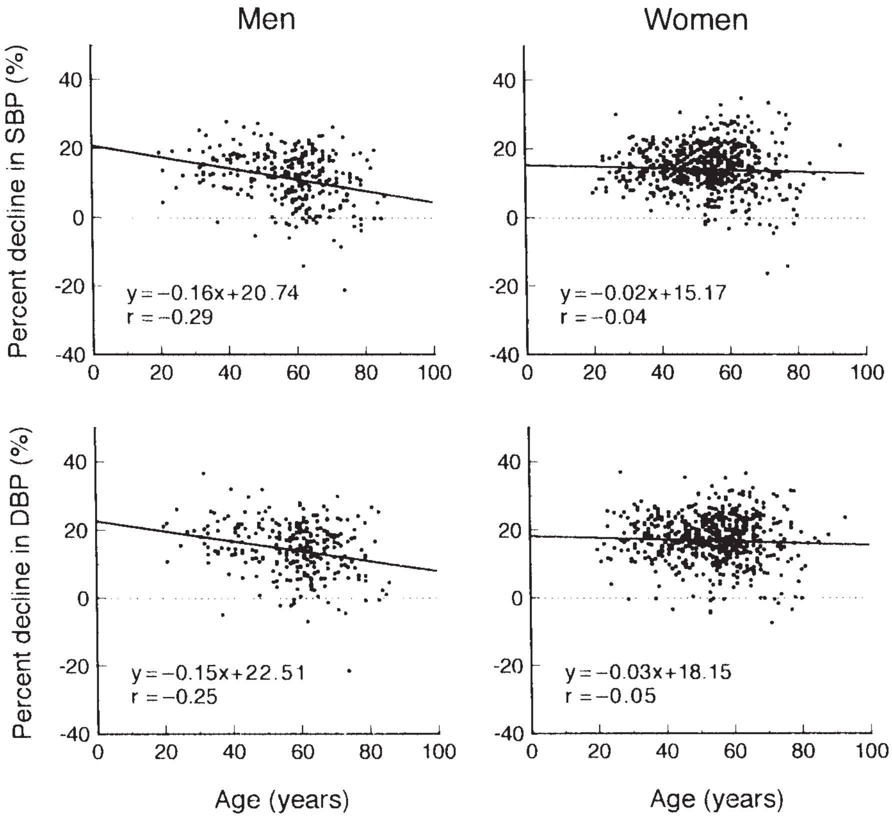

Fig. 3. The relationship between age and the percent decline in the nocturnal blood pressure. SBP, systolic blood pressure; DBP, diastolic blood pressure

magnitude of the nocturnal decline in BP increased with increasing daytime BP levels, the nocturnal BP levels increased with increase in dayitme BP levels (Fig. 2).

Effects of age and blood pressure on the percent decline in the nocturnal blood pressure

The percent decline in the nocturnal BP decreased with increasing age in men but not in women (Fig. 3). The percent decline in nocturnal BP increased with increase in daytime BP (Fig. 4).

The percent decline in nocturnal BP was significantly greater in DBP (men: 14.1±7.8%, $n=274$, women: 16.8±7.1%, $n=549$) than that in SBP (men: 11.3±7.6%, $p<0.001$ and women: 14.0±6.0%, $p<0.001$). When a "non-dipper" pattern was defined as less than a 10% nocturnal decline, non-dippers were observed mainly in the group of subjects≧70 years of age and with daytime SBP <140 mmHg (Table 1). More than 70% of men≧50 years of age and with daytime SBP<120 mmHg were non-dippers (Table 2).

In hypertensive subjects with daytime SBP≧140 mmHg, 24% of them were non-dippers and in those with daytime DBP≧80 mmHg, 12% of them were non-dippers.

When an extreme dipper was defined as equal to or more than a 20%

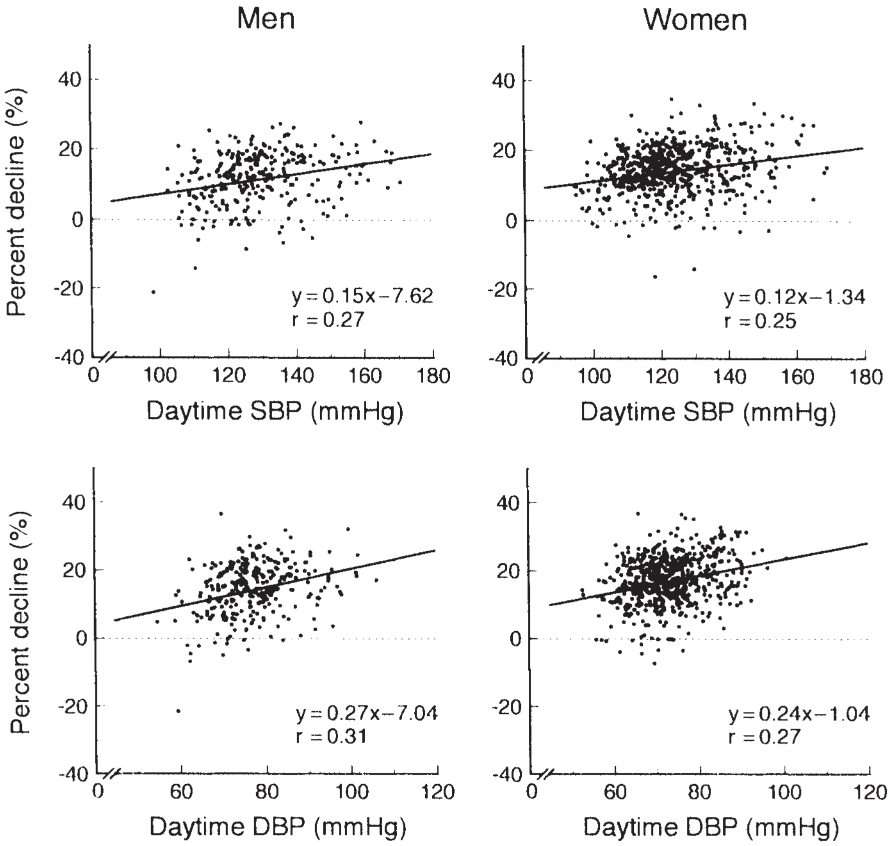

Fig. 4. The relationship between daytime blood pressure (BP) and the percent decline in the nocturnal BP (percent decline).

TABLE 1. *Number of subjects in each age group of men and women*

Age group (years)	20-29	30-39	40-49	50-59	60-69	70-79	80-	Total
Men	7	23	39	63	91	44	7	274
Wemen	21	65	105	173	133	43	9	549
Total	28	88	144	236	224	87	16	823

nocturnal decline, 33% of women but no men $\geqq$70 years of age with daytime SBP$\geqq$140 mmHg were extreme dippers, while it was observed in 47% of women and 23% of men$\geqq$70 years of age with daytime DBP$\geqq$80 mmHg (Table 3). As a whole, 18% of women and 10% of men were extreme dippers on the basis of SBP, and 34% of women and 23% of men were extreme dipper on the basis of DBP.

Nighttime BP in normotensive subjects on the basis of daytime BP (SBP< 120 mmHg or DBP< 70 mmHg) were compared with that in extreme dippers with daytime hypertension (SBP$\geqq$140 mmHg or DBP$\geqq$80 mmHg) (Fig. 5). Nighttime BP in hypertensive patients with extreme dipping (SBP=114.3±7.2 mmHg, DBP=64.7±4.3 mmHg) was significantly higher than that in normotensive subjects (SBP=99.6±8.3 mmHg, DBP=56.2±5.4 mmHg, p<0.001), although the

TABLE 2. *Incidence of non-dipper in men and women classified according to age and blood pressure level*

Age (year)	SBP (mmHg)						DBP (mmHg)					
	<120		≧120<140		≧140		<70		≧70<80		≧80	
	n	% (95% CI)	*n*	% (95% CI)	*n*	% (95% CI)	*n*	% (95% CI)	*n*	% (95% CI)	*n*	% (95% CI)
Men												
<50	14	35.7 (12.8-64.9)	45	20.0 (9.6-34.6)	10	10.0 (0.3-44.5)	13	15.4 (1.9-45.4)	32	6.2 (0.8-20.8)	24	8.3 (1.0-27.0)
≧50<70	43	67.4 (51.5-80.9)	79	27.8 (18.3-39.1)	32	34.4 (18.6-53.2)	27	44.4 (25.5-64.7)	74	32.4 (22.0-44.3)	53	18.9 (9.4-32.0)
≧70	15	73.3 (44.9-92.2)	23	65.2 (42.7-83.6)	13	23.1 (5.0-53.8)	15	60.0 (32.3-83.7)	23	43.5 (23.2-65.5)	13	15.4 (1.9-45.4)
Women												
<50	116	25.0 (17.4-33.9)	70	15.7 (8.1-26.4)	5	20.0 (0.5-71.6)	91	13.2 (7.7-21.6)	88	11.4 (5.6-19.9)	12	16.7 (2.1-48.4)
≧50<70	110	33.6 (24.9-43.3)	146	21.2 (14.9-28.8)	50	18.0 (8.6-31.4)	86	25.6 (16.8-36.1)	139	15.8 (10.2-23.0)	81	7.4 (2.8-15.4)
≧70	10	50.0 (18.7-81.3)	24	45.8 (25.6-67.2)	18	33.3 (13.3-59.0)	15	46.7 (21.3-73.4)	20	20.0 (5.7-43.7)	17	5.9 (0.1-28.7)

SBP, systolic blood pressure; DBP, diastolic blood pressure; CI, Confidence interval; *n*, number of subjects included in each group; %, incidence of non-dipper (the percent decline in the nocturnal BP<10%).

TABLE 3. *Incidence of extreme dipper in men and women classified according to age and blood pressure level*

Age (year)	SBP (mmHg)						DBP (mmHg)					
	<120		≧120<140		≧140		<70		≧70<80		≧80	
	n	% (95% CI)	*n*	% (95% CI)	*n*	% (95% CI)	*n*	% (95% CI)	*n*	% (95% CI)	*n*	% (95% CI)
Men												
<50	14	7.1 (0.2-33.9)	45	11.1 (3.7-24.1)	10	30.0 (6.7-65.2)	13	30.8 (9.1-61.4)	32	37.5 (21.1-56.3)	24	33.3 (15.6-55.3)
≧50<70	43	4.7 (0.6-15.8)	79	11.4 (5.3-20.5)	32	15.6 (5.3-32.8)	27	11.1 (2.4-29.2)	74	18.9 (10.7-29.7)	53	26.4 (15.3-40.3)
≧70	15	0.0 (0.0-18.1)	23	8.7 (1.1-28.0)	13	0.0 (0 .0-20.6)	15	0.0 (0.0-18.1)	23	21.7 (7.5-43.7)	13	23.1 (5.0-53.8)
Women												
<50	116	6.9 (3.5-13.0)	70	24.3 (14.8-36.0)	5	20.0 (0.5-71.6)	91	28.6 (19.6-39.0)	88	38.6 (28.4-49.6)	12	41.7 (15.2-72.3)
≧50<70	110	12.7 (7.1-20.2)	146	24.7 (17.9-32.5)	50	32.0 (19.5-46.7)	86	25.6 (16.8-36.1)	139	32.4 (24.7-40.8)	81	51.9 (40.5-63.1)
≧70	10	0.0 (0.0-25.9)	24	12.5 (2.7-32.7)	18	33.3 (13.3-59.0)	15	13.3 (1.7-40.5)	20	20.0 (5.7-43.7)	17	47.1 (23.0-72.2)

SBP, systolic blood pressure; DBP, diastolic blood pressure; CI, Confidence interval; *n*, number of subjects included in each group; %, incidence of extreme dipper (the percent decline in the nocturnal BP≧20%).

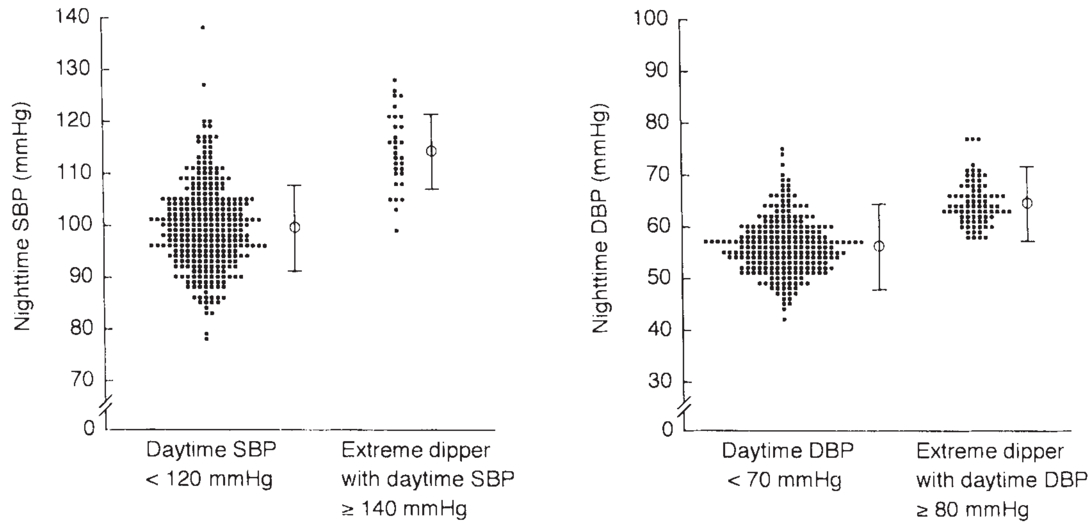

Fig. 5. Distribution of nighttime blood pressure (BP) in normotensive subjects with daytime SBP <120 mmHg or daytime DBP <70 mmHg and in hypertensive extreme dippers with daytime systolic BP $\geqq 140$ mmHg or daytime diastolic BP $\geqq 80$ mmHg.

distribution of the formers entirely overlapped with that in the latters, suggesting that nighttime BP in hypertensive patients with extreme dipping was within the range of nighttime BP in normotensives.

Multivariate stepwise linear regression analysis

Bivariate regression analysis demonstrated that screening BP, 24-hour BP, daytime BP, nighttime BP, age, sex, pulse pressure and BMI were correlated significantly with the magnitude of the nocturnal decline in BP as well as with the

TABLE 4. *Multiple stepwise regression analysis of factors affecting the magnitude of the nocturnal decline in blood pressure*

Dependent variable	Independent variable[a]	β-Coefficient	S.E.	p	Partial R^2
Men					
Magnitude of the nocturnal decline in SBP	Daytime SBP	1.000007	0.000035	<0.001	0.8651
	Nighttime SBP	−1.000064	0.000035	<0.001	0.1349
Magnitude of the nocturnal decline in DBP	Nighttime DBP	−0.999906	0.000055	<0.001	0.7995
	Daytime DBP	0.999911	0.000051	<0.001	0.2005
Women					
Magnitude of the nocturnal decline in SBP	Daytime SBP	−0.999994	0.000026	<0.001	0.8148
	Nighttime SBP	0.999998	0.000024	<0.001	0.1852
Magnitude of the nocturnal decline in DBP	Nighttime DBP	−1.000024	0.000044	<0.001	0.7579
	Daytime DBP	1.000010	0.000040	<0.001	0.2421

SBP, systolic blood pressure; DBP, diastolic blood pressure; S.E., standard error.
[a]The S.D. of the 24-hour blood pressure was excluded.

percent decline in the nocturnal BP ($p<0.05$). Therefore, we used these variables as independent variables for multivariate stepwise regression analysis. Since the S.D. of the 24-hour BP was strongly correlated with the magnitude of the nocturnal decline in BP (SBP, $r=0.617$, $p<0.001$; DBP, $r=0.588$, $p<0.001$) or the percent decline in the nocturnal BP (SBP, $r=0.519$, $p<0.001$; DBP, $r=0.5$, $p<0.001$), we excluded this parameter from the independent variables for multiple regression analysis. Since the sex was also determined as an independent variable, in the first step analysis we studied men and women, separately. Multivariate stepwise regression analysis showed that the daytime SBP was positively and the nighttime SBP was negatively associated with the magnitude of the nocturnal decline in SBP (Table 4). On the contrary, nighttime DBP contributed more than daytime DBP to the nocturnal decline in DBP (Table 4). In this model other variables were not associated with the magnitude of the nocturnal decline in BP.

This trend was also observed in the multivariate stepwise regression analysis when the percent decline in the nocturnal BP was used as the dependent variable (data are not shown).

TABLE 5. *Multivariate stepwise linear regression analysis of the magnitude of the nocturnal decline in SBP in each group with different daytime ambulatory SBP levels, where daytime and nighttime ambulatory BP levels were excluded from the independent variables*

Variable	β-Coefficient	S.E.	p	Partial R^2
Daytime SBP ≧ 140 mmHg ($n=100$)				
Nighttime pulse pressure	−2.606	0.134	0.001	0.3362
24-hour pulse pressure	2.498	0.177	0.001	0.4550
Age	0.160	0.061	0.05	0.1320
			Model R^2	0.8044
Daytime SBP < 140 and ≧ 120 mmHg ($n=335$)				
Nighttime pulse pressure	−1.681	0.0516	0.001	0.5219
Daytime pulse pressure	1.344	0.0725	0.001	0.2377
Nighttime heart rate	−0.098	0.0375	0.01	0.0048
			Model R^2	0.7645
Daytime BP < 120 mmHg ($n=262$)				
Nighttime pulse pressure	−1.519	0.0685	0.001	0.3550
Daytime pulse pressure	1.366	0.0886	0.001	0.3159
Daytime heart rate	−0.135	0.0340	0.001	0.0164
Sex	−1.739	0.6431	0.01	0.0086
			Model R^2	0.6960

BP, blood pressure; SBP, systolic blood pressure
S.E., standard error

Since daytime and nighttime ambulatory BP levels were strongly associated with the magnitude and the percent decline in the nocturnal BP, we performed multivariate stepwise regression analysis in subjects' groups adjusted by ambulatory BP level, where daytime and nighttime ambulatory BP levels were excluded from the independent variables. In each group with different daytime ambulatory SBP levels, the nighttime pulse pressure negatively associated with the magnitude of the nocturnal decline in SBP (Table 5). The daytime pulse pressure positively correlated with the magnitude of the nocturnal decline in SBP in subjects with daytime SBP ≧ 120 and < 140 mmHg and in those with daytime ambulatory SBP < 120 mmHg (Table 5). The 24-hour pulse pressure also positiively correlated with the magnitude of the nocturnal decline in SBP in subjects with daytime SBP ≧ 140 mmHg (Table 5). Such tendency was also observed in the magnitude of the nocturnal decline in DBP (Table 6) or in the percent decline in nocturnal BP (Tables 7 and 8).

TABLE 6. *Multiple stepwise linear regression analysis of the magnitude of the nocturnal decline in DBP in each group with different ambulatory DBP levels, where daytime and nighttime ambulatory BP levels were excluded from the independent variables*

Variable	β-Coefficient	S.E.	p	Partial R^2
Daytime DBP ≧ 80 mmHg (n = 166)				
Nighttime pulse pressure	−1.0824	0.1011	0.001	0.1494
24-hour pulse pressure	1.0709	0.1213	0.001	0.2759
Sex	−1.8754	0.7294	0.05	0.0172
BMI	−0.2547	0.117	0.05	0.0173
			Model R^2	0.4597
Daytime DBP < 80 and ≧ 70 mmHg (n = 323)				
Nighttime pulse pressure	−0.6445	0.0517	0.001	0.1943
Daytime pulse pressure	0.4582	0.0582	0.001	0.1352
Nighttime heart rate	−0.1245	0.0342	0.001	0.0235
Sex	−1.3039	0.5370	0.05	0.0117
			Model R^2	0.3647
Daytime DBP < 70 mmHg (n = 208)				
Nighttime pulse pressure	−0.5835	0.1019	0.001	0.1051
Daytime pulse pressure	0.460	0.1141	0.001	0.0661
Daytime heart rate	−0.2045	0.0464	0.004	0.0485
Age	−0.0642	0.0255	0.01	0.0358
Sex	−1.720	0.7846	0.05	0.0172
			Model R^2	0.2727

BP, blood pressure; DBP, diastolic blood pressure; BMI, body mass index
S.E., standard error

TABLE 7. *Multiple stepwise regression analysis of the percent decline in the nocturnal SBP in each group with different ambulatory SBP levels, where daytime and nighttime ambulatory BP levels were excluded from the independent variables*

Variable	β-Coefficient	S.E.	p	Partial R^2
Daytime SBP≧140 mmHg ($n=100$)				
Nighttime pulse pressure	−0.0163	0.0008	0.001	0.3965
24-hour pulse pressure	0.0146	0.0011	0.001	0.3924
Age	0.0012	0.0004	0.01	0.0156
Sex	−0.0186	0.0073	0.05	0.0123
			Model R^2	0.8168
Daytime SBP<140 and ≧120 mmHg ($n=335$)				
Nighttime pulse pressure	−0.0129	0.0004	0.001	0.5690
Daytime puls pressure	0.0094	0.0005	0.001	0.2007
Nighttime heart rate	−0.0008	0.0003	0.01	0.0061
			Model R^2	0.7758
Daytime SBP<120 mmHg ($n=262$)				
Nighttime pulse pressure	−0.0132	0.0006	0.001	0.3957
Daytime pulse pressure	0.0111	0.0008	0.001	0.2831
Daytime heart rate	−0.0013	0.0003	0.001	0.0176
Age	−0.0004	0.0002	0.05	0.0056
Sex	−0.0135	0.0056	0.05	0.0106
			Model R^2	0.7126

BP, blood pressure; SBP, systolic blood pressure
S.E., standard error

DISCUSSION

Except for an upward shift in the BP profile, the BP pattern in hypertensive patients usually resembles that in normotensive subjects (Millar-Craig et al. 1978; Messerli et al. 1982; Pickering et al. 1982; Imai et al. 1990c). It has been reported that the magnitude of the nocturnal decline in BP is essentially similar among normotensive, borderline hypertensive and established hypertensive patients (Pickering et al. 1982; Middeke and Schrader 1994), while it has also been reported that the higher the preexisting BP, the greater the nocturnal decline in BP (Brooks and Carroll 1912; Irving et al. 1974; Imai et al. 1990c; Staessen et al. 1992). Therefore, correction of the magnitude of the nocturnal decline in BP by BP levels; i.e., the percent decline in the nocturnal BP, is necessary to exclude the influence of the BP level. However, the percent decline was positively correlated with the daytime BP levels, suggesting that BP dependent decline in the nocturnal BP is represent a qualitative as well as quantitative changes. The magnitude

TABLE 8. *Multiple stepwise regressoin analysis of the percent decline in the nocturnal DBP in each group with different ambulatory DBP levels, where daytime and nighttime ambulatory BP levels were excluded from the independent variables*

Variable	β-Coefficient	S.E.	p	Partial R^2
Daytime DBP ≧ 80 mmHg (n = 166)				
Nighttime pulse pressure	−0.0121	0.0012	0.001	0.1915
24-hour pulse pressure	0.0113	0.0014	0.001	0.2355
Sex	−0.0235	0.0083	0.05	0.0209
BMI	−0.0029	0.0013	0.05	0.0176
			Model R^2	0.4655
Daytime DBP < 80 and ≧ 70 mmHg (n = 323)				
Nighttime pulse pressure	−0.0085	0.0007	0.001	0.2073
Daytime pulse pressure	0.0058	0.0008	0.001	0.1245
Nighttime heart rate	−0.0017	0.0005	0.001	0.0252
Sex	−0.0199	0.0007	0.01	0.0157
			Model R^2	0.3726
Daytime DBP < 70 mmHg (n = 208)				
Nighttime pulse pressure	−0.0087	0.0015	0.001	0.1182
Daytime pulse pressure	0.0066	0.0017	0.001	0.0621
Daytime heart rate	−0.0032	0.0007	0.001	0.0510
Age	−0.0010	0.0003	0.001	0.0418
Sex	−0.0271	0.0116	0.05	0.0191
			Model R^2	0.2923

BP, blood pressure; DBP, diastolic blood pressure
S.E., standard error

of the nocturnal decline in BP reportedly decreases with increasing age (Staessen et al. 1992). We previously reported that the magnitude of the nocturnal decline in BP decreases with age in men but not in women (Imai et al. 1993a). However, in the present study the effect of age on the magnitude of the nocturnal decline in BP in women did not appear to be independent of the effect of a concomitant increase in BP (Fig. 1). As a result, the percent decline in the nocturnal BP decreased with increasing age in women. This age-dependent change in the nocturnal decline in BP may be explained, in part, by deterioration in the quality of sleep in elderly subjects. In general, older individuals spend more time in bed than young subjects, but they experience a reduction in slow-wage sleep, and experience more nighttime wakefulness and increased fragmentation of sleep (Prinz et al. 1990). These age-related changes in the circadian sleep-wake rhythm may partly explain the decrease in the magnitude of the decline and the percent decline in the nocturnal BP observed in elderly subjects.

The potential limitation of the present study is the lack of information on the quality of sleep during the monitoring. It has been confirmed that noninvasive BP monitoring disturbs quality of sleep (Degaute et al. 1992; Schwan and Eriksson 1992; Davis et al. 1994). The change in quality of sleep may disturb the normal decline in BP at night and the reproducibility of the circadian BP variation. A poor reproducibility of the circadian BP variation weakens the clinical significance of the nocturnal decline in BP (Staessen et al. 1992; Wester et al. 1996). However, Schwan and Eriksson (1992) also reported that noninvasive BP monitoring did not affect circadian BP variation.

Differences in the level of physicial activity between young and old individuals and between men and women may also explain sex-dependent difference and age-dependent decreases in the nocturnal decline in BP. Decreased physical activity may attenuate diurnal peaking, resulting in decrease in the magnitude of the decline and the percent decline in the nocturnal BP (Pickering and James 1993). However, in the present subjects the activity of daily life was not different between elderly men and elderly women on the basis of inclusion criteria. Furthermore, the present results showed an excessive nocturnal decline in BP in many elderly women but in a few men with daytime hypertension, suggesting that the factors except quality of sleep and the level of physical activity are also involved.

The age-dependent decrease in the magnitude of the decline and the percent decline in the nocturnal BP may also be related to an insensitive baroreceptor reflex in elderly subjects (Gribbin et al. 1971; Conway et al. 1983; Floras et al. 1988; Shimada et al. 1992). In the present study, we observed age-dependent increase in pulse pressure ($r=0.408$, $p<0.0001$), reflecting decreased compliance of the large elastic arteries in the elderly (Avolio et al. 1983; O'Rourke 1990), including the carotid artery, and age-dependent decreases in the S.D. of HR ($r=-0.187$, $p<0.0001$), which indicates a disturbed baroreflex function (Conway et al. 1985). Conway et al. (1985) found that subjects with decreased baroreflex sensitivity showed decreased HR variability. They demonstrated that the fall in BP associated with sleep is accompanied by an increase in baroreflex sensitivity, suggesting that an increase in baroreflex sensitivity during sleep is responsible for part of the nocturnal decline in BP and HR with sleep (Conway et al. 1983). Therefore, the diminished nocturnal decline in BP in elderly may partly be explained by disturbed baroreflex function. It is uncertain why only the nighttime pulse pressure negatively associated with the magnitude of the decline and the percent decline in the nocturnal BP. It is assumed that the nighttime pulse pressure reflects the compliance of large elastic artery and, thus, the baroreflex sensitivity more than daytime pulse pressure, since the daytime systolic BP is affected by the change in cardiac output due to the change in mental and physical activities and to the change in autonomic nerve activities. Orthostatic and postprandial hypotension in elderly subjects with disturbed baroreflex function reduces the daytime BP, and thus may also lead to the diminished nocturnal decline in the elderly (Caird et al. 1973; Lipsitz and Fullerton 1986; Shimada et al. 1986; Peitzman and Berger 1989; Tsuchihashi et al. 1990).

In the present study, the diminished circadian variation in BP was observed mainly in normotensive men over 50 years of age (Table 1), while an extremely dipping pattern was observed in some elderly hypertensive women (Table 2). Studies have suggested that target organ damage is more severe in hypertensive patients with a nondipper nocturnal profile (Kobrin et al. 1984; Gosse et al. 1988; O'Brien et al. 1988; Verdecchia et al. 1990; Klein et al. 1991; Kuwajima et al. 1992; Palatini et al. 1992; Shimada et al. 1992) and that the prognosis may be poorer in these subjects (Verdecchia et al. 1993, 1994). Although the prevalence of non-dipper depends on how wake v.s. daytime BP and sleep v.s. nighttime BP is defined (Van Ittersum et al. 1995; Fagard et al. 1996), Verdecchia et al. (1994) reported that 35.7% of hypertensives and 34.7% of normotensives were non-dippers when non-dippers are defined as subjects with a $<10\%$ nocturnal reduction in the average daytime BP (06 : 00-22 : 00). However, in the present study a rate of non-dippers was rather low in hypertensive subjects but frequent in normotensive subjects in the general population. Furthermore, extremely dipping pattern of circadian BP variation (Kario et al. 1996) was observed in elderly hypertensive women. It has been recently reported that silent cerebrovascular lesions were present in the elderly hypertensive individuals with an extremely dipping pattern (Kario et al. 1996), especially in elderly women (Imai et al. 1996; Watanabe et al. 1996). Nakamura et al. (1995) reported that recurrence of stroke and symptomatic as well as asymptomatic brain lesions was more frequent in stroke survivors receiving drugs with a dipper pattern than those with a non-dipper pattern. The explanation for the marked nocturnal decline in BP in some elderly hypertensive women is unclear. It has been hypothesized that the nocturnal dippers are sometimes consistent with diurnal peakers (Pickering and James 1993). Pressor responsiveness to mental and physical stimuli is exaggerated in menopausal women (Owens et al. 1993), suggesting that diurnal peaking in elderly women may mediate an increased magnitude of the nocturnal decline in BP.

In summary, the magnitude of the nocturnal decline in BP increased with increasing daytime BP but the nocturnal BP levels in hypertensives are still higher than those in normotensives. Therefore, BP must ideally be lowered over a 24-hour period in hypertensive subjects. However, in some elderly hypertensive women, excess nocturnal decline in BP is observed and their nocturnal BP is within the range of the nocturnal BP in normotensives. In such subjects further increase in nocturnal decline in BP does not seem harmless.

Acknowledgments

This work was supported by research grants from the Miyagi Prefectural Kidney

Association, and the Takeda Medical Foundation, by a Research Grant for Cardiovascular Disease (No. 4c-3, 5c-2) from the Ministry of Health and Welfare, by a Research Grant entitled "Evaluation of the effect of drug treatment on hypertension and the chronic disease conditions in the elderly" from the Ministry of Health and Welfare, by a Research Grant for the Health Science for the Elderly 1996, 1997 from the Ministry of Health and Welfare, and by a Research Grant for Scientific Research (0767046 and 07670420) from the Ministry of Education, Science, Sports and Culture of Japan.

References

1) Avolio, A.P., Chen, S.G., Wang, R.P., Zhang, C.L. & O'Rourke, M.F. (1983) Effects of aging on changing arterial compliance and left ventricular load in a northern chinese urban community. *Circulation*, **68**, 50-58.
2) Bevan, A.T., Honour, A.J. & Stott, F.H. (1969) Direct arterial pressure recording in unrestricted man. *Clin. Sci.*, **36**, 329-344.
3) Brooks, H. & Carroll, J.H. (1912) A clinical study of the effects of sleep and rest on blood pressure. *Arch. Intern. Med.*, **10**, 97-102.
4) Caird, F.I., Andrews, G.R. & Kennedy, R.D. (1973) Effects of posture on blood pressure in the elderly. *Br. Heart J.*, **35**, 527-530.
5) Conway, J., Boon, N., Jones, J.V. & Sleight, P. (1983) Involvement of the baroreceptor reflexes in the changes in blood pressure with sleep and mental arousal. *Hypretension*, **5**, 746-748.
6) Conway, J., Boon, N., Vann Jones, J. & Sleight, P. (1985) Mechanisms concerned with blood pressure variability throughout the day. *Clin. Exp. Hypertens.*, **A7**, 153-157.
7) Davis, R.O.J., Jenkins, N.E. & Stradling, J.R. (1994) Effect of measuring ambulatory blood pressure on sleep and on blood pressure during sleep. *Br. Med. J.*, **308**, 850-823.
8) Degaute, J.P., van de Borne, P., Kerkhofs, M., Dramaix, M. & Linkowski, P. (1992) Does non-invasive ambulatory blood pressure monitoring disturb sleep? *J. Hypertens.*, **10**, 879-885.
9) Drayer, J.I.M., Weber, M.A., De, Young, J.L. & Wyle, F.A. (1982) Circadian blood pressure patterns in ambulatory hypertensive patients. Effects of age. *Am. J. Med.*, **73**, 493-499.
10) Fagard, R., Brguljan, J., Thijs, L. & Staessen, J. (1996) Prediction of the actual awake and asleep blood pressure by various methods of 24h pressure analysis. *J. Hypertens.*, **14**, 557-563.
11) Floras, J.S., Hassan, M.O., Jones, P.V., Osikowska, B.A., Sever, P.S. & Sleight, P. (1988) Consequences of impaired arterial baroreflexes in essential hypertension: Effects on pressor responses, plasma noradrenaline and blood pressure variability. *J. Hypertens.*, **6**, 525-535.
12) Gosse, C., Campello, G., Roudaut, T. & Dallocchio, M. (1988) High night blood pressure in treated hypertensive patients: Not harmless. *Am. J. Hypertens.*, **1**, S195-S198.
13) Gribbin, B., Pickering, T.G., Sleight, P. & Peto, R. (1971) Effect of age and high blood pressure on baroreflex sensitivity in man. *Circulation*, **29**, 424-431.
14) Hayashi, H., Hatano, K., Tsuda, M., Kanematsu, K., Yoshikane, M. & Saito, H. (1992) Relationship between circadian variation of ambulatory blood pressure and agae or sex in healthy adults. *Hypertens. Res.*, **15**, 127-135.
15) Imai, Y., Nihei, M., Abe, K., Sasaki, S., Minami, N., Munakata, M., Yumita, S., Onoda, H., Sekino, H., Yamakoshi, K. & Yoshinaga, K. (1987) A finger volume-oscillometric device for monitoring ambulatory blood pressure: Laboratoary and clinical evaluation. *Clin. Exp. Hypertens.*, **A9**, 2001-2025.

16) Imai, Y., Abe, K., Munakata, M., Sakuma, H., Hashimoto, J., Imai, K., Sekino, H. & Yoshinaga, K. (1990a) Circadian blood pressure variations under different pathophysiological conditions. *J. Hypertens.*, **8**, Suppl. 7, S125-S132.
17) Imai, Y., Abe, K., Sasaki, S., Minami, N., Munakata, M., Sekino, H., Nihei, M. & Yoshinaga, K. (1990b) Determination of clinical accuracy and nocturnal blood pressure pattern by new portable device for monitoring indirect ambulatory blood pressure. *Am. J. Hypertens.*, **3**, 293-301.
18) Imai, Y., Abe, K., Sasaki, S., Minami, N., Nihei, M., Munakata, M., Sakuma, H., Hashimoto, J., Imai, K., Sekino, H. & Yoshinaga, K. (1990c) Influence of age on the nocturnal fall of blood pressure and its modulation by long-acting calcium antagonists. *Clin. Exp. Hypertens.*, **A12**, 1077-1094.
19) Imai, Y., Abe, K. & Sekino, H. (1991) Evaluation of automatic devices for blood pressure measurement. In: *Annual Review Nephrology*, edited by S. Koshikawa & T. Nagasawa, Chugai-Igakusha, Tokyo, pp. 55-61. (in Japanese)
20) Imai, Y., Munakata, M., Hashimoto, J., Minami, N., Sakuma, H., Watanabe, N., Yabe, T., Nishiyama, A., Sakuma, M., Yamagishi, T. & Abe, K. (1993a) Age-specific characteristics of nocturnal blood pressure in a general population in a community of northern Japan. *Am. J. Hypertens.*, **6**, 179S-S183S.
21) Imai, Y., Nagai, K., Sakuma, M., Sakuma, H., Nakatsuka, H., Satoh, H., Minami, N., Munakata, M., Hashimoto, J., Yamagishi, T., Watanabe, N., Yabe, T., Nishiyama, A. & Abe, K. (1993b) Ambulatory blood pressure of adults in Ohasama, Japan. *Hypertension*, **22**, 900-912.
22) Imai, Y., Tsuji, I., Nagai, K., Watanabe, N., Ohkubo, T., Sakuma, M., Hashimoto, J., Itoh, O., Satoh, H., Hisamichi, S. & Abe, K. (1996) Circadian blood pressure variation related to morbidity and mortality from cerebrovascular and cardiovascular diseases. *Ann. New York Acad. Sci.*, **783**, 172-185.
23) Irving, J.B., Kerr, F., Ewing, D.J. & Kirby, B.J. (1974) Value of prolonged recording of blood pressure in assessment of hypertension. *Br. Heart J.*, **36**, 859-866.
24) Kario, K., Matsuo, T., Kobayashi, H., Imiya, M., Matsuo, M. & Shimada, K. (1996) Nocturnal fall of blood pressure and silent cerebrovascular damage in elderly hypertensive patients: Advanced silent cerebrovascular damage in extreme dippers. *Hypertension*, **27**, 130-135.
25) Klein, W., Zweiker, R., Eber, B., Dusleag, J., Brussee, H. & Rotman, B. (1991) Circadian blood pressure pattern in patients with treated hypertension and left ventricular hypertrophy. *Angiology*, **42**, 379-386.
26) Kobrin, I., Oigman, W., Kumar, A., Ventura, H.O., Messerli, F.H., Frohlich, E.D. & Dunn, F.G. (1984) Diurnal variation of blood pressure in elderly patients with essential hypertension. *J. Am. Geriatr. Soc.*, **32**, 896-899.
27) Kuwajima, I., Suzuki, Y., Shimosawa, T., Kanemaru, A., Hoshino, S. & Kuramoto, K. (1992) Diminished nocturnal decline in blood pressure in elderly hypertensive patients with left ventricular hypertrophy. *Am. Heart J.*, **123**, 1307-1311.
28) Lipsitz, L.A. & Fullerton, K.J. (1986) Postprandial blood pressure reduction in healthy elderly. *J. Am. Geriatr. Soc.*, **34**, 267-270
29) Littler, W.A., Honour, A.J., Carter, R.D. & Sleight, P. (1975) Sleep and blood pressure. *Br. Med. J.*, **3**, 346-348.
30) Mancia, G., Ferrari A, Gregorini, L., Parati, G., Pomidossi, G., Bertinieri, G., Grassi, G., DiRienzo, M., Pedotti, A. & Zanchetti, A. (1983) Blood pressure and heart rate variabilities in normotensive and hypertensive human beings. *Circ. Res.*, **53**, 96-104.
31) Mancia, G., Sega, R., Bravi, C., DeVito, G., Valagussa, F., Cesana, G. & Zanchetti, A. (1995) Ambulatory blood pressure normality: Results from the PAMELA study. *J. Hypertens.*, **13**, 1377-1390.
32) Messerli, F.H., Glade, L.B., Ventura, H.O., Dreslinski, G.R., Suarez, D.H., MacPhee, A.A., Aristimuno, G.G., Cole, F.E. & Frohlich, E. (1982) Diurnal variations of

cardiac rhythm, arterial pressure, and urinary catecholamines in borderline and established essential hypertension. *Am. Heart J.*, **104**, 109–114.

33) Middeke, M. & Schrader, J. (1994) Nocturnal blood pressure in normotensive subjects and those with white coat, primary, and secondary hypertension. *Br. Med. J.*, **308**, 630–632.

34) Millar-Craig, M.W., Bishop, C.N. & Raftery, E.B. (1978) Circadian variation of blood pressure. *Lancet*, **1**, 795–797.

35) Munakata, M., Imai, Y., Abe, K., Sasaki, S., Minami, N., Hashimoto, J., Sakuma, H., Ichijo, T., Yoshizawa, M., Sekino, H & Yoshinaga, K. (1991) Assessment of age-dependent changes in circadian blood pressure rhythm in patients with essential hypertension. *J. Hypertens.*, **9**, 407–415.

36) Nakamura, K., Oita, J. & Yamaguchi, T. (1995) Nocturnal blood pressure dip in stroke survivors. A pilot study. *Stroke*, **26**, 1373–1378.

37) O'Brien, E., Sheridan, J. & O'Malley, K. (1988) Dippers and non-dippers. *Lancet*, **2**, 397.

38) O'Brien, E., Murphy, J., Tyndall, A., Atkins, N., Mee, F., McCarthy, G., Staessen, J., Cox, J. & O'Malley, K. (1991) Twenty-four-hour ambulatory blood pressure in men and women aged 17 to 80 years: The Allied Irish Bank Study. *J. Hypertens.*, **9**, 355–360.

39) O'Rourke, M. (1990) Arterial stiffness, systolic blood pressure, and logical treatment of araterial hypertension. *Hypertension*, **15**, 339–347.

40) Owens, J.F., Stoney, C.M. & Matthews, K.A. (1993) Menopausal status influences ambulatory blood pressure levels and blood pressure changes during mental stress. *Circulation*, **88**, 2794–2802.

41) Palatini, P., Penzo, M., Racioppa, A., Zugno, E., Guzzardi, G., Anaclerio, M. & Pessina, A.C. (1992) Clinical relevance of nighttime blood pressure and of daytime blood pressure variability. *Arch. Intern. Med.*, **152**, 1855–1860.

42) Peitzman, S.J. & Berger, S.R. (1989) Postprandial blood pressure decrease in well elderly persons. *Arch. Intern. Med.*, **149**, 286–288

43) Pickering, T.G. & James, G.D. (1993) Determinants and consequences of the diurnal rhythm of blood pressure. *Am. J. Hypertens.*, **6**, 166S–169S.

44) Pickering, T.G., Harshfield, G.A., Kleinert, H.D., Blank, S. & Laragh, J.H. (1982) Blood pressure during normal daily activities, sleep, and exercise: Comparison of values in normal and hypertensive subjects. *J.A.M.A.*, **247**, 992–996.

45) Prinz, P.N., Vitiello, M.V., Raskind, M.A. & Thorpy, M.J. (1990) Geriatrics: Sleep disorders and aging. *N. Engl. J. Med.*, **323**, 520–526.

46) SAS Institute Inc. (1988) *SAS/STAT User's Guide, Release 6.03 Edition.* SAS Institute Inc., Cary.

47) Schwan, A. & Eriksson, G. (1992) Effect on sleep - but not on blood pressure - of nocturnal noninvasive blood pressure monitoring. *J. Hypertens.*, **10**, 189–194.

48) Shimada, K., Kitazumi, T., Ogura, H., Sadakane, N. & Ozawa, T. (1986) Differences in age-independent effects of blood pressure on baroreflex sensitivity between normal and hypertensive subjects. *Clin. Sci.*, **70**, 489–494.

49) Shimada, K., Kawamoto, A., Matsubayashi, K., Nishinaga, M., Kimura, S. & Ozawa, T. (1992) Diurnal blood pressure variations and silent cerebrovascular damage in elderly patients with hypertension. *J. Hypertens.*, **10**, 875–878.

50) Staessen, J., Bulpitt, C.J., O'Brien, E., Cox, J., Fagard, R., Stanton, A., Thijs, L., Van Hulle, S., Vyncke, G. & Amery, A. (1992) The diurnal blood pressure profile: A population study. *Am. J. Hypertens.*, **5**, 386–395.

51) Tsuchihashi, T., Abe, I., Tsukashima, A., Kobayashi, K. & Fujishima, M. (1990) Effects of meal and physical activity on blood pressure variability in elderly patients: A preliminary study. *Am. J. Hypertens.*, **3**, 943–946.

52) Van Ittersum, F.J., Ijzerman, R.G., Stehower, C.D.A. & Donker, A.J.M. (1995)

Analysis of twenty-four-hour ambulatory blood pressure monitoring: What time period to assess blood pressure during waking and sleeping. *J. Hypertens.*, **13**, 1053-1058.

53) Verdecchia, P., Schillaci, G., Guerrieri, M., Gatteschi, C., Benemio, G., Boldrini, F. & Porcellati, C. (1990) Circadian blood pressure changes and left ventricular hypertrophy in essential hypertension. *Circulation*, **81**, 528-536.

54) Verdecchia, P., Schillaci, G., Gatteschi, C., Zampi, I., Battistelli, M., Bartoccini, C. & Porcellati, C. (1993) Blunted nocturnal fall in blood pressure in hypertensive women with future cardiovascular morbid events. *Circulation*, **88**, 986-992.

55) Verdecchia, P., Porcellati, C., Schillaci, G., Borgioni, C., Ciucci, A., Battistelli, M., Guerrieri, M., Gatteschi, C., Zampi, I., Santucci, A., Santcci, C. & Reboldi, G. (1994) Ambulatory blood pressure: An independent predictor of prognosis in essential hypertension. *Hypertension*, **24**, 793-801.

56) Watanabe, N., Imai, Y., Nagai, K., Tsuji, I., Satoh, H., Sakuma, M., Sakuma, H., Kato, J., Onodera-Kikuchi, N., Yamada, M., Abe, F., Hisamichi, S. & Abe, K. (1996) Nocturnal blood pressure and silent cerebrovascular lesions in elderly Japanese. *Stroke*, **27**, 1319-1327.

57) Wester, P.J., Robinson, J.E., Watt, P.A.C & Thurston, H. (1996) Reproducibility of the circadian blood pressure fall at night in healthy young volunteers. *J. Hum. Hypertens.*, **10**, 165-166.

58) Wiinberg, N., Hoegholm, A., Christensen, H.R., Bang, L.E., Mikkelsen, K.L., Nielsen, P.E., Svendsen, T.L., Kampmann, J.P., Madsen, N.H. & Bentzon, M.W. (1995) 24-h ambulatory blood pressure in 352 normal Danish subjects, related to age and gender. *Am. J. Hypertens.*, **8**, 978-986.