

Prognostic Significance for Stroke of a Morning Pressor Surge and a Nocturnal Blood Pressure Decline

The Ohasama Study

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Abstract—There is continuing controversy over whether the pattern of circadian blood pressure (BP) variation that includes a nocturnal decline in BP and a morning pressor surge has prognostic significance for stroke risk. In this study, we followed the incidence of stroke in 1430 subjects aged ≥ 40 years in Ohasama, Japan, for an average of 10.4 years. The association between stroke risk and the pattern of circadian BP variation was analyzed with a Cox proportional hazards model after adjustment for possible confounding factors. There was no significant association between total stroke risk and the nocturnal decline in BP (percentage decline from diurnal level) or between total stroke risk and the morning pressor surge. The cerebral infarction risk was significantly higher in subjects with a $< 10\%$ nocturnal decline in BP as compared with subjects who had a $\geq 10\%$ nocturnal decline in BP ($P=0.04$). The morning pressor surge was not associated with a risk of cerebral infarction. On the other hand, an increased risk of cerebral hemorrhage was observed in subjects with a large morning pressor surge (≥ 25 mm Hg; $P=0.04$). Intracerebral hemorrhage was also observed more frequently in extreme dippers (those with a $\geq 20\%$ nocturnal decline in BP) than dippers (those with a 10% to 19% decline; $P=0.02$). A disturbed nocturnal decline in BP is associated with cerebral infarction, whereas a large morning pressor surge and a large nocturnal decline in BP, which are analogous to a large diurnal increase in BP, are both associated with cerebral hemorrhage. (*Hypertension*. 2006;47:149-154.)

Key Words: clinical trials ■ population ■ risk factors ■ blood pressure monitoring
■ blood pressure monitoring, ambulatory

The morning pressor surge is an abrupt increase in blood pressure (BP) that occurs as a person awakens in the morning.¹ Recently, the morning pressor surge has been examined as a risk factor for stroke. Kario et al² defined the “sleep-trough” morning pressor surge as the difference between the morning systolic BP (SBP) and the lowest SBP during sleep and reported that this surge was significantly and independently associated with the risk of stroke. However, they failed to find any significant associations between stroke risk and the “sleeping-to-waking” morning pressor surge defined as the morning SBP minus prewaking SBP. Gosse et al³ also reported that a 1-mm Hg increase in sleeping-to-waking morning pressor surge in SBP was associated with a 3.3% increase in the risk of cardiovascular events. On the other hand, Staessen et al⁴ reported that an increased slope of the sleeping-to-waking morning pressor surge (indirectly calculated by fitting a regression line) was associated with a lower risk of cardiovascular events. Therefore, the relation-

ship between the morning pressor surge and the risk of stroke remains controversial.

It has also been reported that the magnitude of the nocturnal decline in BP can predict morbidity and mortality of stroke, as well as the prevalence of asymptomatic stroke.⁴⁻⁷ We reported previously in the Ohasama study that a diminished nocturnal decline in BP was significantly associated with a higher risk for cardiovascular mortality but that a large nocturnal decline in BP was not.⁸ In contrast, Kario et al² reported that a large nocturnal decline in BP was a risk factor for stroke. Thus, the role of the nocturnal decline in BP as a risk factor for cardiovascular events is also controversial.

It has been assumed that a high BP in the morning is associated with the onset of cardiovascular diseases.⁹⁻¹¹ However, a high BP in the morning is not necessarily associated only with a morning pressor surge but can also be associated with a sustained elevation of nocturnal BP (non-

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dippers and inverted dippers).¹² In the present study, we investigated the risk of the morning pressor surge and the nocturnal decline in BP for stroke incidence in the population of Ohasama, Japan. The relationship between the pattern of circadian BP variation and subtype of stroke was also examined.

Methods

Study Population

The present study is part of a longitudinal observational study of subjects who have been participating in the BP measurement project in Ohasama, Iwate Prefecture, Japan, since 1987. The characteristics of this cohort have been described previously.¹³ For this study, 1542 subjects who were ≥ 40 years old in Ohasama gave their informed consent and participated, and their representativeness has been fully described previously.¹³ We excluded 32 subjects because of a lack of morning BP values and 80 subjects because of a previous history of stroke or transient ischemic attack (TIA) at entry, because the aim of this study was to analyze the relationship between the onset of the first stroke and circadian BP variation. The remaining 1430 subjects were followed. The study protocol was approved by the Institutional Review Board of Tohoku University School of Medicine and by the Department of Health of the Ohasama town government. Informed consent was obtained from each subject.

Ambulatory BP Monitoring

Ambulatory BP monitoring was performed with the ABPM-630 (Nippon Colin), a fully automatic cuff-oscillometric method device, which was preset to measure BP every 30 minutes. The device has been validated and meets the criteria of the Association for the Advancement of Medical Instrumentation.¹⁴ An ambulatory BP monitoring device was attached by well-trained public health nurses who visited each participant on a weekday morning and detached the monitor the next morning. The participants were asked to report their daily activities, including the time they went to bed and the time they got up.

The records that were analyzed included ≥ 8 hours of daytime measurements, 4 hours of sleep time measurements, and 2 hours of morning time measurements both before and after waking. These periods were estimated from the participants' diaries. Artifacts during recordings were defined according to criteria described previously¹⁵ and were omitted from the analysis.

Calculation of the Morning Pressor Surge and the Nocturnal Decline in BP

The amplitude of the morning pressor surge was calculated as follows: morning pressor surge in SBP = 2-hour average of SBP after waking - 2-hour average of SBP before waking. The percentage decline in nocturnal SBP was calculated as follows: nocturnal decline in SBP = (daytime SBP - nighttime SBP) \times 100/daytime SBP.

We classified the subtypes of nocturnal decline in SBP as follows: extreme dipper ($\geq 20\%$ nocturnal decline in SBP from the diurnal level), dipper (10% to 19% nocturnal decline in SBP), nondipper (0% to 9% nocturnal decline in SBP), and inverted dipper ($< 0\%$ nocturnal decline in SBP or nocturnal elevation).⁸ These cutoff points were based on the results of previous studies that investigated the relationship between the nocturnal decline in BP and cardiovascular complications.^{6,7} The morning pressor surge of the diastolic BP (DBP) and the percentage decline in nocturnal DBP were calculated in the same manner.

Follow-Up and Outcome

Residence in Ohasama was confirmed by residents' registration cards. In Japan, these cards are accurate and reliable, because they are used for pensions and social security benefits. Based on the residents' registration cards, we followed stroke-free survival until December 31, 2001. The incidence of stroke was obtained from the

Stroke Registration System of Iwate Prefecture, death certificates, National Health Insurance receipts, and questionnaires sent to each household at the time of ambulatory BP monitoring.

Stroke and TIA were defined as clinical disorders with focal brain dysfunction. The diagnostic criteria of stroke, TIA, and their subtypes were based on the Classification of Cerebrovascular Disease III by the National Institute of Neurological Disorders and Stroke.¹⁶ Subtypes of stroke were clinically defined on the basis of computed tomography scan and/or MRI.

Statistical Analysis

The association between the morning pressor surge and the risk of a first stroke and the association between the nocturnal decline in BP and the risk of a first stroke were estimated using a Cox proportional hazards model adjusted for 24-hour SBP level; age; gender; smoking; the use of antihypertensive drugs at baseline; and a history of cardiovascular complications, diabetes mellitus, and hypercholesterolemia. When we examined the risk of stroke and TIA, we censored death from causes other than a fatal stroke event. Homogeneity between subgroups was tested by adding interaction terms to the relevant Cox models.

A 2-tailed *P* value < 0.05 was taken to indicate statistical significance. We analyzed data using the SAS package (Version 8.2, SAS Institute Inc). The relative hazard (RH) was expressed with 95% CIs. Values are expressed as mean \pm SD.

Results

Baseline Characteristics

The mean age of participants was 61.1 ± 10.6 years, and 64% were women (Table). Of 1430 subjects, 230 (18%) were classified as current or past smokers, and 387 (27%) were receiving antihypertensive medication. A history of cardiovascular complications was observed in 18 subjects (1.3%), a history of diabetes in 245 (17%), and a history of hypercholesterolemia in 221 (15%).

Ambulatory SBP/DBP values were $122.9 \pm 13.0 / 71.9 \pm 7.7$ mm Hg for the 24-hour period, $128.5 \pm 13.8 / 75.9 \pm 8.4$ mm Hg for the daytime period, and $111.9 \pm 14.3 / 63.8 \pm 8.0$ mm Hg for the nighttime period. The mean nocturnal decline in SBP/DBP was found to be $12.8 \pm 7.9 / 15.7 \pm 7.8\%$. The mean amplitudes of the morning pressor surge in SBP/DBP were $13.9 \pm 13.9 / 9.9 \pm 8.4$ mm Hg.

A higher amplitude of the morning pressor surge was associated with a smaller proportion of men, lower nighttime BP, lower prewaking BP level, higher daytime BP, higher postwaking BP level, and a higher amplitude of nocturnal decline in BP (Table). A higher amplitude of the nocturnal decline in BP was associated with a lower frequency of men, lower nighttime BP level, lower prewaking BP level, higher daytime BP level, and a higher amplitude of the morning pressor surge (Table). The amplitude of the morning pressor surge was significantly correlated with the amplitude of the nocturnal decline in BP ($R = 0.59$; $P < 0.01$).

Follow-Up and Outcome

The mean duration of follow-up was 10.4 years (maximum 14.6 years). Of the 1430 study subjects, there were 262 deaths (17%), and 30 subjects (2%) moved out of the region and were lost to follow-up. There were 128 cases of a first stroke. Of these 128 cases, 86 were cerebral infarctions (67%), 27 were intracerebral hemorrhages (21%), 10 were subarachnoid hemor-

Characteristics of Quintiles of Amplitude of the Morning Pressor Surge and 4 Groups of Nocturnal SBP Decline

Characteristics	Amplitude of Morning Pressor Surge (mm Hg)							Nocturnal SBP Decline (%)				
	Total	<3	3≤11	11≤17	17≤25	≥25	P Value	<0	0≤10	10≤20	≥20	P Value
No. of individuals	1430	268	316	277	297	272		88	389	701	252	
Age (y)	61 (11)	63 (10)	60 (11)	60 (10)	61 (11)	62 (10)	<0.001	68 (10)	64 (11)	59 (10)	61 (10)	<0.001
Men (%)	36	42	42	33	34	28	0.001	57	43	33	24	<0.001
Smoking status, ever-smoker (%)	18	18	19	18	19	17	0.9	23	22	17	14	0.05
Antihypertensive medication (%)	27	26	26	24	26	34	0.06	40	32	22	30	<0.001
Previous history (%)												
Diabetes	15	16	17	17	18	18	0.9	14	15	17	15	0.5
Hypercholesterolemia	17	14	15	13	20	16	0.2	11	19	16	15	0.6
Cardiovascular complication	1.2	1.1	1.2	1.8	0.8	1.5	0.8	1.1	2.3	0.9	0.8	0.2
Ambulatory BP (mm Hg)												
24-h systolic	123 (13)	124 (14)	121 (14)	121 (12)	124 (12)	126 (12)	<0.001	127 (14)	124 (13)	122 (13)	123 (12)	<0.001
24-h diastolic	72 (8)	72 (8)	71 (8)	71 (8)	72 (7)	73 (7)	0.006	73 (8)	72 (8)	72 (8)	72 (7)	0.4
Daytime systolic	128 (14)	127 (15)	126 (14)	127 (13)	129 (13)	135 (13)	<0.001	125 (14)	127 (14)	128 (14)	134 (13)	<0.001
Daytime diastolic	76 (8)	74 (9)	75 (8)	75 (8)	76 (8)	79 (8)	<0.001	73 (9)	75 (8)	76 (8)	79 (8)	<0.001
Night-time systolic	112 (14)	119 (16)	112 (15)	110 (12)	110 (13)	109 (13)	<0.001	131 (15)	119 (13)	109 (12)	102 (10)	<0.001
Nighttime diastolic	64 (8)	67 (9)	64 (8)	63 (8)	63 (7)	62 (7)	<0.001	72 (8)	67 (8)	62 (7)	59 (6)	<0.001
Before-waking systolic	115 (17)	127 (19)	116 (16)	112 (15)	111 (15)	108 (15)	<0.001	136 (18)	122 (16)	111 (15)	104 (13)	<0.001
Before-waking diastolic	66 (10)	71 (10)	67 (9)	64 (9)	64 (8)	62 (8)	<0.001	74 (9)	70 (9)	64 (9)	60 (8)	<0.001
After-waking systolic	129 (18)	121 (18)	123 (16)	126 (15)	131 (15)	142 (16)	<0.001	132 (19)	129 (18)	127 (17)	130 (18)	0.011
After-waking diastolic	76 (10)	72 (11)	74 (10)	74 (10)	77 (9)	82 (9)	<0.001	76 (11)	76 (11)	75 (10)	76 (11)	0.6
Nocturnal decline in BP (%)												
Systolic	13 (8)	6 (8)	11 (6)	13 (6)	15 (6)	19 (6)	<0.001	-5 (5)	6 (3)	15 (3)	24 (3)	<0.001
Diastolic	16 (8)	9 (8)	14 (6)	16 (6)	17 (7)	21 (7)	<0.001	1 (6)	9 (4)	17 (4)	26 (4)	<0.001
Amplitude of morning pressor surge (mm Hg)												
Systolic	14 (14)	-6(8)	7 (2)	14 (2)	20 (2)	34 (8)	<0.001	-4 (13)	7 (12)	16 (11)	26 (13)	<0.001
Diastolic	10 (8)	0 (6)	7 (5)	10 (5)	13 (5)	20 (7)	<0.001	2 (9)	6 (8)	11 (7)	16 (8)	<0.001

Data are mean (SD) or %. Statistical significance was tested using χ^2 test for categorical variables and ANOVA for continuous variables.

rhages (8%), 4 were TIAs (3%), and 1 was of an undefined type (1%).

Association Between Morning Pressor Surge and Stroke Risk

There was no consistent association between the morning pressor surge, grouped by quintile, and the risk of total stroke (Figure 1). As a continuous variable, there was also no significant association between the morning pressor surge and the risk of total stroke [RH: 1.10 (95% CI, 0.94 to 1.31); $P=0.20$]. A significantly high risk for cerebral hemorrhage was observed in the fifth quintile group of the morning pressor surge (an amplitude of the morning pressor surge ≥ 25 mm Hg) [RH: 4.0 (95% CI, 1.08 to 14.63); $P=0.04$], when the second quintile of the morning pressor surge (amplitude of the morning pressor surge: 3 to 11 mm Hg) was set as the reference category (Figure 1). Antihypertensive treatment did not interact with this tendency ($P=0.9$). As a

continuous variable, a higher magnitude of morning pressor surge tended to be associated with an increased risk of cerebral hemorrhage [RH per 1 SD increase of morning pressor surge (=13.8 mm Hg): 1.34 (95% CI, 0.95 to 1.89); $P=0.10$]. The amplitude of the morning pressor surge was not associated with the risk of cerebral infarction either on quintile analysis (Figure 1) or on continuous variable analysis.

In a previous study, Kario et al² reported the predictive value of a morning surge, defined as a “sleep-trough” morning pressor surge calculated as the difference between the morning SBP and the lowest SBP during sleep. In the present study population, we also examined the prognostic significance of the sleep-trough morning pressor surge. The results showed that the predictive value of the sleep-trough morning surge was broadly similar to sleeping-to-waking morning surge. Namely, the fifth quintile of the sleep-trough morning pressor surge with ≥ 40 mm Hg had a significantly higher risk for intracerebral hemorrhage than the second quintile of the sleep-

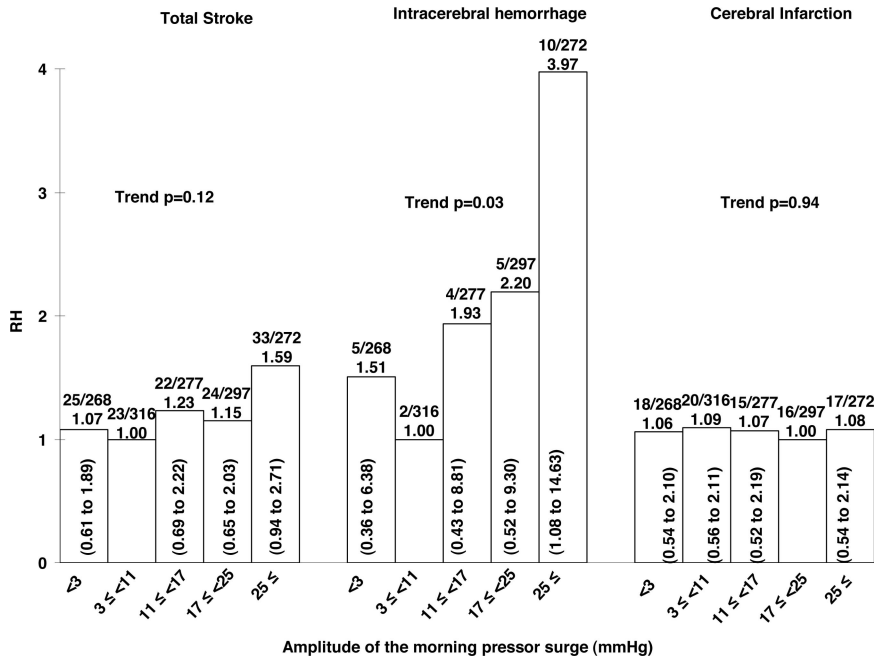


Figure 1. Risk of stroke among quintiles of morning pressor surge. RHs and 95% CIs (inside the bars) for the risk of total stroke, intracerebral hemorrhage, and cerebral infarction among quintiles of amplitude of the morning pressor surge (mm Hg), adjusted for age, gender, smoking status, use of antihypertensive medication, history of cardiovascular disease, hypercholesterolemia, diabetes mellitus, and 24-hour SBP. Incidence/number of subjects in each group are shown on each bar. Amplitude of morning pressor surge was calculated as 2-hour SBP after waking minus 2-hour average of SBP before waking.

trough morning pressor surge with 16 to 23 mm Hg [RH, 8.88 (95% CI, 1.14 to 69.2)].

In all of the analyses, additional adjustment for daytime BP variability expressed as SD of daytime BP or 24-hour BP variability expressed as [(SD of daytime BP)×(daytime hours)+(SD of nighttime BP)×(nighttime hours)/24] did not modify the associations with outcomes.

Association Between Nocturnal Decline in BP and Stroke Risk

No consistent association was observed between the dipping pattern and the risk of total stroke (Figure 2), and the data did not fit a linear model [RH per 1 SD increase of nocturnal decline in BP, 1.06 (95% CI, 0.81 to 1.39); *P*=0.68]. Extreme dippers, who are analogous to diurnal risers (those with ≥20% nocturnal decline of BP), tended to have a higher risk of cerebral hemorrhage (Figure 2). Comparing the risk in

extreme dippers with the risk in patients whose nocturnal decline was <20% (dippers, nondippers, and inverted dippers) showed that extreme dippers had a significantly higher risk of cerebral hemorrhage [RH, 2.69 (95% CI, 1.14 to 6.36); *P*=0.02]. In the linear model, the risk of intracerebral hemorrhage was significantly increased with an increase in the nocturnal decline in SBP as a continuous variable [RH per 1 SD (12.7%) increase in nocturnal decline in BP, 1.89 (95% CI, 1.02 to 3.48); *P*=0.04]. Inverted dippers or nondippers (those with a <10% decline) tended to be at a relatively higher risk for cerebral infarction (Figure 2). When we compared the risk in those with a <10% nocturnal decline (inverted dippers and nondippers) with the risk in those with a ≥10% decline (dippers and extreme dippers), we found that the inverted dippers and nondippers had a significantly higher risk for cerebral infarction [RH, 1.59 (95% CI, 1.03 to 2.46); *P*=0.04]. The use of antihypertensive treatment did not

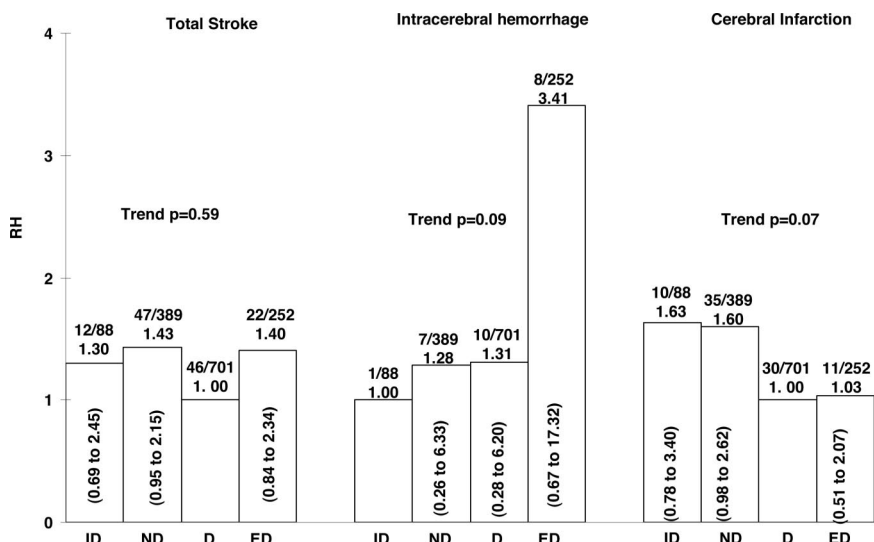


Figure 2. Risk of stroke among the 4 groups of nocturnal decline in BP. RHs and 95% CIs (inside the bars) for the risk of total stroke, intracerebral hemorrhage, and cerebral infarction among 4 groups of individuals with a nocturnal decline in SBP (%), adjusted for age, sex, smoking status, use of antihypertensive medication, history of cardiovascular disease, hypercholesterolemia, diabetes mellitus, and 24-hour SBP. Incidence/number of subjects in each group are shown on each bar. Nocturnal decline in SBP was calculated as follows: (daytime SBP–nighttime SBP)×100/daytime SBP. Inverted dipper (ID): nocturnal decline in SBP <0%, nondipper (ND): 0≤<10%, dipper (D): 10≤<20%, extreme dipper (ED): ≥20%.

interact with these relationships ($P=0.7$). Additional adjustment for daytime BP variability or 24-hour BP variability did not affect the outcomes.

Morning Pressor Surge Versus Nocturnal Decline in BP for the Risk of Intracerebral Hemorrhage

Because most extreme dippers had a large morning surge, and most subjects who had a large morning surge were extreme dippers, we included both indexes simultaneously in the Cox model to compare their predictive value for intracerebral hemorrhage. Neither large morning surges nor extreme dippers were significantly associated with the risk of intracerebral hemorrhage when both indexes were simultaneously included in the same Cox model [large morning surges: RH=1.95 (95% CI, 0.80 to 4.73; $P=0.14$); extreme dippers: RH=2.01 (95% CI, 0.78 to 5.18; $P=0.15$)]. This might be because of the collinearity between the 2 pressure changes.

Discussion

In the present study, we examined the relationship between the pattern of circadian BP variation and the type of cerebrovascular diseases present in a representative sample of the general population of Ohasama, a cohort of Northern Japan. The results demonstrate that the various patterns of circadian BP variation, including the morning pressor surge, are associated with different stroke subtypes.

Recently, morning BP levels and the morning pressor surge were found to be risk factors for cerebrovascular and cardiovascular diseases.^{1,3,17} Certain patterns of circadian BP variation (nondipper, inverted dipper,^{6,8,18} and extreme dipper⁷) have also been identified as risk factors for cerebrovascular and cardiovascular diseases. In the Syst-Eur substudy, Staessen et al⁴ reported that an increase in the slope of the morning BP rise by 1 mm Hg per hour was associated with an 8% decrease in all cardiovascular events. Extreme dippers have a large amplitude and a steep slope of the morning pressure rise, whereas nondippers and inverted dippers have a small amplitude and a gentle slope or a negative slope of the morning pressure rise. Therefore, the results of the Syst-Eur substudy would suggest that the nondipper and the inverted dipper patterns of circadian BP variation have a poor prognosis, whereas the extreme dipper pattern of circadian BP variation is a rather benign condition.

On the other hand, Kario et al² argued that both the extreme dipper pattern of circadian BP variation and the morning pressor surge were risk factors for stroke. They speculated that the extreme dipper pattern of circadian BP variation mediates an excess lowering of BP at night and that excessive nocturnal BP lowering may induce ischemic stroke.^{2,7} In contrast, we have reported previously that nocturnal BP levels in hypertensive subjects with an extreme dipper pattern of circadian BP variation were apparently higher than those in normotensive subjects, suggesting that no excess lowering of the nocturnal BP occurs even in hypertensives who are extreme dippers,¹⁹ although an excess diurnal BP rise may occur. However, Kario et al² additionally reported that there was no significant difference in the rate of different stroke subtypes between those with a morning surge and those without a morning surge. In the present study, however, it is

apparent that those with a large morning pressor surge, as well as those with an extreme dipper pattern of circadian BP variation (including those with a diurnal rise), were at a high risk for cerebral hemorrhage but not for cerebral infarction (Figure 1).

The difference between the present results and the results of Kario et al² may be partly because of differences in the study populations. In the present study, a representative sample of the general population aged ≥ 40 years was studied. The mean age of our study subjects was 61 years, mean 24-hour SBP/DBP values were 123/72 mm Hg, and the rate of stroke incidence was 8.9% during the 10.4 year follow-up period. On the other hand, Kario et al² studied older subjects (mean age, 72 years) who had higher BP values (24-hour SBP/DBP: 139/78 mm Hg) and a higher stroke incidence (8.5% during 3.4 year follow-up period).² Moreover, in our study, 30% of subjects were treated with antihypertensive medications. Our subjects were asked to take their antihypertensive drugs on the day of ambulatory BP monitoring,² whereas treated subjects in the study of Kario et al² were asked to stop medication ≥ 14 days before the ambulatory BP monitoring. These differences in the characteristics of the study populations might explain the different prognostic significance of morning surge observed in the 2 studies.

Both the quality of sleep and the degree of morning activity have been reported to be associated with poor reproducibility of the nocturnal BP fall.²⁰ Because in this study we did not use an electronic device to record daily activity and quantify nocturnal sleep, it is possible that there could be some misclassification of nocturnal dipping and/or morning BP rise. However, another study reported that both the diary entries and electronically measured physical activity are significantly correlated with diurnal BP variability.²¹ Therefore, although there could be a certain amount of misclassification, it would not be so large as to substantially affect the association with outcomes found in the present study.

The present results might postulate the possibility that inhibition of the morning pressor surge through antihypertensive medication could reduce the risk for intracerebral hemorrhage and that the lowering of nocturnal BP levels by antihypertensive treatment in nondippers and inverted dippers could reduce the risk of cerebral infarction. In fact, several clinical pharmacological studies dealing with the control of morning hypertension have reported that several antihypertensive drugs successfully control morning hypertension.^{22–27} However, one study, the Controlled ONset Verapamil INvestigation of Cardiovascular End points (CONVINCE) trial,²² which appears to be relevant in terms of sample size, did not show any benefit in decreasing the risk of cardiovascular events with verapamil controlled-onset extended-release therapy that aimed to reduce an abrupt morning BP surge. Because the CONVINCE trial was discontinued, and ambulatory BP monitoring was not done,²² it remains to be seen whether antihypertensive treatments that alter circadian BP variation can decrease the risk of cardiovascular events.

Perspectives

A large-amplitude morning pressor surge reflects a sharp BP rise in the morning and is associated with cerebral hemor-

rhage, possibly through hemodynamic effects. On the other hand, a continuous high BP load throughout the night, including in the early morning, as occurs in the nondipper and the inverted dipper patterns of circadian BP variation, is associated with cerebral infarction. The present results obtained from a sample of the general population were not consistent with previous studies partly because those studies did not examine the stroke subtypes separately and partly because their study subjects were mainly hypertensive patients. Nevertheless, it might be inappropriate to generalize the present results and claim that all patients with a morning pressor surge and the extreme dipper pattern of circadian BP variation are at risk for strokes of any type. A large study to examine the risk of each stroke subtype in both hypertensive and normotensive subjects is needed to better elucidate the prognostic significance of circadian BP variation.

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