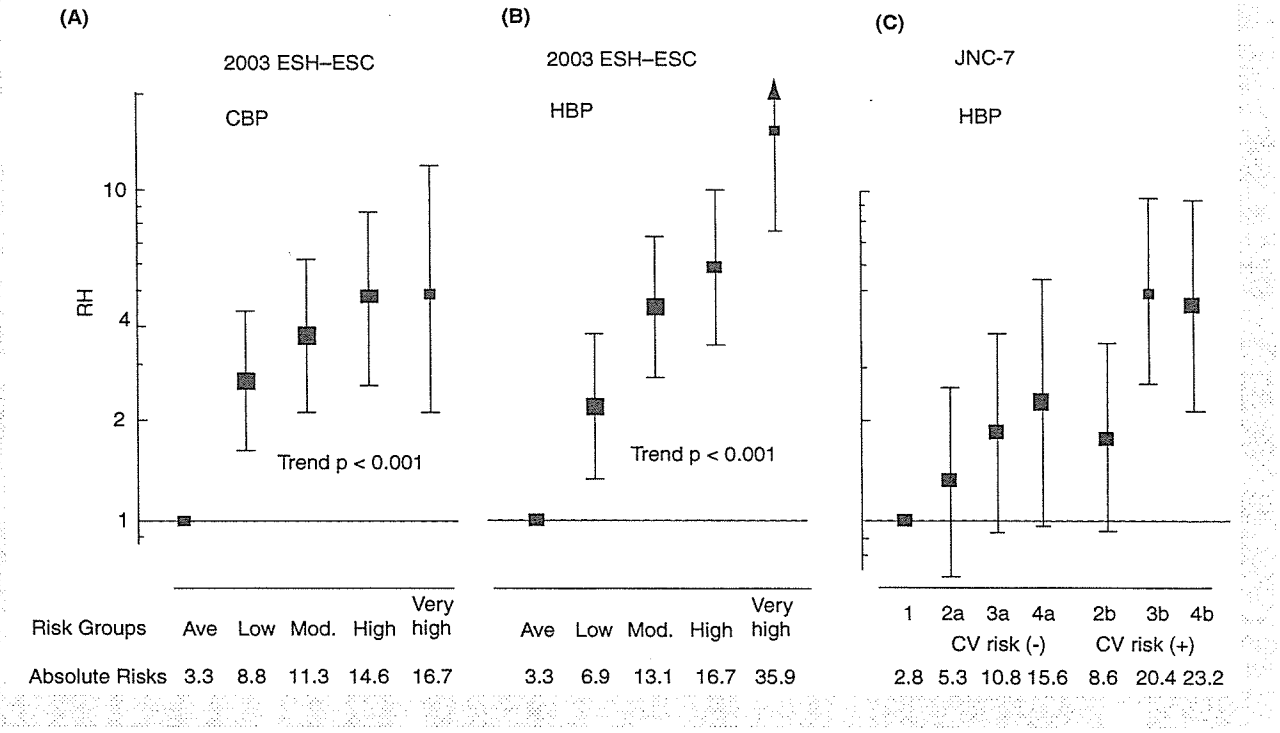

Figure 3. Risk of stroke based on HBP or CBP values and cardiovascular risk. (A) and (B) demonstrate RH and 95% confidence intervals (CI) for the first stroke plotted on a log scale among all groups classified by CBP (A) and HBP (B) values. (C) demonstrates RH and 95% CI for first stroke according to JNC-7 classification based on HBP values. Absolute risks display incidence per 1000 person-years. Group definitions are shown in TABLE 1. The average group (2003 ESH-ESC) or group 1 (JNC-7) is treated as the reference category. Solid squares indicate the RH point and are sized in proportion to the number of events observed. Vertical lines extending from squares represent 95% CI. Trend p values express the linearity among groups.
Ave: Average-risk group; Low: Low added-risk group; Mod.: Moderate added-risk group; High: High added risk group; Very High: Very high added-risk group.
Adapted with permission from [13].

value. Guidelines based on individualized treatment, such as the 2003 ESH–ESC guidelines, are more useful and applicable than those based on simple BP-oriented treatment, such as the JNC-7. Home BP measurement is a useful tool to improve awareness of hypertension and to predict future incidence of cerebrovascular disease.

Five-year view

Home BP variability

Circadian BP variation has received attention as a risk factor in cardiovascular diseases. In the Ohasama study, we also found that those with diminished nocturnal decline (so-called nondippers) had a high risk of cardiovascular mortality [24]. Such BP information was obtained only by ambulatory BP monitoring. However, a new home BP device incorporating an integrated circuit memory and timer has been developed recently (HEM 747 IC-N, Omron Kyoto, Japan) [25]. This device is being used in a large-scale interventional study in Japan using home BP measurements and the internet, known as the Hypertension Objective Treatment Based on Measurement by Electrical Device of BP (HOMED-BP) study [26]. In this study, the devices are preset to work automatically at 2:00 am, since the nadir of the nocturnal BP was observed at around this time in the population of the Ohasama study. Using the device set to work once at 2:00 am, the subject can recall after waking the quality of sleep during the measurement [25]. However, it is impossible to evaluate the quality of sleep during ABPM, since one cannot define the quality of sleep during measurements every 30 min. Although determination of nocturnal BP by home measurement devices is not yet widespread, this procedure is significant for determination of the circadian BP variation and the nocturnal BP level. In the Ohasama study, home BP was also measured once every evening before going to bed, although the difference in predictive power between morning and home BP values remains to be investigated. In the future, predictive values of circadian BP variation, including nocturnal BP decline determined by home BP measurements, may be reported.

Short-term BP variability is a risk factor for cardiovascular diseases [27]. Such short-term information is available from ambulatory BP monitoring, while the information on day-by-day variability is obtained only with home BP measurements. Preliminary analysis of the Ohasama study demonstrated that day-by-day variability reflects the risk of cardiovascular diseases [28].

If future research demonstrates the prognostic significance of BP variability, including circadian BP changes, home BP measurements may be able to replace ambulatory BP

monitoring. Comparison of prognostic value of multiple self-measurement of home BP and ambulatory BP also awaits further follow-up results from the Ohasama study.

Record of home BP values

All measurements of home BP should be documented without selection. This should help to prevent over-estimation or underestimation of the home BP values. Mengden and colleagues reported that, among participants who measured home BP, excess reports, insufficient reports, and even reports of phantom records were observed frequently [29]. Therefore, the best way to rule out biases is to use equipment incorporating an integrated circuit memory. However, a personal computer is currently needed to read out the memory, and thus this function does not necessarily work efficiently in general practitice. Furthermore, discrimination among the data from multiple users is not possible with the present form of the device, and thus a separate device is required for each user, and each user must be informed that the device is only for their personal use. Such problems may be solved in the future since new devices to overcome such problems are in development.

Key issues

- Each 10/5 mmHg elevation in home systolic/diastolic blood pressure (BP) is associated with an approximate 30/20%, respectively, higher risk of total, hemorrhagic and ischemic stroke.
- The predictive value of home BP increases progressively with the number of measurements. There is no threshold for the number of home BP measurements within the range of 1–14 measurements for increasing the predictive power of stroke risks.
- Even the initial-first home BP values (one measurement) show a significantly greater relation with stroke risk than conventional BP values (mean of two measurements).
- Guidelines based on individualized categorizations, such as the 2003 ESH–ESC guidelines, are more useful in predicting stroke than those based on simple BP-oriented categorizations, such as the JNC-7. Home BP increases the predictive power of categorizations of guidelines compared with conventional BP.

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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 ≥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 ≥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 al[2] 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 al[3] 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 al[4] 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 relationship 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 al[2] 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. Artifactual measurements during recordings were defined according to criteria described previously[15] 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)×100/daytime SBP.

We classified the subtypes of nocturnal decline in SBP as follows: extreme dipper (≥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±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±13.0/ 71.9± 7.7 mm Hg for the 24-hour period, 128.5±13.8/75.9± 8.4 mm Hg for the daytime period, and 111.9±14.3/ 63.8±8.0 mm Hg for the nighttime period. The mean nocturnal decline in SBP/DBP was found to be 12.8±7.9/ 15.7±7.8%. The mean amplitudes of the morning pressor surge in SBP/DBP were 13.9±13.9/9.9±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

	Amplitude of Morning Pressor Surge (mm Hg)							Nocturnal SBP Decline (%)				
Characteristics	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, these 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 al[2] 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-

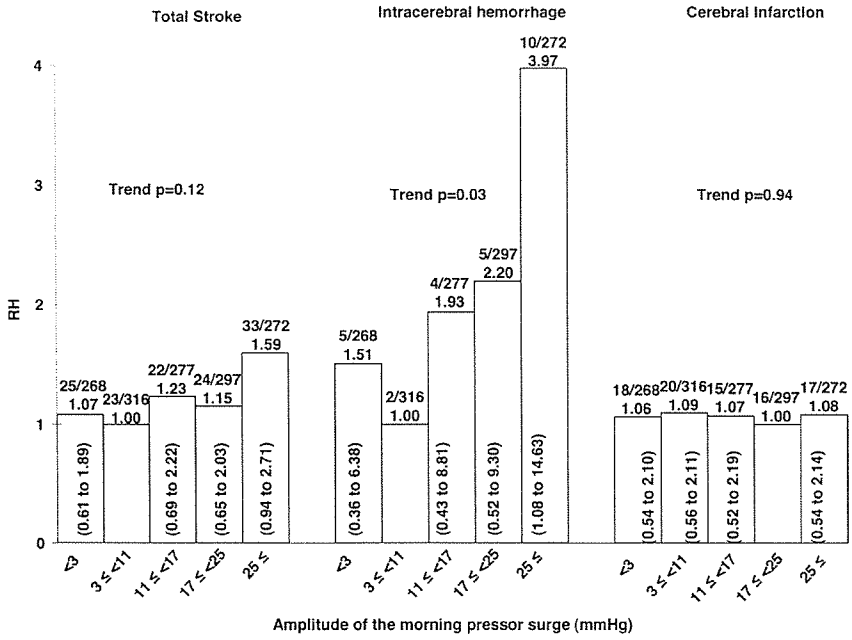

Figure 1. Risk of stroke among quintiles of morning pressor surge. RHs and 95% CIs (inside the bars) for the risk of total stroke, intracerebral hemorrhage, and cerebral infarction among quintiles of amplitude of the morning pressor surge (mm Hg), adjusted for age, gender, smoking status, use of antihypertensive 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

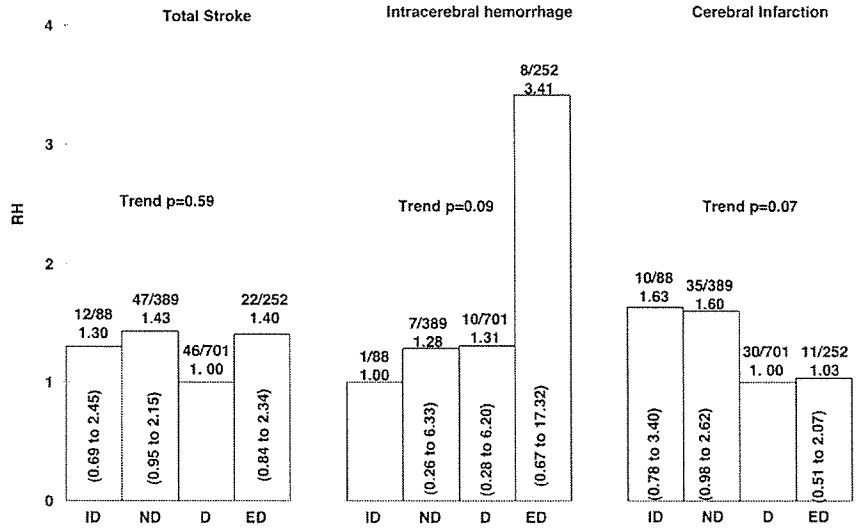

Figure 2. Risk of stroke among the 4 groups of nocturnal decline in BP. RHs and 95% CIs (inside the bars) for the risk of total stroke, intracerebral hemorrhage, and cerebral infarction among 4 groups of individuals with a nocturnal decline in SBP (%), adjusted for age, sex, smoking status, use of antihypertensive 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 dipper[7]) have also been identified as risk factors for cerebrovascular and cardiovascular diseases. In the Syst-Eur substudy, Staessen et al[4] 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 al[2] 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 al[2] 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 al[2] 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 al[2] 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 al[2] 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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AJH 2006; 19:27–32

BP Measurement

Enhanced Radial Late Systolic Pressure Augmentation in Hypertensive Patients With Left Ventricular Hypertrophy

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Background: Wave reflection augments central blood pressure (BP) in late systole, thus increasing cardiac afterload. We examined the relationship between late systolic pressure augmentation in the peripheral radial artery pulse wave and the existence of left ventricular hypertrophy (LVH) in hypertension.

Methods: Brachial BP, radial augmentation index (AI_r), and carotid-femoral pulse wave velocity (PWV_{cf}) were determined in 77 untreated hypertensive patients aged 56 ± 10 years. Cardiac structure and function were assessed by ultrasound, and LVH was defined based on the LV mass index (LVMI). Using multivariate analysis, patient characteristics were compared between those with (+) and without (−) LVH.

Results: The LVMI was correlated independently and positively with AI_r ($\beta = 0.33$, $P = .004$) and the brachial mean arterial pressure (MAP; $\beta = 0.25$, $P = .03$). The ratio of early to atrial peak velocities (E/A ratio) of the diastolic transmitral flow tended to be correlated negatively with the AI_r. The LVH (+) group had a significantly higher AI_r than the LVH (−) group [LVH (+), 97% *v* LVH (−), 89%, $P = .003$]; this difference remained significant even after adjustment for age, gender, MAP, and heart rate. The adjusted relative risk of LVH was 1.99 for each 10% AI_r increase ($P = .005$). In contrast, LVMI was not correlated with the PWV_{cf}, and the PWV_{cf} was not different between the LVH (+) and LVH (−) groups. Moreover, there was no significant correlation between PWV_{cf} and AI_r.

Conclusions: These results suggest that the peripheral AI_r measurement is clinically useful in predicting LVH. Enhanced wave reflection may be related to the development of LVH in hypertensive patients. Am J Hypertens 2006;19:27–32 © 2006 American Journal of Hypertension, Ltd.

Key Words: Left ventricular hypertrophy, radial pulse wave, wave reflection, augmentation index, hypertension.

Left ventricular hypertrophy (LVH) is a powerful independent cardiovascular risk factor and the most common cardiac abnormality associated with hypertension.[1] The development of LVH is generally ascribed to hemodynamic overload of the heart.[2] However, previous studies have shown that the LV mass index (LVMI) is not necessarily correlated with conventionally measured brachial artery blood pressure (BP).[3,4] One possible explanation for the lack of correlation might be that the cardiac afterload depends on the central aortic BP rather than on the peripheral brachial BP.

The BP pulse waveform is generated by the superposition of the reflected backward wave on the incident forward wave.[5] The early wave reflection that returns in late systole augments the BP in the ascending aorta. It has been proposed that this late systolic pressure augmentation could increase cardiac afterload. In fact, a few studies have shown that this augmentation, which is described by the augmentation index (AI),[6] is associated with particular left ventricular structure characteristics in normotensive subjects[7] and hemodialysis patients.[8] However, in essential hypertension there are little clinically relevant data about

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the relationship between late systolic augmentation and LVH.

The amplitude and the timing of the wave reflection are closely associated with arterial compliance. Various pulse wave-based indices, including pulse wave velocity (PWV) and AI, have been used as noninvasive measures of arterial structure and function.[9–12] These different indices appear to provide different information about arterial properties,[10–15] as PWV depends on regional large artery stiffness, whereas AI depends not only on systemic arterial elasticity but also on arterial geometry and tone.[5,10,15] However, it is not yet fully understood how these measurements relate to the cardiac and arterial changes seen in various disease states.

To date, central aortic augmentation has been evaluated noninvasively by mathematically transforming the radial artery pulse waveform to the aortic pulse waveform.[16,17] Recent research has demonstrated that the central AI (AI_c) could be estimated by the radial AI (AI_r) directly without the need for a transfer function.[18,19] Thus, in the present study, we measured AI_r in hypertensive patients to examine the association between radial late systolic pressure augmentation and LVH. We also compared carotid-femoral PWV (PWV_{cf}) and AI_r with respect to their relevance to cardiac structure.

Methods

Study Subjects

The subjects included 77 consecutive, untreated patients with essential hypertension seen at Kojinkai Central Clinic, Sendai, Japan. With the patient in the sitting position, the BP was measured three times. Hypertension was defined as a mean systolic BP ≥140 mm Hg or a mean diastolic BP ≥90 mm Hg. None of the subjects had a previous history of major cardiovascular complications, renal insufficiency (serum creatinine >2 mg/dL), or severe underlying diseases. None of the patients was taking any vasoactive drugs. Informed consent was obtained from all subjects participating in the study, and the study was approved by the institutional review board.

BP and Pulse Wave Measurements

All measurements were conducted in a quiet room kept at a constant temperature. First, after a 5-min rest and with the subject seated, brachial BP was measured using an automatic cuff oscillometric device (HEM-907, Omron Healthcare, Kyoto, Japan). The average of two readings was used to determine systolic BP, diastolic BP, mean arterial pressure (MAP), and pulse pressure (PP). Next, the radial pulse wave was recorded by using automated applanation tonometry (HEM-9010AI, Omron Healthcare). Briefly, the device consists of three units: a sensor unit, a pulse measurement unit, and a personal computer. The wristwatch-shaped sensor unit has a pressure sensor with an array of multiple 40 microtransducer elements on its inner surface. Once the sensor is placed on the left wrist over the radial artery, the device automatically flattens the artery, adjusts the applanation hold-down pressure, and selects an optimal sensing element to record the pulse wave appropriately. The obtained pressure signals are digitized at 500 Hz inside the pulse measurement unit and then transmitted to a personal computer. Continuous steady-state 40-sec data were recorded for each subject. According to previous studies,[18,20] AI_r was calculated as the ratio of the amplitude of the late systolic peak (P2) to the amplitude of the early systolic peak (P1; Fig. 1). The AI_r was determined for each pulse, and the mean value for all pulses assessed over a 40-sec time period was used in the subsequent analysis. The radial pulse waveform recorded with this device has been shown to correspond well with those collected from intra-arterial recordings.[21] The standard deviation for intraobserver AI_r differences was 2.9%, and for interobserver AI_r differences it was 4.4%.

After obtaining the AI_r recording, the PWV_{cf} was determined with the subject in the supine position. The details of the measurement method have been described in our previous report.[11] Briefly, the PWV_{cf} is measured using an automatic device, FCP-4731 (Fukuda Denshi, Tokyo, Japan), with pressure transducers placed at the base of the neck to assess the left common carotid artery and in the inguinal region to assess the left femoral artery. The PWV_{cf} measuring device has been previously validated.[22]

Echocardiography

Two-dimensionally guided M-mode echocardiography was performed using a ProSound SSD-5500 (Aloka, Tokyo, Japan) with a 3-MHz transducer. Left ventricular dimensions were measured according to the recommendations of the American Society of Echocardiography, and left ventricular mass (LVM) was calculated using the Penn

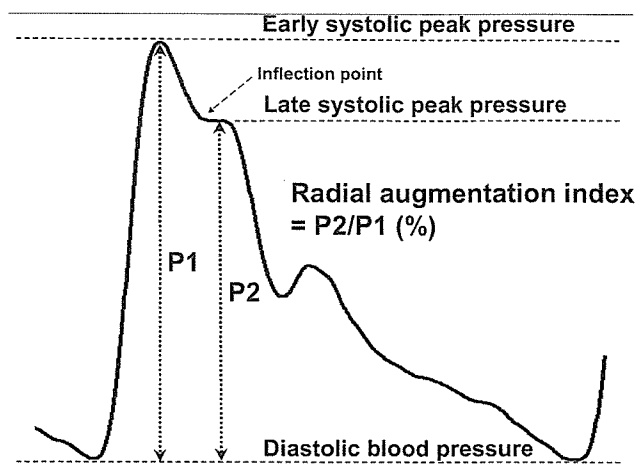

FIG. 1. Definition of radial augmentation index (AI). P1 indicates the amplitude of the early systolic peak pressure, P2 the amplitude of the late systolic peak pressure. The radial AI was defined as the ratio of P2 to P1.

convention.[23] The LVM index (LVMI) was calculated by dividing LVM by the body surface area. According to a previous study by Devereux et al,[24] LVH was defined as LVMI >118 g/m^2 for men and LVMI >108 g/m^2 for women. The LV ejection fraction (EF) and the fractional shortening (FS) were also examined as measures of cardiac function. In addition, a pulsed-wave Doppler recording was made to determine the early peak (E) and the atrial peak (A) of the diastolic transmitral flow velocity, and to calculate their ratio (the E/A ratio).

Statistical Analysis

First, Pearson's correlation coefficient was calculated for LVMI and various other parameters. Multivariate regression analysis was used successively to evaluate the independence of the relationship between AI_r and LVMI with respect to other confounding variables. Covariates entered into the stepwise model included: age, gender, body height, body mass index (BMI), brachial MAP (or systolic BP), heart rate (HR), biochemical parameters, treatment of diabetes, and treatment of hypercholesterolemia. To compare the effects of the AI_r and the brachial systolic BP on LVMI, tertile group differences were tested using analysis of variance (ANOVA) and Scheffe's post hoc test.

Next, the subjects were divided into two groups according to the presence (+) or absence (−) of LVH. Differences between the two groups were compared using Student t test and χ^2 test when appropriate. Then, the difference in the AI_r between the groups was further evaluated by analysis of covariance (ANCOVA) using age, gender, MAP, and HR as covariates. The effect of increasing AI_r on the risk of LVH was examined by logistic regression analysis.

Data are expressed as means ± SD or percentage, unless stated otherwise. Differences at $P < .05$ were considered statistically significant. All statistical analyses were performed using SPSS version 11.0 software (SPSS Inc., Chicago, IL).

Results

Baseline characteristics of the subjects are shown in Table 1. There were 54 men and 23 women with a mean age of 56 ± 10 years (range, 27 to 75 years). The mean systolic BP was 160 mm Hg, and the mean diastolic BP was 96 mm Hg. Of the 77 subjects, 8 subjects had diabetes, and 1 of these 8 was treated with a sulfonylurea agent. Hypercholesterolemia was present in 17 subjects, and 9 of these patients were treated with statins.

On univariate analysis, LVMI was correlated significantly and positively with AI_r ($r = 0.29$, $P = .01$). The LVMI was also correlated positively with brachial systolic BP ($r = 0.24$, $P = .04$) and age ($r = 0.23$, $P = .05$), whereas it was not correlated with MAP, diastolic BP, body height, or BMI. Neither LVMI nor AI_r was correlated with brachial PP. The LVMI was negatively correlated with the HR ($r = -0.24$, $P = .04$). The LVMI was not significantly different between male and female subjects (121 ± 20 g/m^2 v 119 ± 28 g/m^2). There were no significant correlations between LVMI and biochemical parameters (such as serum creatinine, total cholesterol, HDL-cholesterol, and fasting blood glucose). In contrast to AI_r, PWV_{cf} did not correlate with LVMI ($r = 0.11$). In addition, no significant correlation was observed between AI_r and PWV_{cf} ($r = 0.14$). Echocardiographic parameters of LV systolic function, including EF and FS, were not

Table 1. Clinical characteristics of the subjects

	All Subjects (n = 77)	LVH (−) Group (n = 33)	LVH (+) Group (n = 44)	P
Age (yr)	55.7 ± 10.0	52.7 ± 9.5	57.9 ± 9.9	.02
Gender (male, %)	70.1	75.8	65.9	NS
Body height (cm)	164.0 ± 8.3	165.8 ± 7.8	162.7 ± 8.4	NS
Body mass index (kg/m^2)	25.6 ± 3.2	24.9 ± 2.9	26.1 ± 3.4	NS
Systolic blood pressure (mm Hg)	159.5 ± 19.2	155.9 ± 16.9	162.2 ± 20.6	NS
Diastolic blood pressure (mm Hg)	96.3 ± 11.5	96.0 ± 11.9	96.7 ± 11.3	NS
Mean arterial pressure (mm Hg)	117.4 ± 11.8	116.0 ± 12.5	118.4 ± 11.3	NS
Pulse pressure (mm Hg)	63.1 ± 18.0	59.9 ± 12.1	65.6 ± 21.2	NS
Heart rate (beats/min)	74.0 ± 13.8	76.8 ± 15.4	71.8 ± 12.3	NS
Serum creatinine (mg/dL)	0.79 ± 0.21	0.79 ± 0.16	0.78 ± 0.24	NS
Total cholesterol (mg/dL)	206.1 ± 32.5	210.9 ± 30.5	202.5 ± 33.8	NS
HDL cholesterol (mg/dL)	50.5 ± 11.5	51.9 ± 12.1	49.4 ± 11.0	NS
Fasting blood glucose (mg/dL)	108.8 ± 23.1	111.4 ± 29.0	106.9 ± 17.7	NS
Current smokers (%)	41.6	33.3	47.7	NS
Diabetes (%)	10.4	15.2	6.8	NS
Hypercholesterolemia (%)	22.1	21.2	22.7	NS
Radial augmentation index (%)	93.5 ± 10.9	89.3 ± 10.8	96.7 ± 10.0	.003
Carotid–femoral PWV (m/s)	9.04 ± 1.38	8.84 ± 1.26	9.18 ± 1.46	NS

LVH = left ventricular hypertrophy; PWV = pulse wave velocity; NS = not significant.
P values for comparisons between LVH (−) and LVH (+) groups.

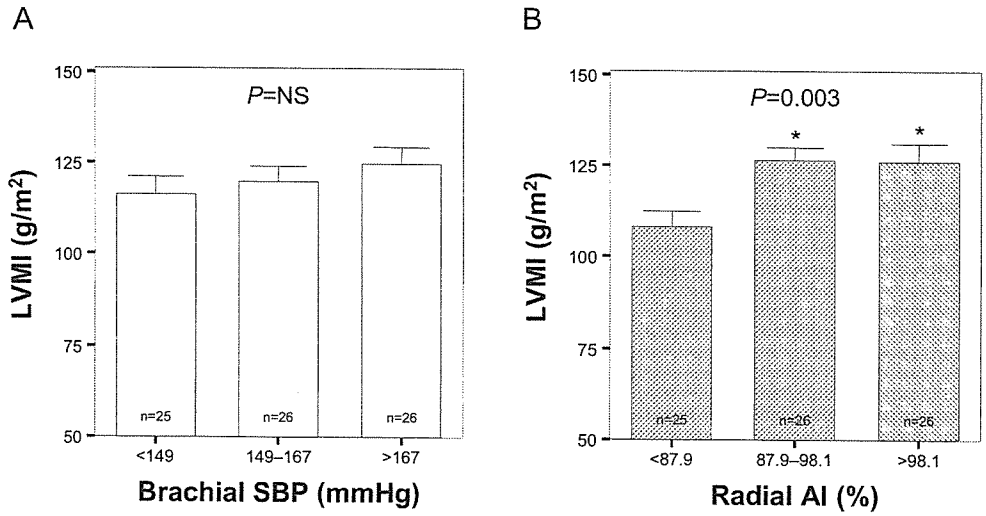

FIG. 2. Left ventricular mass index in the tertile groups classified by (**A**) brachial systolic blood pressure (SBP) and (**B**) radial augmentation index (AI). Data are shown as means ± SEM. LVMI = left ventricular mass index; NS = not significant. *$P < .05$ *v* the lowest tertile.

correlated with AI_r. The diastolic A filling velocity was significantly correlated with AI_r ($r = 0.26$, $P = .02$), although the E velocity was not. As a result, the E/A ratio tended to be negatively correlated with AI_r ($r = -0.22$, $P = .058$).

Multivariate stepwise linear regression analysis revealed that LVMI was independently correlated only with AI_r ($\beta = 0.33$, $P = .004$) and brachial MAP ($\beta = 0.25$, $P = .03$). When systolic BP (instead of MAP) was entered into the model, AI_r continued to be a significant independent correlate of LVMI ($\beta = 0.30$, $P = .007$), along with systolic BP ($\beta = 0.25$, $P = .02$). The LVMI was not independently related to age, gender, body height, BMI, HR, biochemical parameters, or the treatment of diabetes or hypercholesterolemia.

When the subjects were classified into tertile groups according to the AI_r level, LVMI was significantly different among the groups (Fig. 2). The highest and the middle AI_r tertiles had a greater LVMI than did the lowest AI_r tertile. On the other hand, when the subjects were classified by brachial systolic BP, LVMI did not differ significantly among the tertile groups.

The subject characteristics of LVH (+) and LVH (−) groups are shown in Table 1. Although the LVH (+) group was slightly older than the LVH (−) group, there were no other differences in baseline characteristics. The AI_r was greater in the LVH (+) group than in the LVH (−) group. This difference was highly statistically significant, and remained significant even after adjustment for age alone ($P = .02$) or for multiple covariates including age, gender, MAP, and HR ($P = .04$). Similar significance was noted when MAP was replaced with systolic BP as a covariate ($P = .04$). In contrast, PWV_{cf} did not differ between the LVH (+) group and the LVH (−) group (Table 1).

Univariate and multivariate logistic regression analyses revealed that the risk of LVH was elevated about twofold for each 10% increase in the AI_r (Table 2). Even after controlling for potentially relevant factors, an increase in the AI_r was found to be a significant independent risk factor for LVH.

Discussion

The present study demonstrated that LVMI is correlated independently with AI_r in untreated hypertensive patients.

Table 2. The relative risk of left ventricular hypertrophy for each 10% increase in the radial augmentation index (logistic regression analysis)

Model	Odds Ratio	95% CI	*P*
Model 1 (unadjusted)	1.99	1.23–3.23	.005
Model 2 (age and gender adjusted)	1.84	1.20–3.29	.007
Model 3 (adjusted for age, gender, MAP, and HR)	1.84	1.04–3.25	.035
Model 4 (multiple adjusted)*	1.83	1.01–3.32	.047
Model 5 (multiple adjusted, stepwise)*	1.99	1.23–3.23	.005

CI = confidence interval.

* Adjusted for age, gender, body mass index, mean arterial pressure (MAP), heart rate (HR), fasting blood glucose, total cholesterol, HDL cholesterol, treatment for diabetes, and treatment for hyperlipidemia.

Even when controlled for other possible relevant factors, patients with LVH had a significantly greater AI_r than those without LVH. The adjusted relative risk of LVH was approximately doubled for each 10% increase in the AI_r. In contrast, there was no relationship between LVH and PWV_{cf}. To our knowledge, this study is the first to demonstrate a significant association between AI_r and LVH in essential hypertension.

In this study, we used AI_r as a surrogate for central augmentation index (AIc) to examine the potential influence of late systolic pressure augmentation on the development of LVH.[7,8] The rationale for the use of peripheral AI_r was a recent report by Millasseau et al[18] showing a strong linear correlation between AI_r and the AI_c estimated by a generalized transfer function. Taking this finding into account, our results indicate that even an untransformed radial pulse wave can, by itself, provide information about the LV load, as it is influenced by central late systolic augmentation. Alternatively, it is also possible that, in subjects that develop LVH, hypertrophy of the myocardium is accompanied by hypertrophy of vascular smooth muscle in the small arteries, which are the ones that determine pressure wave reflection. Although the use of AI_r rather than AI_c is a departure from the usual approach, the current results suggest that this simple approach would be clinically applicable.

Our tertile group analyses showed that the AI_r had a closer association with LVMI than did brachial systolic BP. Furthermore, despite having similar brachial systolic BP levels, patients with LVH showed a significantly higher AI_r than those without LVH. Recently, Pauca et al[25] demonstrated that in hypertensive patients the second peak, but not the first peak, of the radial artery pressure wave corresponds with the aortic systolic BP. This result implies that the radial late systolic peak pressure that is augmented by wave reflection, rather than the radial early systolic peak pressure (corresponding to the radial systolic BP, in most cases) that is little influenced by wave reflection, represents the aortic systolic BP, which determines the LV load. In this connection, Vlachopoulos et al[26] showed that late systolic augmentation significantly contributes to the elevation of central systolic BP, does not affect peripheral systolic BP, but does affect peripheral late systolic peak pressure. These previous observations are concordant with our present results. This suggests that including the evaluation of peripheral late systolic augmentation could provide a more reasonable noninvasive method for estimating LV load than measuring brachial systolic BP alone.[27]

There was an interesting tendency for the diastolic E/A ratio to be negatively correlated with AI_r. Central augmentation delays the systolic peak of the pressure wave, and the delay in the systolic peak and the degree of augmentation have been shown to correlate with delayed diastolic ventricular relaxation.[28] Therefore, this observation suggests that enhanced pressure augmentation might affect myocardial relaxation during early diastole and hence lead to diastolic dysfunction. However, it is also possible that LVH by itself may be involved in diastolic dysfunction.[29]

Of note, we found that AI_r significantly correlated with LVMI, whereas PWV_{cf} did not. Furthermore, the AI_r was a better diagnostic indicator of LVH than PWV_{cf}. The different relationships of AI_r and PWV_{cf} to cardiac structure that were found in our study could be explained by assuming that these two measurements provide different information about arterial structure and function.[10–15] In fact, we observed no significant correlation between AI_r and PWV_{cf} in the present study population. This lack of correlation between AI_r and PWV_{cf} suggests that, at least in hypertensive subjects, AI_r is determined to a much greater extent by the amount of the pressure wave reflection than by its timing. In addition, it is generally thought that the PWV_{cf} offers information about the regional stiffness of the arterial segment under investigation, whereas the AI is thought to offer information about systemic arterial elasticity, geometry, and tone.[10] Therefore, our results indicate that the interaction between the vascular tree and the left ventricle (namely, the ventricular–vascular interaction) depends on the entire array of arterial properties (as expressed by AI_r) rather than on segmental large arterial properties (as expressed by PWV_{cf}). It also seems likely that, in our untreated hypertensive patients, the influence of the wave reflection on late systolic augmentation was determined primarily by the reflection coefficient dependent on the state of distal vasoconstriction and geometry rather than by central arterial stiffening.

There are some limitations to the present study. First, the observed association between AI_r and LVMI was relatively modest in a limited number of subjects. Second, we did not measure AI_c or central BP. Therefore, although the peripheral AI_r showed a closer association with LVMI than did the brachial systolic BP, we could not determine whether central systolic BP or AI_c would better correlate with LVMI. Finally, because this study was cross-sectional, the causal relationship between AI_r and LVH remains to be fully established. Prospective studies are necessary to resolve this important issue.

In conclusion, our present results suggest that enhanced wave reflection, as shown by an increase in the AI_r, is closely related to LVH in hypertensive patients. There is increasing evidence that various antihypertensive drug classes have different effects on reducing late systolic pressure augmentation.[5,30] Thus, the current findings warrant future studies that would clarify whether antihypertensive treatment designed specifically to reduce augmentation could substantially contribute to the regression of LVH.

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Prognosis of "Masked" Hypertension and "White-Coat" Hypertension Detected by 24-h Ambulatory Blood Pressure Monitoring

10-Year Follow-Up From the Ohasama Study

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OBJECTIVES We sought to investigate the prognosis in subjects with "white-coat" hypertension (WCHT) and "masked" hypertension (MHT), in which blood pressure (BP) is lower in clinical measurements than during ambulatory monitoring.

BACKGROUND The prognostic significance of WCHT remains controversial, and little is known about MHT.

METHODS We obtained 24-h ambulatory BP and "casual" BP (i.e., obtained in clinical scenarios) values from 1,332 subjects (872 women, 460 men) ≥40 years old in a representative sample of the general population of a Japanese community. Survival and stroke morbidity were then followed up for a mean duration of 10 years.

RESULTS Composite risk of cardiovascular mortality and stroke morbidity examined using a Cox proportional hazards regression model for subjects with WCHT (casual BP ≥140/90 mm Hg, daytime BP <135/85 mm Hg; relative hazards [RH])1.28; 95% confidence interval [CI] 0.76 to 2.14) was no different from risk for subjects with sustained normal BP (casual BP <140/90 mm Hg, daytime BP <135/85 mm Hg). However, risk was significantly higher for subjects with MHT (casual BP <140/90 mm Hg, daytime BP ≥135/85 mm Hg; RH 2.13; 95% CI 1.38 to 3.29) or sustained hypertension (casual BP ≥140/90 mm Hg, daytime BP ≥135/85 mm Hg; RH 2.26; 95% CI 1.49 to 3.41) than for subjects with sustained normal BP. Similar findings were observed for cardiovascular mortality and stroke morbidity among subgroups by gender, use of antihypertensive medication, and risk factor level (all p for heterogeneity >0.2).

CONCLUSIONS Conventional BP measurements may not identify some individuals at high or low risk, but these people may be identifiable by the use of ambulatory BP. (J Am Coll Cardiol 2005;46: 508–15) © 2005 by the American College of Cardiology Foundation

The utility of ambulatory blood pressure (BP) monitoring has been recognized, and the practice has been adopted widely (1,2). This method of measuring BP evaluates BP during the daily life of the patient and has revealed a subgroup of individuals who display elevated BP in clinical scenarios (i.e., "casual" BP) but normal ambulatory BP. The term "white-coat" hypertension (WCHT) has been used to describe this phenomenon (3). Another subgroup has recently gained attention that comprises individuals with elevated ambulatory BP but normal casual BP. Pickering et al. (4) named this trait "masked" hypertension (MHT). Two cross-sectional studies have shown a higher prevalence of target organ damage in MHT groups (5,6). A cohort of an unusual population (all exactly 70-year-old men, without major cardiovascular complications and without antihypertensive medication) has suggested a poor prognosis for MHT detected by ambulatory BP monitoring compared with normotensive subjects (7). However, the applicability of this finding to the general population remains unclear.

Several longitudinal studies have investigated the prognostic significance of WCHT as detected by ambulatory BP monitoring (8–13). Although three of the studies used control subjects with normal BP (8,11,13), these were volunteer subjects and thus did not comprise a representative sample. Results were ambiguous: two studies with mean

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Abbreviations and Acronyms

BP = blood pressure
CI = confidence interval
MHT = masked hypertension
RH = relative hazard
SHT = sustained hypertension
SNBP = sustained normal blood pressure
TIA = transient ischemic attack
WCHT = white-coat hypertension

follow-up periods of less than five years showed similarly low cardiovascular risks in WCHT and normotensive control patients (8,11), but one study with a longer follow-up of 10 years demonstrated a higher risk compared with normotensive control patients (13). Thus, the question of the long-term prognosis of WCHT remains unanswered.

We initiated ambulatory BP monitoring in a representative sample of men and women in a Japanese community (14) and have since been monitoring survival status and stroke occurrence (15,16). The present longitudinal study compared risks in subjects with WCHT, MHT, sustained hypertension (SHT), and sustained normal blood pressure (SNBP) in this representative cohort of a general population, including a broad range of subgroups, using data from a 10-year follow-up.

METHODS

Design. This report was based on longitudinal observations of subjects who have been participating in an ambulatory BP measurement project in Ohasama, Iwate Prefecture, Japan, since 1987. Socioeconomic and demographic characteristics of this region and details of the study project have been described previously (14–16). All study protocols were approved by the Institutional Review Board of Tohoku University School of Medicine and by the Department of Health of the Ohasama town government.

Study cohort. Selection of study subjects has been described previously (15). Of the 2,716 residents of Ohasama who were ≥40 years of age, 575 were excluded because they worked outside of town. This exclusion criterion was necessary because public health nurses visited subjects to attach ambulatory BP monitoring devices during workdays. Individuals who were in hospital (n = 121) or who were suffering dementia or bedridden (n = 31) also were excluded. Of the remaining 1,989 eligible residents, 1,542 provided informed consent and participated in the study. Casual BP measurements were not obtained from 210 individuals who did not participate in annual health checkups; therefore, the study cohort comprised 1,332 people, representing 67% of the total eligible population. Mean age was 61.0 years, and the male:female ratio was 40:60. The representative nature of the study cohort has been fully reported elsewhere (15).

Ambulatory BP monitoring. Well-trained public health nurses visited participants on a weekday morning to attach the ambulatory BP monitoring device and returned to detach it the next morning. Participants were asked to keep a diary in which they recorded daily activities, including times at which they went to bed and got up. Ambulatory BP data were included in the analysis if the monitoring period included more than 8 h of time spent during the waking period (daytime) and more than 4 h during which the subject was in bed (nighttime). These periods were estimated from subject diaries. Artifactual readings during ambulatory BP monitoring were defined according to previously described criteria (17) and were omitted from analysis. Mean 24-h, daytime, and nighttime values for ambulatory BP were calculated for each subject.

Casual BP measurements. BP was measured twice by nurses or technicians at local medical centers using an automatic device with subjects in a seated position after resting for at least 2 min. Casual BP was defined as the mean of the two readings.

BP monitoring device. Ambulatory BP was monitored using a fully automatic ABPM-630 device (Nippon Colin, Komaki, Japan) (18) preset to measure BP every 30 min. Although systolic and diastolic BP were measured using both cuff-oscillometric and microphone methods, only data obtained by the cuff-oscillometric method was used for analysis. Casual BP was measured using an automatic USM-700F device (UEDA Electronic Works, Tokyo, Japan) based on the Korotkoff sound technique (microphone method). Devices used to measure ambulatory and casual BP have been previously validated (18,19) and meet all criteria of the Association for the Advancement of Medical Instrumentation (AAMI) (20). The device used to measure casual BP also was calibrated annually by the Department of Health in Ohasama.

Classification of subjects. Subjects were classified into four groups on the basis of daytime ambulatory BP and casual BP levels: 1) SNBP (n = 739, 55%), displaying casual BP <140/90 mm Hg and daytime ambulatory BP <135/85 mm Hg; 2) WCHT (n = 170, 13%), displaying casual BP ≥140/90 mm Hg and ambulatory BP <135/85 mm Hg; 3) MHT (n = 221, 17%), displaying casual BP <140/90 mm Hg and ambulatory BP ≥135/85 mm Hg; and 4) SHT (n = 202, 15%), displaying casual BP ≥140/90 mm Hg and ambulatory BP ≥135/85 mm Hg. Cut-off values were derived from several guidelines (21–24). In the present analysis, subjects with SNBP included untreated subjects with "SNBP" and treated subjects with "controlled SNBP." The WCHT group included treated subjects with uncontrolled BP status only under medical settings. Similarly, the MHT group included those with "masked uncontrolled hypertension" that would represent uncontrolled BP status "masked" by the use of casual BP measurement alone. These concepts are consistent with those used in a previous study (25) and are based on previous reports showing that an insufficient duration of action for antihypertensive drugs represents an important factor in causing higher ambulatory or home BP values compared with casual BP (26).

Follow-up and outcomes. The residence of patients in Ohasama as of December 31, 2001, was confirmed using residents' registration cards, which are considered accurate and reliable, as they are the basis for pension and social security benefits in Japan. Causes of death by December 31, 2001, were investigated with reference to the national mortality registry, in which underlying cause of death was classified by death certificate according to the recommendations of the International Classification of Diseases-Tenth Revision (ICD-10). Primary outcome was determined as the composite of cardiovascular mortality and stroke morbidity. Secondary outcomes comprised: 1) cardiovascular mortality and 2) stroke morbidity. Cardiovascular mortality was defined as death from diseases of the circulatory system (ICD-10 code "I"). Incidence of stroke and transient ischemic attack (TIA) by December 31, 2001, was investigated with reference to the Stroke Registration System of Iwate Prefecture, national mortality registry, National Health Insurance receipts, and questionnaires sent to each household at the time of ambulatory BP monitoring. Results were then confirmed by checking the medical records of Ohasama Hospital, which is the only hospital in the town and is where >90% of patients undergo regular check-ups. Death certificates comprised the sole source of information for only 2% of stroke cases. Most cases were admitted to Ohasama Hospital, where diagnosis was confirmed by computed tomography or magnetic resonance imaging of the brain. Diagnostic criteria for stroke and stroke subtypes were based on the Classification of Cerebrovascular Disease 3 by the National Institute of Neurological Disorders and Stroke (27).

Data analysis. Associations between each BP category and outcome risks were examined using the Cox proportional hazard regression model (28). In all Cox analyses, the SNBP group was treated as the reference category. Among participants who experienced more than one outcome event during follow-up, survival time to the first relevant event was used in each analysis. If a participant experienced more than one type of outcome event during follow-up, each event contributed to the relevant outcome analysis, but only the first event for any individual contributed to the combined outcome analysis (stroke morbidity or cardiovascular mortality). For example, if a participant experienced a nonfatal stroke on December 12, 1998, and then died from coronary heart disease on February 7, 2001, the time from baseline to December 12, 1998, was used as the survival time for stroke morbidity analysis and for combined outcome, whereas time from baseline to February 7, 2001, was used as the survival time for analysis of cardiovascular mortality. Participants who died from other causes or who were lost to follow-up were treated as censored. In Cox analyses, age; gender; smoking status; use of antihypertensive medications; and history of cardiovascular disease, hypercholesterolemia, or diabetes mellitus were included as possible confounding variables in multivariate models.

Three subgroup analyses were conducted for the composite outcome of cardiovascular mortality and stroke morbidity: 1) comparison of risks in BP category between men and women; 2) comparison of risks in BP category between subjects with and without antihypertensive medications; and 3) comparison of risks in BP category among subjects classified as low risk (no history of cardiovascular disease or diabetes, and no risk factors), middle risk (no history of cardiovascular disease or diabetes, but one to two risk factors), or high risk (history of cardiovascular disease or diabetes or three risk factors). Risk factors comprised: age >55 years for men; age >65 years for women; ever smoker; and hypercholesterolemia. Information on smoking status; use of antihypertensive medications at baseline; and history of heart disease, diabetes mellitus, or hypercholesterolemia was obtained from questionnaires sent to each household at the time of ambulatory BP measurements and from medical records at Ohasama Hospital. Subjects who were administered lipid-lowering drugs or who had serum cholesterol levels of ≥5.68 mmol/l (220 mg/dl) were considered to have hypercholesterolemia. Subjects with a fasting glucose level of ≥77 mmol/l (140 mg/dl) or nonfasting glucose level of ≥11.11 mmol/l (200 mg/dl) or who used insulin or oral antihyperglycemic drugs were defined as having diabetes mellitus.

Estimated relative hazards (RHs) and 95% confidence intervals (CIs) for variables were derived from the coefficient and standard error of the mean as determined using the Cox proportional hazards regression model (28). Homogeneity between subgroups was tested by adding interaction terms to the relevant Cox models. Data are shown as (mean [SD]). Values of $p < 0.05$ were accepted as statistically significant. All statistical analyses were conducted using SAS version 8.2 software (SAS Institute, Cary, North Carolina).

RESULTS

Baseline characteristics. Mean ambulatory systolic BP (123.3 [13.0] mm Hg) and diastolic BP (72.0 [7.7] mm Hg) were significantly lower than casual systolic BP (131.2 [18.5] mm Hg) and diastolic BP (74.1 [11.3] mm Hg). Of the 1,332 study subjects, 272 (20%) were classified as current or ex-smokers, and 405 (30%) were using antihypertensive medications at baseline. A history of cardiovascular disease, diabetes mellitus, or hypercholesterolemia was present in 75 (6%), 232 (17%), and 217 subjects (16%), respectively.

Table 1 shows subject characteristics in each group. The WCHT and MHT groups displayed similar ages, gender ratios, and proportions of other risk factors. The SHT group was older and included a higher proportion of men, smokers, and hypercholesterolemic subjects compared with the WCHT and MHT groups. The SNBP group displayed lower proportions of risk factors compared with the other groups. Casual systolic/diastolic BP was significantly higher in the WCHT group (152/82 mm Hg) than in the MHT group (127/73 mm Hg), whereas 24-h ambulatory systolic/

Table 1. Baseline Characteristics

	Sustained Normal BP (n = 739)	White-Coat Hypertension (n = 170)	Masked Hypertension (n = 221)	Sustained Hypertension (n = 202)	p Value
Age (yrs)	60 (10)	64 (9)	63 (9)	66 (10)	<0.001
Male (%)	30	38	36	47	<0.001
Casual BP (mm Hg)					
Systolic	121 (12)	152 (12)	127 (9)	155 (15)	<0.001
Diastolic	70 (9)	82 (12)	73 (9)	86 (11)	<0.001
Ambulatory BP (mm Hg)					
24-h					
Systolic	116 (8)	120 (7)	136 (8)	140 (10)	<0.001
Diastolic	68 (5)	70 (5)	79 (6)	81 (7)	<0.001
Daytime					
Systolic	121 (8)	125 (7)	143 (8)	147 (9)	<0.001
Diastolic	72 (6)	74 (6)	84 (6)	86 (7)	<0.001
Nighttime					
Systolic	106 (10)	111 (11)	122 (13)	127 (14)	<0.001
Diastolic	61 (6)	63 (7)	70 (8)	71 (8)	<0.001
Antihypertensive treatment (%)	21	45	34	48	<0.001
Current or ex-smoker (%)	19	19	22	26	0.2
History of cardiovascular disease (%)	4	9	6	7	0.06
History of hypercholesterolemia (%)	14	21	20	18	0.02
History of diabetes (%)	15	19	19	22	0.01

Continuous values are shown as mean (SD).
BP = blood pressure.

diastolic BP was significantly lower in the WCHT group (120/70 mm Hg) than in the MHT group (136/79 mm Hg). Similar tendencies were observed for daytime and nighttime ambulatory BP.

Follow-up and outcomes. Mean duration of follow-up was 10.2 (2.7) years. A total of 26 subjects (2%) moved away and were lost to follow-up, whereas 67 cardiovascular deaths (5%) and 124 noncardiovascular deaths (9%) were recorded. The number of deaths was somewhat increased compared with the number during the pilot phase based on a five-year follow-up (37 cardiovascular deaths, 56 noncardiovascular deaths) (15). Of the cardiovascular deaths, 35 (52%) were due to stroke and 32 (48%) were due to heart disease. Of the 32 deaths due to heart disease, 12 were due to coronary heart disease (myocardial infarction, n = 9; angina pectoris, n = 3), whereas the remaining were due to congestive heart failure (n = 7), arrhythmia (n = 3), and other heart diseases (n = 10), respectively. Stroke or TIA occurred in 112 subjects (8%), because of cerebral infarction in 75 (67%), intracerebral hemorrhage in 23 (21%), subarachnoid hemorrhage in 10 (9%), TIA in 3 (3%), and unknown causes in 1 (1%). Of the 112 subjects who experienced stroke or TIA, 27 (24%: 23 due to stroke, 4 due to heart disease) died during the follow-up period. Composite cardiovascular mortality and stroke morbidity thus comprised 152 events.

Figure 1 shows risk of primary and secondary outcomes in each group. RH for the composite events was significantly higher in the SHT (RH = 2.26, $p < 0.0001$) and MHT groups (RH = 2.13, p = 0.0006) compared with the SNBP group, whereas no difference was identified with the WCHT group (RH = 1.28, p = 0.4). Similar relationships were observed for risk of cardiovascular mortality and stroke morbidity (Fig. 1). Further adjustment for casual systolic and diastolic BP levels did not change the increased risk in

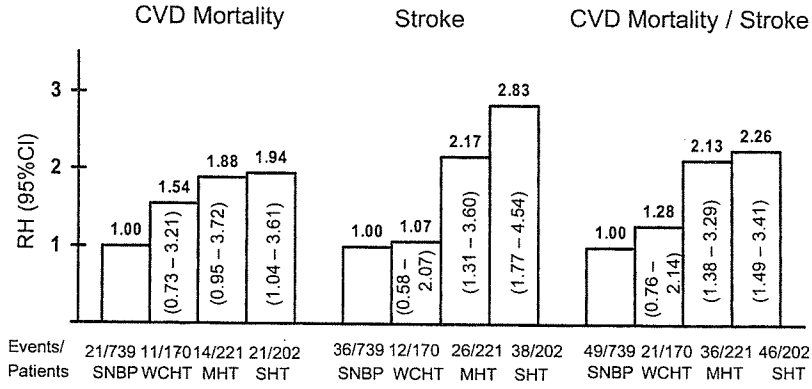

Figure 1. Relative hazards (RH) and 95% confidence intervals (CI) of sustained normal blood pressure (SNBP), white-coat hypertension (WCHT), masked hypertension (MHT), and sustained hypertension (SHT) for cardiovascular disease (CVD) mortality, stroke morbidity, and the composite of CVD mortality/stroke morbidity. **Numbers inside bars** indicate 95% CI. The SNBP group was treated as the reference category.

Table 2. RH and 95% CIs With a BP Increase of 10 mm Hg for CVD Mortality, Stroke Morbidity, and the Composite of CVD Mortality/Stroke Morbidity

Models*	CVD Mortality		Stroke		CVD Mortality/Stroke	
BP Variables	RH (95% CI)	p Value	RH (95% CI)	p Value	RH (95% CI)	p Value
Systolic BP						
Casual + 24 h						
Casual	1.04 (0.91–1.19)	0.5	1.04 (0.94–1.15)	0.3	1.05 (0.96–1.15)	0.3
24-h	1.27 (1.04–1.55)	0.02	1.40 (1.21–1.62)	<0.0001	1.33 (1.17–1.51)	<0.0001
Casual + daytime						
Casual	1.06 (0.93–1.21)	0.4	1.03 (0.93–1.15)	0.4	1.05 (0.96–1.15)	0.3
Daytime	1.17 (0.97–1.41)	0.1	1.37 (1.19–1.57)	<0.0001	1.27 (1.12–1.43)	0.0001
Casual + nighttime						
Casual	1.05 (0.92–1.20)	0.5	1.08 (0.98–1.19)	0.09	1.07 (0.99–1.17)	0.1
Nighttime	1.33 (1.11–1.58)	0.002	1.26 (1.10–1.43)	<0.0001	1.26 (1.13–1.41)	<0.0001
Diastolic BP						
Casual + 24 h						
Casual	1.00 (0.80–1.25)	0.9	1.07 (0.90–1.27)	0.4	1.05 (0.91–1.22)	0.5
24-h	1.27 (0.89–1.80)	0.2	1.73 (1.35–2.21)	<0.0001	1.54 (1.24–1.92)	<0.0001
Casual + daytime						
Casual	1.02 (0.81–1.27)	0.9	1.06 (0.90–1.26)	0.4	1.06 (0.91–1.23)	0.4
Daytime	1.14 (0.83–1.58)	0.4	1.67 (1.33–2.10)	<0.0001	1.43 (1.17–1.75)	0.0005
Casual + nighttime						
Casual	0.99 (0.80–1.23)	0.9	1.14 (0.96–1.34)	0.1	1.08 (0.94–1.25)	0.3
Nighttime	1.45 (1.05–1.99)	0.02	1.46 (1.16–1.85)	<0.0001	1.47 (1.20–1.80)	0.0002

*All models were adjusted for age, gender, smoking status, use of antihypertensive medications, and history of cardiovascular disease, hypercholesterolemia, or diabetes mellitus, and simultaneously adjusted for each BP value.
BP = blood pressure; CI = confidence interval; CVD = cardiovascular disease; RH = relative hazard.

the MHT group: RHs (95% CI) in the MHT group compared with the SNBP group for cardiovascular mortality, stroke morbidity, and composite events were 1.88 (0.94 to 3.74), 2.13 (1.28 to 3.56), and 2.01 (1.30 to 3.11), respectively. In a multivariate Cox model with continuous BP variables, ambulatory BP parameters represented a significant predictor of cardiovascular outcomes, whereas casual BP did not represent a significant predictor after simultaneous adjustment for ambulatory BP parameters (Table 2).

Subgroup analyses. Similar relationships were observed among men and women (Fig. 2); among subjects with and without antihypertensive medications (Fig. 3); and among subjects classified as low, middle, or high risk (Fig. 4) for risk of composite outcomes. No significant interactions were observed for risk among the aforementioned subgroups (p for interaction >0.2 for all).

DISCUSSION

This study was based on a 10-year observation of a representative sample of the general population in Japan. We demonstrated that risk of cardiovascular mortality and stroke morbidity in subjects with MHT or SHT was significantly higher than risk in subjects with SNBP, whereas the risk in subjects with WCHT did not differ from that for subjects with SNBP. Importantly, these relationships were observed among a broad range of subgroups without significant heterogeneity. To the

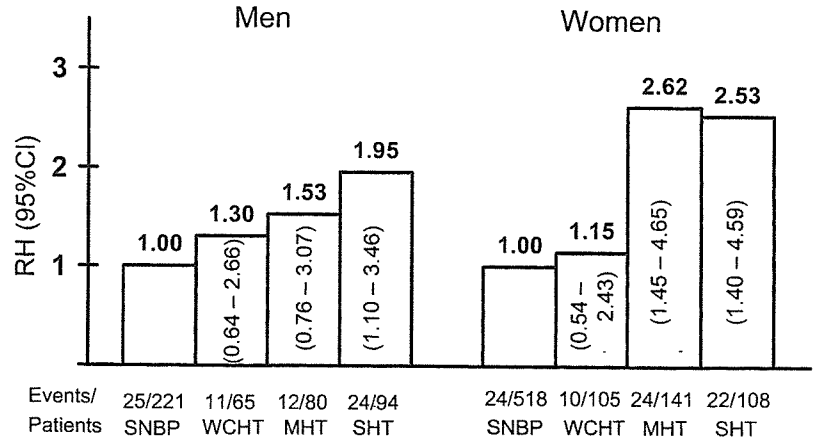

Figure 2. Relative hazards (RH) and 95% confidence intervals (CI) of sustained normal blood pressure (SNBP), white-coat hypertension (WCHT), masked hypertension (MHT), and sustained hypertension (SHT) for risk of the composite of cardiovascular disease (CVD) mortality/stroke morbidity by gender. **Numbers inside bars** indicate 95% CI. The SNBP group was treated as the reference category.